COllaborative Management Platform for detection and Analyses of (Re-) emerging and foodborne outbreaks in Europe

Deliverable

14.5 Assessment of options for refining selected elements of COMPARE in view of improving the overall cost-effectiveness of the system, with recommendations

Part 1: Final results of case studies and conclusions for improving cost-effectiveness of using WGS for identification and surveillance of pathogens

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1. Introduction

This is the fifth deliverable of Work Package 14, which aims to develop a standardised framework for estimating the cost-effectiveness of the COMPARE system and related methods and tools, including the value of safety. The activities of the work package are carried out jointly by WP partners Civic Consulting and Erasmus University Rotterdam (EUR). Deliverable 14.5 consists of two parts.

Part 1 (this document) presents the final results of the cost-effectiveness case studies, and the final results of the assessment of costs and the benefits of using WGS on a routine basis for pathogen identification and surveillance based on a detailed analysis of the data provided by the case study institutions.[1] This is complemented by a break-even analysis, which estimates the number of cases of illness (for the example of salmonellosis) that would need to be avoided each year through the use of WGS in order to 'break even' on costs, i.e. in order to make the use of WGS cost-neutral. On this basis, we discuss conclusions on cost-effectiveness that can be drawn from the case studies, and discuss options for improving the overall cost-effectiveness of the system.[2]

Part 1 of deliverable 14.5 is structured as follows:

- Section 2 provides a summary of the case study methodology;
- Section 3 contains the final case study reports;
- Section 4 presents the final results of the case studies and provides a comparision of costs and benefits across case studies;
- Section 5 presents the results of the break-even analysis
- Section 6 discusses conclusions from the case studies with respect to factors affecting cost-effectiveness and options for improving overall cost-effectiveness of the system.

[1] An initial version of the assessment based on preliminary results was presented in Deliverable 14.4.

[2] See section 2.2.1 for a definition of the system subject to the assessment.

2. Summary of methodology

According to the description of Work Package 14, the cost-effectiveness of COMPARE and related methods and tools will be estimated using case studies. For the definition of the scope of the case studies and the methodology for the cost-effectiveness estimation it is essential to clarify the following aspects of the analytical framework (see also Deliverables 1 to 4):

- *Criteria for case-study selection*, including an overview of the case studies conducted and their main characteristics;
- *Setting and context*, including a definition of the system and activities to be assessed for the case studies; and
- *Scope of the evaluation,* including the study perspective, comparators (i.e. the counterfactual against which the system is assessed), and time horizon.

These aspects are separately discussed in the following sub-sections.

2.1. Criteria for case study selection

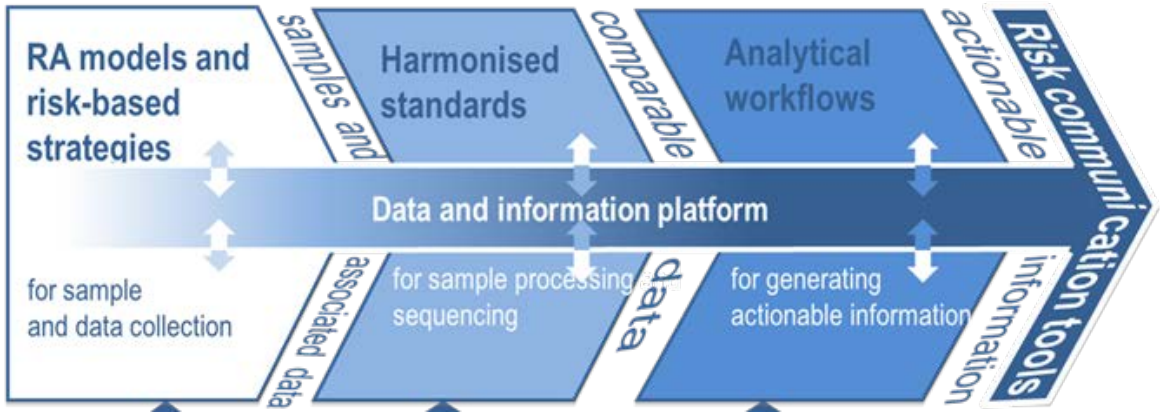
Case studies were conducted with eight reference laboratories that use WGS on a routine basis within the existing structure for pathogen identification and surveillance. The case studies spanned seven different countries in Europe and the Americas. Five of these institutions – Istituto Zooprofilattico Sperimentale della Lombardia e dell'Emilia-Romagna (IZSLER, Italy), Administración Nacional de Laboratorios e Institutos de Salud (INEI-ANLIS, Argentina), Maryland Department of Health (MDH, USA), Public Health Agency Canada (PHAC, Canada), and Public Health England (PHE, UK) – use WGS for characterisation of bacterial isolates in foodborne pathogen surveillance (mostly Salmonella, Listeria, E.coli and Shigella). Two reference laboratories use WGS to support avian influenza outbreak investigations, the Animal and Plant Health Agency (APHA, UK) and Friedrich-Loeffler-Institut (FLI, Germany). The last case study concerns the introduction of WGS on clinical samples to direct selection of strains for further characterisation through culture based routine human influenza virus at Erasmus Medical Centre (EMC, The Netherlands). The institutions were selected to ensure broad coverage of diverse surveillance contexts and applications, including sector of application (food safety, animal health, and public health), coverage of viral (influenza) and bacterial (foodborne) pathogens, routine surveillance and outbreak contexts, as well as the use of different sequencing technologies (see Table 3 below for more details).

2.2. Setting and context

2.2.1. Definition of the system subject to the cost-effectiveness estimation

The economic evaluation is carried out within the framework of the EU-funded COMPARE project. The core system targeted by the COMPARE project can be understood as *a process of information creation and analysis for pathogen identification and surveillance based on WGS*, which starts with risk-based sample and data collection strategies, continues with sample processing and sequencing based on harmonised standards, and aims at generating actionable information for pathogen and outbreak detection and related risk communication – all facilitated by a data and information sharing platform. The following figure illustrates the core system of COMPARE.

Figure 1: The core COMPARE system



Source: Adapted from COMPARE proposal.

To analyse the cost-effectiveness of this process requires its practical application in specific situations and geographical areas, which is complicated by the fact that the COMPARE project is very broad in scope (being a cross-sector and cross-pathogen framework for a globally linked data and information sharing platform), and does not only concern the practical implementation of such a system, but also intends to first develop the necessary standards and tools for sampling, processing, sequencing and data analysis and interpretation. In line with the case study approach for the cost-effectiveness estimation it was therefore decided to focus on specific application cases with a defined sectoral and geographic scope, considering specifically the costs and benefits of a routine use of WGS for pathogen identification and surveillance. As the routine use of WGS in pathogen identification and surveillance is still relatively rare, it was also decided to widen the perspective to also include other systems that are similar to COMPARE, in that they involve harmonised methods and the use of a centralised data and information sharing platform, even if they are not directly linked to COMPARE (such as the US Genome Trakr network).

In conclusion, it was decided to define the 'system' to be assessed in the cost-effectiveness case studies as follows:

- A system for pathogen identification and surveillance using WGS on a routine basis;
- With harmonised methods (e.g. regarding data collection strategies, sample processing and sequencing, analytical tools and methods); and
- Using a centralised data and information sharing platform for sequences and related metadata.

This definition of the 'system' subject to the cost-effectiveness estimation (hereafter referred to as 'WGS-based surveillance system') has been used for the identification of suitable case studies and for developing the methodological approach for the case studies.

2.2.2. Activities to be assessed

A system for pathogen identification and surveillance using WGS on a routine basis can be conceptualised as consisting of a process of data flow, which we divide into the following three main steps:

1. *Data acquisition*, which includes sampling and sequencing as well as all intermediate steps (sample processing, library preparation);

2. *Data analysis and storage*, which includes the bioinformatics analysis and storage of data in a reference database; and
3. *Data application,* which includes outbreak identification and response as well as other practical and research applications of genomic data.

Most of these steps are relevant for any surveillance system using WGS, independent from whether all steps and activities are conducted by one institution, or whether separate institutions are involved in data acquisition, data analysis and storage and data application.

With the exception of the steps that are directly related to WGS (such as sequencing and bioinformatics analysis), other key steps and the related data flow from sampling to outbreak identification and response also characterise surveillance systems that use conventional (non-WGS) laboratory methods. This model of data flow is therefore used as analytical basis for identifying the costs and benefits of WGS-based surveillance systems as well as of traditional surveillance systems.

A key question in terms of scope is to what extent response activities have to be considered when analysing the costs and benefits of a WGS-based surveillance system (i.e. the degree to which step 3 - data application should and could be included in the assessment). The COMPARE system as depicted in the figure above leads to actionable information for outbreak detection and analysis as well as risk communication, and does not necessarily include other outbreak response measures. The WHO Guide on evaluating the costs and benefits of national surveillance and response systems concludes that an analysis of costs and benefits should consider surveillance and response systems together.[3] Nevertheless, data on costs and benefits of response activities are often very difficult to obtain ex-post, and measurement problems are significant, mostly due to the need to assess an appropriate counterfactual (such as the size of an outbreak if a specific response measure had not been taken). Therefore, while we have recorded the effects of WGS on outbreak response as concretely experienced and reported by the case study institutions, the main economic evaluation focuses rather on the first two steps concerning data acquisition and data analysis and storage, which are objectively observable and more readily quantifiable.

2.3. Scope

2.3.1. Study perspective

The economic evaluation of costs and benefits on the basis of the case studies focuses on the institutional perspective, i.e. the 'investment case' for implementing WGS from the perspective of the reference laboratories. The costs considered therefore include equipment, consumables, staff and other costs that are directly accrued by each of the eight institutions. The benefits are assessed primarily from the perspective of the reference laboratories, focusing on the effects of using WGS on sampling and sampling strategies, analytical results and processes, research and methods applied, and outbreak identification and response, as experienced by each institution. Although the focus is on the costs and benefits accruing to the reference laboratories, we also follow the recommendation of the WHO to adopt a broader societal perspective where possible[4] and therefore report on the broader effects of the intervention for society where such effects have been concretely observed.

[3] World Health Organisation, Evaluating the Costs and Benefits of National Surveillance and Response Systems: Methodologies and Options, 2005, p. 10-1.

[4] Edejer T. Tan-Torres, R. Baltussen, T. Adam, R. Hutubessy, A. Acharya, D.B. Evans, and CJL. Murray, Making Choices in Health: WHO Guide to Cost-Effectiveness Analysis, 2003, p. 18-9.

2.3.2. Comparators

For each of the eight reference laboratories, the economic evaluation compares the costs of using WGS to a counterfactual of processing the same number of samples during the specified reference period with the next-best conventional methods for pathogen identification and characterisation. The next-best conventional methods have been defined by each individual reference laboratory, taking into account their own standard practice prior to the implementation of WGS. The next-best conventional methods vary considerably by institution (as specified in Table 2 below). The focus of the analysis is therefore on the measurement and valuation of the marginal (incremental) costs and benefits of using WGS in the surveillance systems subject to this research.

2.3.3. Time horizon

In line with WHO recommendations for the economic evaluation of surveillance systems, the time horizon of the analysis is limited to a reference timeframe[5]. For the five reference laboratories that conduct surveillance of foodborne pathogens, the reference timeframe is typically one year, usually the last twelve month period for which data was available. For the two reference laboratories that conduct surveillance of avian influenza in an outbreak context, the reference timeframe is limited to the duration of the outbreak, which in practice has been three and eight months. All reference timeframes covered at least a part of the year 2017, except in the human influenza case study (EMC), which covered the flu season 2018/19 (this case study was included at a later stage to cover routine use of Nanopore sequencing).

2.3.4. Evaluation of costs

Based on a combination of the relevant WHO guidance as well as previous studies concerning the evaluation of genomic sequencing technologies[6,7], the costs assessed for each case study are broken down by both analytical step and type of cost. The analytical steps that were considered within the scope of the economic evaluation for WGS are *sample preparation and sequencing* and *bioinformatics and other analyses.* Costs related to *outbreak response* were not considered, as data on costs and benefits of response activities are often difficult to obtain ex-post, and measurement problems are substantial. In addition, there were differences in the response mandate across case study institutions (e.g. while some are involved in determining response measures, others are not). Therefore, while we have recorded the benefits of WGS for outbreak response as concretely experienced by the case study institutions, the evaluation of costs focused *on the analytical process from receipt and opening of an incoming sample until interpretation and reporting of results by the reference laboratory*, both when using WGS and when using conventional methods, with the key result of the assessment being *the differential cost between both methods on a per-sample basis.* Four cost categories were selected for the assessment based on the

[5] World Health Organisation, Evaluating the Costs and Benefits of National Surveillance and Response Systems: Methodologies and Options, 2005, p. 18.

[6] Edejer T. Tan-Torres, R. Baltussen, T. Adam, R. Hutubessy, A. Acharya, D.B. Evans, and CJL. Murray, Making Choice in Health: WHO Guide to Cost-Effectiveness Analysis, 2003.

[7] Buchanan, James, Sarah Wordsworth, and Anna Schuh, "Issues Surrounding the Health Economic Evaluation of Genomic Technologies", Pharmacogenomics, Vol. 14, No. 15, 2013, Appendix 3: Costs which could be included in economic evaluations of genomic technologies. http://www.futuremedicine.com/doi/abs/10.2217/pgs.13.183.

relevant WHO guidance and past studies by the authors[8,9]: equipment costs, consumables costs, staff costs and other costs (e.g. for sub-contracting). The assessment of *equipment costs* is based on the original purchase costs for sequencers and other major laboratory equipment as reported by each institution. It uses estimated lifespans for equipment (5 years for computers and 10 years for major laboratory equipment) to calculate annualised costs consistently across case studies. Basic laboratory equipment (e.g. refrigerators or pipettes, but also standard office computers and software such as Word and Excel) as well as low-cost equipment of less than EUR 450 were not included. The assessment includes maintenance costs and considers the use rate of equipment (e.g. if a sequencer in a case study institution was used only 70% of the time for the analysis of the samples considered in the case study, and 30% for other purposes, the annualised costs of the sequencer were reduced accordingly). For *consumables*, the reported purchase costs were adjusted for batch size and for the failure rate of analytical processes. *Staff costs* include wages and social contributions and consider hands-on staff time per sample, i.e. the amount of staff time used for an activity, and not the duration of the activity: unsupervised processes (such as incubation periods or sequencing runs) are not included in the estimates. Hands-on staff time was monetised using country-specific labour costs for professional and technician staff categories (using EUROSTAT data, for EU countries), or average staff cost data provided by the case study institutions (Argentina, Canada, US), plus 25% for overhead costs. Cost data was collected from each case study institution in the local currency, with the exception of INEI-ANLIS (Argentina), which reported costs in US dollars, due to exchange rate fluctuations in the national currency, and also because part of consumables and equipment (including the sequencer) for that period of time were purchased in the USA in the framework of an international pilot project. Where the local currency was not the Euro, costs were converted into Euro based on the reference exchange rate of the European Central Bank for the relevant year. Costs are reported in EUR 2017, except where the reference periods extended into 2018 (EMC, INEI-ANLIS, PHAC). As the reference periods had a maximum length of one year, no discount rate has been applied.

The following tables provide details on WGS equipment used in the case study institutions, and the conventional methods used as comparator, by institution and pathogen.

[8] Edejer T. Tan-Torres, R. Baltussen, T. Adam, R. Hutubessy, A. Acharya, D.B. Evans, and CJL. Murray, Making Choice in Health: WHO Guide to Cost-Effectiveness Analysis, 2003.

[9] Civic Consulting (2016), Study on cost–benefit analysis of reference laboratories for human pathogens: final report, study conducted for CHAFEA of the European Commission and Civic Consulting (2009), Cost of National Prevention Systems for Animal Diseases and Zoonoses in Developing and Transition Countries, study conducted for the OIE.

Table 1: Type and total purchase costs of WGS equipment used by case study institutions, by analytical step

		APHA (UK)	FLI (DE)	EMC (NL)	IZSLER (IT)	INEI-ANLIS (ARG)	MDH (USA)	PHAC (CAN)	PHE (UK)
Pathogens		Av. influenza	Avian influenza	Influenza	Foodborne*	Foodborne*	Foodborne*	Foodborne*	Foodborne*
Batch size for sample processing/sequencing		1-2	6	30	24	12	24	32	Processing: 40 Sequencing: 96
No. of samples analysed in reference period		26 *(in 8 months)*	30 *(in 3 months)*	630 *(in 5 months)*	175 *(in 12 months)*	320 *(in 12 months)*	1 767 *(in 12 months)*	8 630 *(in 12 months)*	15 791 *(in 12 months)*
Analytical steps	Sample processing	Basic lab equipment only (€ 0)**	- *Covaris sonicator* - *Agilent bioanalyser* (€ 49 300)	- *Gel electro-phoresis system* (€ 4 000)	Basic lab equipment only**	- *Qiacube DNA* (€ 13 724)	- *MagNA Pure 24* (€ 44 260)	Basic lab equipment only**	- *2 Qiasymphony* - *Roche Magna Pure 96* (€ 218 582)
	Library preparation	Basic lab equipment only (€ 0)**	Basic lab equipment only (€ 0)**	- *PCR machine* - *Qubit* - *Magnate 96 wells* (€ 8 800)	- *Biorad-T100 thermal cycler* - *Biorad-CFX96 RT-system* - *Microplate Genie-Shake* (€ 29 100)	- *Qubit 3.0* - *Bioshake iQ Thermomixer* (€ 2 943)	- *Multichannel & Single Channel Pipette* (€ 3 203)	- *Tapestation* - *Blue Pippin* - *QUBIT* (€ 51 641)	- *2 cBot Cluster Generation System* - *2 LabChip GX* - *3 Assy-Sciclone G3* - *LabChip-DS Spectrophotometer 96* - *2 Glomax: 96 well plate Fluorometer* - *Biomek NXP Span-8 with integrated sealer and chilled storage* - *Biomek NXP Span-8* - *3 Biomek NXP Multichannel* (€ 1 033 590)
	Sequencing	- *Illumina MiSeq* (€ 104 826)	- *IonTorrent PGM* (€ 93 000)	- *GridION* (€ 45 000)	- *Illumina MiSeq* (€ 100 000)	- *Illumina MiSeq* (€ 75 273)	- *2 Illumina MiSeq* (€ 155 624)	- 3 Illumina MiSeq (€ 264 345)	- *2 Illumina HiSeq* (€ 1 212 821)
	Bioinformatics	- *Workstation*(€ 2 355)	- *Server* (€ 34 700)	- *Server* - *Storage* - *CLC* (€ 16 560)	- *3 Workstations* - *Storage* - *BioNumerics* (€ 44 220)	- *Server* - *2 Computers* (€ 26 702)	- *CLC* - *BaseSpace subscription* - *PC* (€ 5 665)	- *Storage* - *Networking* - *Servers* - *BioNumerics* (€ 2 892 662)	- *Computing system* - *Network* - *Storage* (No purchase cost provided)
Total purchase costs		**€ 107 181**	**€ 177 000**	**€ 74 360**	**€ 173 320**	**€ 118 641**	**€ 208 751**	**€ 3 208 648**	**€ 2 464 922†**

Source: Own compilation based on case study results. * Foodborne pathogens: *Salmonella* (all), Listeria (IZSLER, PHE, PHAC, MDH), E.coli/shigella (PHE, INEI-ANLIS, MDH), Campylobacter (PHE, MDH), Vibrio (MDH). **Costs for basic laboratory equipment are not included in the assessment. Purchase costs of € 0 therefore imply that no other equipment than basic laboratory equipment was used by the institution. † Not including bioinformatics costs.

Table 2: Overview of conventional methods used as comparator, by institution and pathogen (with percentage of samples typically analysed using each method)

	APHA (UK)	FLI (DE)	EMC (NL)	IZSLER (IT)	INEI-ANLIS (ARG)	MDH (USA)	PHAC (CAN)	PHE (UK)
Avian influenza	Sanger sequencing – HA/NA analysis (100%)	Sanger sequencing – whole genome (100%)	-	-	-	-	-	-
Influenza A and B	-	-	Real Time PCR (100%), virus isolation (17%), phenotyping of virus isolates - Hemagglutination inhibition (5%) and/or Virus neutralization (3%) and/or NA-Star (4%) - and Sanger Sequencing of a representative subset (4%)	-	-	-	-	-
Salmonella	-	-	-	Serotyping (100%) PFGE (100%) PCR (50%) MLVA (60%)	Biochemical testing (100%) Serotyping (100%) MaldiTOF (5%) PFGE (100%)	PFGE (100%)	Biochemical analysis (100%) Serotyping (100%) PFGE (65%)	PCR x2 (73%, 10%) MLVA (48%) Serotyping (98%) Phage typing (99%) PFGE (3%) D-Tartrate (3%) Glucose gas (8%) AMR (68%)
Listeria	-	-	-	PFGE (100%)	-	PFGE (100%)	Biochemical analysis (100%) PFGE (100%)	PCR x2 (100%) fAFLP (100%)
E. Coli & Shigella	-	-	-	-	Biochemical testing (100%) PCR typing (100%) MaldiTOF (5%) PFGE (100%)	PFGE (100%) PCR (100%)	-	PCR (100%) MLVA (100%) Serotyping (100%) Phage typing (100%) Biochemistry (100%)
Campylo-bacter	-	-	-	-	-	PFGE (100%) MaldiTOF (100%)	-	PCR (100%) MLST (52%) Serotyping (12%) Phage typing (38%)
Vibrio	-	-	-	-	-	PFGE (100%) PCR (100%)	-	-

Source: Own compilation based on case study results. Figures in parentheses are the share of samples typically processed using the method.

2.3.5. Evaluation of benefits

Based on the results of exploratory research, we identified key areas in which benefits of using WGS for pathogen identification and surveillance might be expected to accrue. Benefits in each area were analysed on basis of assessments provided by each of the reference laboratories as to whether or not they had experienced positive effects of WGS (using a Likert scale), in-depth interviews with all case study institutions with respect to the effects they had observed, and a review of their scientific publications and reports on research conducted (e.g. related to specific outbreaks they had analysed ex-post or in real time using WGS).

2.3.6. Breakeven analysis

The breakeven analysis calculates the cost of illness in terms of health care utilisation costs, productivity loss, and premature death, and compares this to the additional cost of using WGS. As the analysis focuses only on offsetting the cost of illness and does not take into account additional benefits of using WGS for pathogen identification and surveillance in terms of e.g. effects on research, trade, or industry, its results should be understood to be a conservative estimate. The analysis focuses on *Salmonella*, as all five case study institutions dealing with foodborne pathogens use WGS to sequence *Salmonella* samples. There is also an existing body of work on the costs of salmonellosis infection, making this pathogen the most suitable candidate for the breakeven analysis. Our approach closely follows (with some adaptations) the methodology used in the cost-benefit analyses of reducing *Salmonella* in breeding pigs and slaughter pigs, which were conducted for the European Commission in 2010 and 2011 in close coordination with the European Food Safety Authority (EFSA)[10,11]. It also draws on the latest cost of illness model developed by the US Department of Agriculture (USDA)[12]. The detailed approach for the breakeven analysis, including a sensitivity analysis in which key assumptions were varied, is presented in Section 5.

[10] European Commission (2010),European Commission (2011), *Analysis of the costs and benefits of setting a target for the reduction of Salmonella in slaughter pigs – Final report*, p. 69-102. (study conducted by the FCC Consortium)

[11] European Commission (2011), *Analysis of the costs and benefits of setting a target for the reduction of Salmonella in breeding pigs – Final report*, p. 23-8. (study conducted by the FCC Consortium)

[12] USDA Economic Research Service (2014), *Cost estimates of foodborne illnesses. https://www.ers.usda.gov/webdocs/DataFiles/48464/Salmonella.xlsx?v=3347.8 [last accessed on 25.06.2019]*

3. Final case study reports

This section presents the final case study reports for the cost-effectiveness case studies.

3.1. Animal and Plant Health Agency (APHA)

Avian Influenza outbreaks – APHA, UK	
I. Institution	
Name of institution	The Animal and Plant Health Agency (APHA)
Type of institution	Public veterinary institution
Description	The Animal and Plant Health Agency (APHA) is an executive agency of the Department for Environment, Food & Rural Affairs (Defra). It also provides services to the Scottish and Welsh Governments, other government departments, and other clients. APHA is responsible for identifying and controlling endemic and exotic diseases and pests in animals, plants and bees, and for surveillance of new and emerging pests and diseases. APHA maintains essential disease investigation and response capability, as well as supporting trade in plants, animals and associated products though certification, audit and inspection, e.g. through import controls of animals, plants, seeds and products of animal origin. APHA conducts scientific research and acts as a national and international reference laboratory for the World Health Organisation (WHO), World Organisation for Animal Health (OIE), and United Nations Food and Agriculture Organisation (FAO), covering many farm animal diseases, including avian influenza. APHA was the EU reference laboratory (EU-RL) for avian influenza until the summer of 2018.
Location	Surrey, UK
II. Activities covered by case study	
Activity	Outbreak investigation[13]
Reference period	1 December 2016 – 31 July 2017
Pathogen(s) covered	Highly Pathogenic Avian Influenza (HPAI) H5N8
Outbreak summary	The outbreak of highly pathogenic avian influenza H5N8 in 2016-2017 occurred in both wild birds and poultry, infecting 13 premises across England and Wales. These included turkey and chicken producers as well as premises involved in gamebird production. The H5N8 infections in poultry are thought to have arisen independently as a result of contact with wild birds, except in the case of a cluster of three infected premises of the same commercial enterprise in Lancashire, where genomic analysis confirmed that secondary infections were likely to have occurred.[c),d)] Note that related H5N8 outbreaks also occurred in continental Europe during this period, but only samples taken in the UK are included in this case study.
Type of sample	Primarily isolates where the virus has been cultivated prior to sequencing.

[13] APHA provided data on two outbreaks: a 2016-2017 outbreak of HPAI H5N8 in wild birds and poultry and a 2017-2018 outbreak of HPAI H5N6 in wild birds only. Data on the outbreak of HPAI N5N6 is presented in Annex II for comparison purposes.

	However, in some time-sensitive cases the clinical sample is sequenced as-is without growing the virus first, after selecting the 'best' samples in terms of viral content based on the pre-screen PCR.		
Region covered by sampling	UK		
Number of samples analysed in reference period	*Pathogen*	*Samples analysed by conventional methods*	*Samples sequenced using WGS*
	HPAI H5N8	104 (32 HA, 72 NA)	26
Conventional methods used as reference for costing	▸ Sanger sequencing (HA and NA analyses, used on 100% of samples) ▸ Manual extraction of RNA using guanidine lysis buffer and silica column purification, generation of target double stranded DNA amplicon (150nt) by RT-PCR using specific primers according to target, BigDye method of labelling and ABI Capillary sequencing		
Sample preparation WGS	▸ Manual extraction of RNA using guanidine lysis buffer and silica column purification, 'shotgun' generation of double stranded cDNA by RT-PCR of RNA in sample with random hexamers, library generation with Nexterra kit and Illumina WGS		
Sequencer used for WGS	▸ Illumina MiSeq		
Batch size for WGS analysis	▸ During the outbreak, APHA typically sequenced batch sizes of only 1 or 2 samples due to the time-sensitivity of the results, and this number is the basis for the following cost analysis (outside outbreaks, the typical batch size of amplified isolates would be up to 10 using the MiSeq sequencer).[14]		
Reference dataset used for WGS	▸ Reference sequences are chosen from the GISAID database for initial mapping based on assumptions as to the strain identity, then the mapped reads are used in a Blast search of all GenBank sequences to determine an optimal reference sequence for each viral segment. The new reference is then used in the subsequent mapping iterations.		
Additional information	▸ WGS is not done on all incoming avian influenza samples at APHA. Sanger sequencing (HA and NA analyses) is still the standard workflow and is required as a confirmatory test. ▸ WGS is currently employed on a routine basis as an additional 'research' test, particularly in the initial stages of an outbreak, in cases that show unusual clinical characteristics (e.g. infection of an unexpected species), or in cases where an assessment of the risk to humans is needed. Once the sequence of the index case is known, decisions to sequence additional samples are also made based on epidemiological data. ▸ All incoming avian influenza samples are subject to a pre-screening using real time PCR. From the PCR results, the best samples with the highest virus content are selected for sequencing. The virus would typically be grown further before Sanger sequencing and WGS; however, depending on the time sensitivity of results, it may be sequenced directly from the clinical sample submitted.		

III. Detailed overview of costs of WGS and conventional methods

In the following, all costs are provided on a per-sample basis. Equipment costs are annualised and incorporate the annual maintenance costs as reported by the institution. They are adjusted for the

[14] APHA also has an Illumina NextSeq sequencer which can process batch sizes of up to 40 and which has been used by APHA in their capacity as the EURL for avian influenza. However, this sequencer was not used for the UK outbreaks subject to this case study.

percentage use of the equipment for the listed pathogens samples during the reference period (i.e. if a sequencer was also used for other purposes, this is taken into account). Consumables costs are adjusted for the failure rate (i.e. the percentage of consumables wasted, e.g. due to failed runs). Staff time is provided in terms of the minutes of hands-on staff time per sample, for both professionals and technicians. For the calculation of total costs, staff time is then monetised based on Eurostat data on country-specific labour costs for 2017 (by staff category), plus a 25% surcharge for overheads. For comparison purposes only, we have also provided staff costs monetised based on EU average labour costs. More detailed cost data is provided in Annex I.		
a) Costs of using WGS[15]		
Sample preparation and sequencing	*Cost type*	*Cost per sample*
	Equipment costs	€ 57.33
	Consumables	€ 830.97
	Other costs	€ 0
	Staff time professionals	*0 minutes*
	Staff time technicians	*210 minutes*
	Staff costs, monetised based on labour cost data for the UK (in brackets: based on labour cost data for the EU as a whole)	€ 87.50 (85.75)
	Total	**€ 975.80**
Bioinformatics and other analyses	*Cost type*	*Cost per sample*
	Equipment costs	€ 1.20
	Other costs	€ 0.00
	Staff time professionals	*60 minutes*
	Staff time technicians	*0 minutes*
	Staff costs, based on labour cost data for the UK (for EU)	€ 39.63 (45.13)
	Total	**€ 40.83**
b) Costs of conventional methods		
Sanger Sequencing (assuming use for 100% of avian influenza samples)	*Cost type*	*Cost per sample*
	Equipment costs	€ 78.55
	Consumables	€ 21.91
	Other costs	€ 0
	Staff time professionals	*60 minutes*
	Staff time technicians	*360 minutes*
	Staff costs, based on labour cost data for the UK (for EU)	€ 189.63 (192.13)

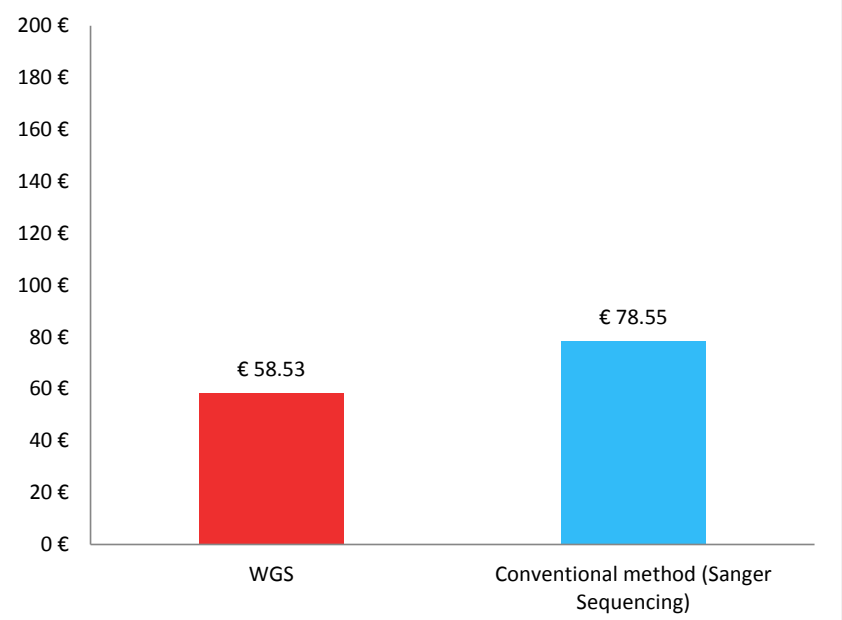
[15] APHA originally provided cost data in pounds sterling. These have been converted to Euro for comparison with the other case studies using the European Central Bank's yearly average reference exchange rate for the relevant year (i.e. the year of purchase for equipment, or 2017 otherwise).

	Total	**€ 290.08**

IV. Costs of using WGS compared to the costs of conventional methods

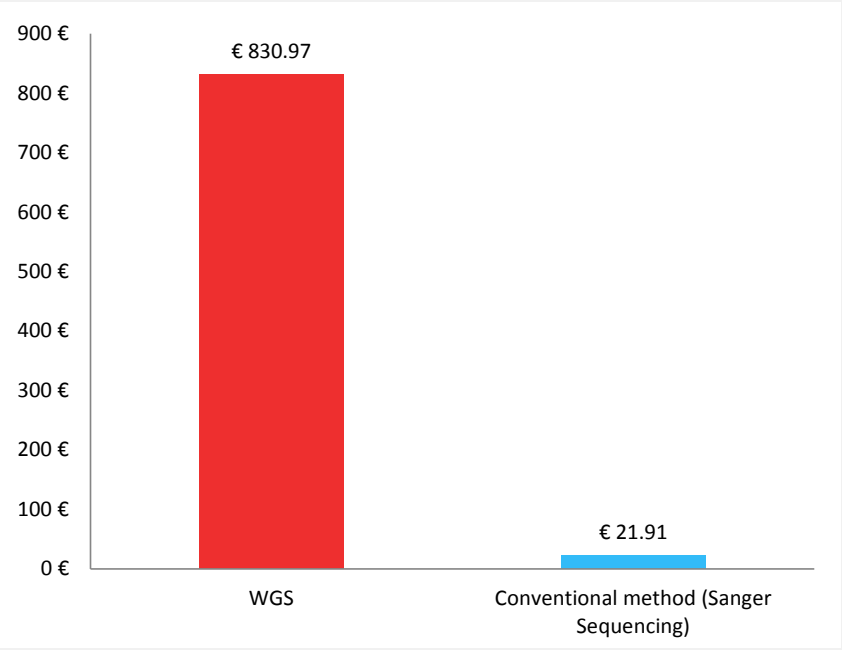
The following provides a comparison of costs per sample using WGS compared to the costs of conventional methods. See Annex I for more details.

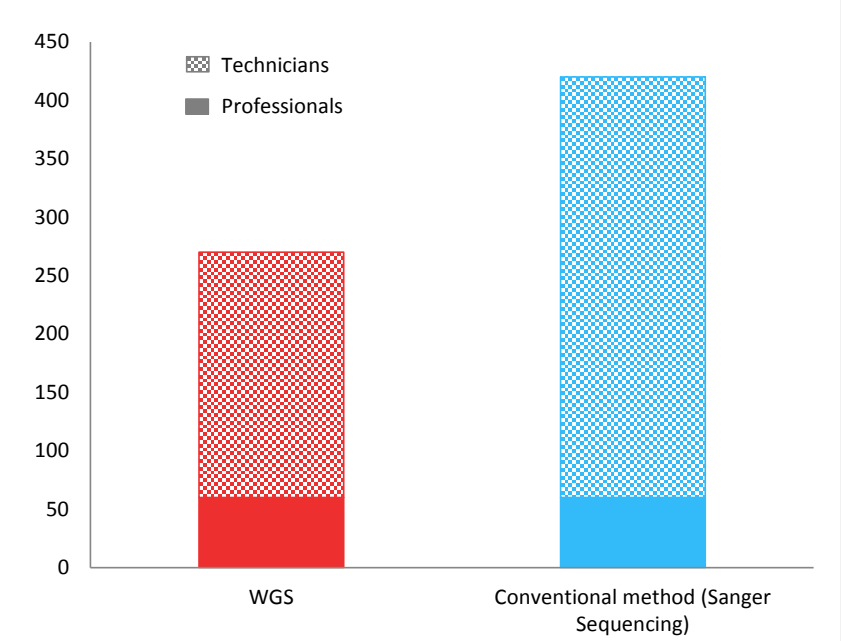
Comparison of equipment costs



Equipment costs are lower for WGS than for Sanger sequencing (€ 58.53 vs. € 78.55 per sample). One of the factors driving the differential cost is the cost of the sequencer itself: the Illumina MiSeq used for WGS, purchased in 2012 for approximately € 105 000, is lower in price than the ABI Capillary sequencer used for Sanger sequencing, which was purchased in 2009 for approximately € 200 000. Sanger sequencing also makes use of a thermocycler and requires specialised commercial software with a licence that must be renewed annually.

Comparison of costs of consumables



	The cost of consumables for WGS is considerably higher than for Sanger sequencing. The large difference in costs is attributable to the cost of the Nextera XT library preparation kit used for WGS and the reagent for the Illumina run, which costs approximately € 1200 and is used to process only one or two samples at a time in an outbreak situation.[16] In contrast, the consumables used for Sanger sequencing are both cheaper and utilisable for larger batch sizes ranging from 50 to 250.
Comparison of staff time used (in minutes)	 The amount of staff time required for WGS is lower than for Sanger sequencing. Although both methods require the same amount of professional time (60 minutes), Sanger sequencing requires considerably more technician time per sample (360 minutes vs 210 minutes for WGS). All professional staff time required for WGS comes in at the bioinformatics stage; all earlier steps (sample processing, library preparation, sequencing) are handled by technician staff.

Comparison of overall costs	*Cost type*	*Cost per sample (WGS)*	*Cost per sample (Sanger sequencing)*
	Equipment costs	€ 58.53	€ 78.55
	Consumables	€ 830.97	€ 21.91
	Other costs	€ 0.00	€ 0
	Staff time professionals	*60 minutes*	*60 minutes*
	Staff time technicians	*210 minutes*	*360 minutes*
	Staff costs, based on labour cost data for the UK (for EU)	€ 127.13 (130.88)	€ 189.63 (192.13)

[16] APHA indicated that they were able to batch process samples in groups of two more than half of the time during the relevant outbreak. We have therefore assumed an average batch size of 1.6 for the Nextera XT library preparation kit.

	Total	**€ 1 016.62**	**€ 290.08**

Summary of differential costs	**A sample analysed with WGS costs considerably more than a sample analysed with Sanger sequencing, with a cost difference of € 726.54 per sample** (€ 1 016.62 vs € 290.08). The difference in total per-sample cost is entirely attributable to the large difference in the cost of consumables, which results from a combination of the cost of the Nexterra kit and the small batch size of 1-2 samples. Note that the cost data provided by APHA regarding a second (H5N6) outbreak led to very similar results, with a cost difference of € 720.10 per sample (€ 1 028.86 vs € 308.76). For details, see Annex II.

V. Effects of using WGS results

a) Turnaround time. Turnaround time is defined as the usual number of days of work from receipt and opening of an incoming sample until the reporting of results. Turnaround time does not include weekends and holidays, except in case that work has been conducted on these days, e.g. for a sequencing run or other analyses.

Turnaround time	The turnaround time for the analysis of an avian influenza sample is: ▸ Using WGS, a minimum of 3-5 days of work to sequence in a case where no virus amplification is needed. ▸ Using Sanger sequencing, a minimum of 1-2 days of work in a case where no virus amplification is needed. APHA indicated that the difference in turnaround time between Sanger sequencing and WGS arises due to machine processing time and especially the time required for analysis, as WGS results are vastly more complex and require special software to interpret. However, it indicated that the turnaround time for Sanger sequencing depends on making an accurate estimate as to the correct primers to use, and reported that the turnaround time for Sanger sequencing could be longer if the initially-selected primers are incorrect and new primers need to be designed or ordered. In cases where virus amplification (i.e. prior growth of the virus) is needed, turnaround time is higher, depending on how quickly the virus grows. The process of growing the virus adds an additional 4-6 days (on average: 4).

b) Positive effects of using WGS for pathogen identification and surveillance during the reference period

Note that or this case study, APHA provided data on two outbreaks: for the above described H5N8 outbreak (outbreak 1) and for a subsequent H5N6 outbreak (Annex II). The positive effects of using WGS described below were experienced for both outbreaks, except where indicated otherwise.

Sampling and sampling strategies	▸ APHA indicated that it saw very significant positive effects with respect to the simplification of the type of samples needed, noting that WGS was able to reduce the pre-processing required for the sample in cases where no viral amplification was necessary. This results in time savings of approximately 2 work days for generating run-ready samples. However, APHA noted that viral amplification is needed more often for WGS. ▸ APHA noted that each outbreak of HPAI was different, and that the consideration of positive effects of WGS therefore also different between cases. During the H5N8 outbreak, for example, no further effects on sampling and sampling strategies were noted, as APHA indicated that the sampling is determined by clinical findings and epidemiology, independent from whether WGS or Sanger sequencing is used. For the H5N6 outbreak, however, which was smaller and limited to isolated outbreaks in wild birds, APHA indicated that there had also been a reduction in the number of samples needed, simplification in sample storage/transport, and a

	reduction in the overall costs of sampling. It indicated that this was because WGS analysis allowed for confirmation that the separate UK isolates were all highly similar to viruses present in Continental Europe and were not direct introductions from South-East Asia.
Analytical results and processes	▸ APHA considered that using WGS had led to very significant positive effects on the accuracy, sensitivity, and specificity of results. In particular, it commented that WGS produced many reads of a sequence, resulting in higher accuracy and greater statistical confidence in the outputs, and also allowed viral genome-spanning information to be rapidly obtained regarding the genotype, pathotype, mutations, etc. ▸ APHA also noted that WGS is adaptable to high-throughput and automated pipelines. For example, APHA noted that a robot can be used for the library preparation stages (although this is not currently done at APHA). ▸ The institution indicated that another positive effect of WGS is that no prior knowledge of the target sequence is required, so no assumptions need to be made regarding the primers needed for WGS sample preparation. In contrast, if the primers available for Sanger sequencing fail to produce an amplicon, considerable time can be needed to design, order and receive new primers. ▸ During the H5N6 outbreak, APHA considered that using WGS had a significant positive effect on the simplification of laboratory work flows. This is in contrast to the situation reported in the H5N8 outbreak, where APHA considered that WGS had only a minor effect in this area. ▸ APHA considered that during the H5N6 outbreak there had been slightly more significant effects of using WGS concerning a reduction in the consumables and staff time required for the analysis than during the H5N8 outbreak, although this was not reflected in the cost data. While similar numbers of samples underwent WGS, in the case of the H5N6 outbreak, this reduced the need for additional sample analysis.
Outbreak identification and response	▸ Positive effects of using WGS were reported with respect to improved information on outbreak epidemiology, improved information for imposing additional control or biosecurity measures, and improved detection that outbreaks are related. APHA indicated that the information provided by WGS was already changing outbreak response in terms of being able to better assess the public health risk, for example by revealing the presence of mutations for mammalian host adaptation and the possible emergence of reassortant strains. It added that WGS also allowed for useful supporting information to be disseminated during outbreaks. ▸ In the H5N8 outbreak, APHA indicated that there had been a very significant positive impact of using WGS on the earlier detection of an initial outbreak, especially for the index case. APHA indicated that the information gained from WGS allows them to better assess whether the virus sampled poses a risk of transmission to humans. This effect was less pronounced for the H5N6 outbreak, once it was determined that the H5N6 outbreak strain was distinct from the H5N6 lineage associated with human infection in South-East Asia. APHA commented that WGS sometimes allows for the earlier confirmation of an outbreak and noted that WGS is still not an accredited method in the UK, but that results are given unofficially and inform the interpretation of all results. ▸ In the H5N8 outbreak, fewer positive effects were observed with respect to a reduction in the duration of the outbreak, reduction in the overall costs for outbreak identification and response, and reduction in the disease burden for livestock and humans. These effects were considered to have been comparatively larger in the H5N6 outbreak.
Research and methods applied	▸ With respect to the effects on research and methods applied, APHA reported that there had been positive effects regarding the understanding of disease transmission, an improvement in epidemiological methods, and

	the development of better diagnostic tests, although it assessed these benefits to have been higher in the case of the H5N6 outbreak than in the case of the H5N8 outbreak. Regarding the use of diagnostic tests, APHA indicated that the information gained from WGS helped determine which conventional tests to use later on in the outbreak. ▸ APHA indicated that WGS provides a lot of added value in dealing with the influenza virus, given the amount of variation observed. WGS can be used to identify novel viruses, reassortants, and mixed infections (e.g. mixed avian influenza subtypes or other pathogens) which would otherwise be missed using conventional methods. WGS also provides information on the host of origin. ▸ With respect to the H5N6 outbreak, APHA indicated that the use of WGS had allowed them to infer zoonotic risk according to mammalian adaptation signatures and to determine the likelihood or not of pre-existing immunity.
Effects on wider society	▸ APHA indicated that in the H5N8 outbreak, positive effects of using WGS could be observed with respect to a reduction in the negative effects of outbreaks for the livestock industry, for tourism, for trade, and for the wider society. Trade in particular was emphasised as an area where APHA observed positive effects from using WGS, given that HPAI had been discovered in domestic poultry. In the H5N6 outbreak, in contrast, APHA observed less significant impacts on all these domains, as the outbreak had remained confined to wild birds and did not infect poultry.
c) Negative effects of using WGS	
Negative effects of using WGS	None identified/reported other than the higher cost, although APHA indicated that from their perspective, the cost-benefit ratio of using WGS in terms of the information obtained was more favourable.
VI. Outlook	
Balance of costs and benefits achieved	▸ In general, APHA expected the balance of costs and benefits to improve. It commented that as WGS becomes more mainstream, there will be an economies of scale effect with more samples sequenced and individual run costs decreasing. Technological advances (e.g. related to the MinION) are also expected to result in further cost reductions (see below) as well as the ability to sequence clinical samples directly and to potentially sequence RNA directly.
Potential for cost reductions of using WGS for pathogen identification and surveillance in the future (through e.g. techno-logical advances)	▸ APHA expected that there will be further cost reductions in using WGS for pathogen identification and surveillance as the technology becomes more mainstream. APHA also indicated that they are currently looking at ways of optimising costs by batching samples for analysis or sequencing directly from clinical samples, thereby avoiding the virus amplification step and saving time and money. In this respect, they consider that advances in direct RNA sequencing methods and/or other technologies such as the MinION will result in considerable time and cost savings.
Future opportunities and challenges	▸ APHA considered that the cross-pathogen potential of WGS will become a reality, including across different networks and contexts. Nevertheless, APHA considered that there were unlikely to be cost reductions resulting from the cross-pathogen potential of WGS in the influenza field. However, it did see considerable future potential in the influenza field for coordination between the veterinary and public health sectors under a One Health approach. ▸ APHA commented that the bioinformatics and analysis aspect of WGS formed a sort of 'bottleneck', given that it currently relies on 'freeware'

	and the coding ability of individuals who have a rare combination of IT skills and an understanding of virology. In this respect, it considered that the COMPARE project was filling a significant gap. ▸ APHA commented that although the knowledge gained from WGS was often applied in decision-making and outbreak management, it does not easily fit into the strict quality confines of statutory testing and considered that this posed a large hurdle to making the technology 'mainstream'.

VII. Key sources/references	
Questionnaire	Questionnaire completed by APHA
Preparatory phone interview	a) Background information and description of activities
Case study visit and follow up	b) Additional data and clarifications provided
Scientific literature	c) Animal and Plant Health Agency (APHA). (2017). *National epidemiology report - Highly Pathogenic Avian Influenza H5N8 - Annex 1: Three additional infected small-holder premises - April to May 2017*. d) Animal and Plant Health Agency (APHA). (2017). *National epidemiology report - Highly Pathogenic Avian Influenza H5N8: December 2016 to March 2017*. e) Poen, M. J., Verhagen, J. H., Manvell, R. J., Brown, I., Bestebroer, T., van der Vliet, S., … Fouchier, R. A. M. (3016). Lack of virological and serological evidence for continued circulation of highly pathogenic avian influenza H5N8 virus in wild birds in the Netherlands, 14 November 2014 to 31 January 2016. *Eurosurveillance*, 21(38). h) Department for Environment Food and Rural Affairs (Defra). (2018). *Rapid Risk Assessment on the finding of H5N6 HPAI in wild birds in England and Wales.* i) Department for Environment Food and Rural Affairs (Defra). (2018). *Rapid Risk Assessment on the finding of H5N6 HPAI in wild birds in Dorset.* j) Department for Environment Food and Rural Affairs (Defra), Animal and Plant Health Agency (APHA), and Veterinary & Science Policy Advice Team - International Disease Monitoring. (2018). *Situation Assessment #4: Update on H5N6 HPAI in UK/Europe and H5N8 HPAI in Europe/Western Russia - 9 July 2018.* k) Department for Environment Food and Rural Affairs (Defra), Animal and Plant Health Agency (APHA), and Veterinary & Science Policy Advice Team - International Disease Monitoring. (2018). *Situation Assessment #3: Update on H5N6 HPAI in UK/Europe and H5N8 HPAI in Europe - 4 April 2018.* l) Department for Environment Food and Rural Affairs (Defra), Animal and Plant Health Agency (APHA), and Veterinary & Science Policy Advice Team - International Disease Monitoring. (2018). *Situation Assessment #2: Findings of H5N6 HPAI in wild birds in UK / Ireland and LPAI in poultry in France - 14 February 2018.* m) Department for Environment Food and Rural Affairs (Defra), Animal and Plant Health Agency (APHA), and Veterinary & Science Policy Advice Team - International Disease Monitoring. (2018). *Situation Assessment: Findings of H5N6 HPAI in wild birds - 30 January 2018.*
Other sources	f) APHA, Annual Report and Accounts 2016/17 g) APHA website https://www.gov.uk/government/organisations/animal-and-plant-health-agency

3.2. Friedrich-Loeffler-Institut (FLI)

Avian Influenza outbreak – FLI, Germany	
I. Institution	
Name of institution	Friedrich-Loeffler-Institut (FLI)
Type of institution	Public veterinary institution
Description	The Friedrich-Loeffer-Institut (FLI) is the National Institute for Animal Health in Germany. It is a federal research institute and independent higher federal authority under the Federal Ministry for Food and Agriculture. Its work aims at the prevention of diseases, the improvement of animal welfare and the production of high quality animal-based foodstuffs. The institute performs epidemiological investigations during outbreaks of animal diseases. It also prepares risk assessments on various infectious diseases of farm animals. FLI hosts the National Reference Laboratory for Avian Influenza, which conducts application-oriented research in the field of avian influenza virus diagnostics, epidemiology and pathogenesis. It is also active within the EU-RL network for Avian Influenza. As a reference laboratory of the World Organisation for Animal Health (OIE) and of the Food and Agriculture Organization (FAO) of the United Nations, the laboratory provides advice and diagnostic assistance to countries outside Europe. FLI has a laboratory for WGS and Microarray Diagnostics. The main task of the laboratory for WGS and microarray diagnostics is full-length DNA or RNA virus genome sequencing. Beyond the sequencing activities, establishing new technical equipment, molecular biological methods, and implementing new ways for data analyses are among FLI's focus areas.[j)]
Location	Greifswald, Mecklenburg-Vorpommern, Germany
II. Activities covered by case study	
Activity	Outbreak investigation
Reference period	24/12/2016 – 28/03/2017
Pathogen(s) covered	Avian Influenza (AI)
Outbreak summary	In 2016/2017 a regional outbreak of notifiable H5 Highly Pathogenic Avian Influenza (HPAI) occurred in Lower Saxony in domestic poultry farms, principally of avian influenza subtype H5N8 with some infections of subtype H5N5. Several turkey fattening farms were affected. This was the largest outbreak in one area ever recorded in Germany, with about 30 farms affected. Culling and cleaning procedures, commercial restrictions and compensation led to high costs (estimated at EUR 500 000 per farm, depending on the number of hold poultry). Epidemiological connections were initially unknown to authorities, which therefore sought the help of FLI. Analysis using whole-genome sequencing was able to indicate that transmission occurred not only through wild birds but also through secondary infection between farms, exposing gaps in biosecurity measures in addition to other potential risk factors.[c)] The regional outbreak in Lower Saxony was part of a larger outbreak of HPAI across Germany, with more than 1 150 cases of H5Nx infection reported in wild birds and 107 outbreaks among birds kept in captivity (including both poultry and zoos) between November 8, 2016 and September 30, 2017, resulting in the death or slaughtering of approximately 1.2 million birds. Estimated direct economic losses of the total outbreak across Germany were about EUR 17 million.[f)]

Type of sample	Isolates		
Region covered by sampling	Lower Saxony, Germany		
Number of samples analysed in reference period	*Pathogen*	*Samples analysed by conventional methods*	*Samples sequenced using WGS*
	H5 Highly Pathogenic Avian Influenza Virus	The cost calculation is based on previous experiences with the listed conventional method, assuming the same number of samples as with WGS	30
Conventional method used as reference for costing	▸ Sanger sequencing of complete genomes ▸ Manual sample preparation ▸ 13 PCR products per sample, 2-fold coverage		
Sample preparation WGS	▸ Manual sample preparation		
Sequencer used for WGS	▸ Ion Torrent PGM bundle		
Batch size for WGS analysis	▸ The data provided is based on batches of 6 samples per sequencing run.		
Reference dataset used for WGS	▸ FLI maintains its own reference dataset for avian influenza, which is manually created and curated. The dataset is updated via public databases on a regular basis. Data are also shared between reference laboratories prior to publication.		
Additional information	▸ Activities covered by this case study include analyses of known avian influenza samples within the context of the relevant outbreak. ▸ Note that FLI is a research institution handling a large number of different pathogens of varying virulence. To avoid cross-contaminations, very strict laboratory procedures are applied, as was emphasised by FLI. This may lead to increased staff time and consumable costs for specific analyses. For example, when handling samples, gloves are changed after each analytical step.		

III. Detailed overview of costs of WGS and conventional methods

In the following, all costs are provided on a per-sample basis. Equipment costs are annualised and incorporate the annual maintenance costs as reported by the institution. They are adjusted for the percentage use of the equipment for the listed pathogens samples during the reference period (i.e. if a sequencer was also used for other purposes, this is taken into account). Consumables costs are adjusted for the failure rate (i.e. the percentage of consumables wasted, e.g. due to failed runs). Staff time is provided in terms of the minutes of hands-on staff time per sample, for both professionals and technicians. For the calculation of total costs, staff time is then monetised based on Eurostat data on country-specific labour costs for 2017 (by staff category), plus a 25% surcharge for overheads. For comparison purposes only, we have also provided staff costs monetised based on EU average labour costs.

More detailed cost data is provided in Annex I.

a) Costs of using WGS

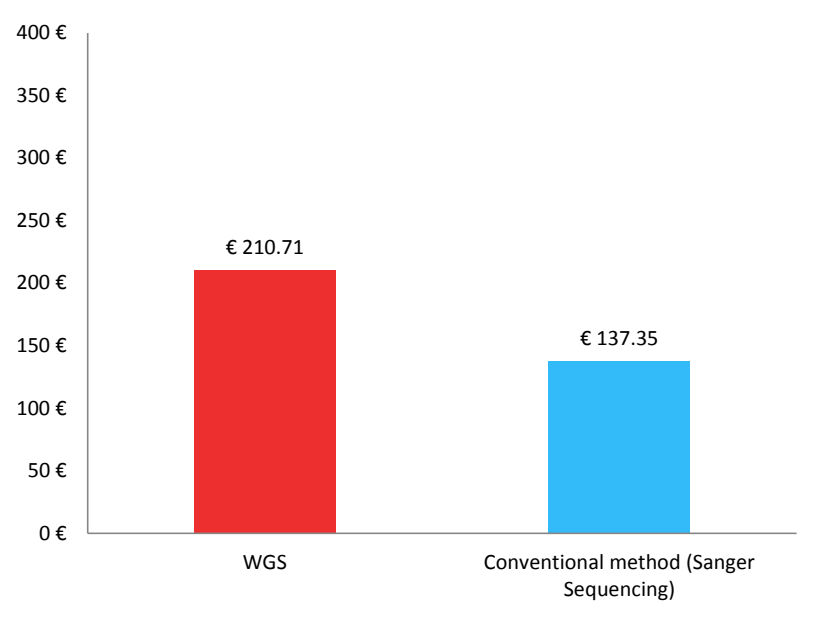
Sample preparation and sequencing	*Cost type*	*Cost per sample*
	Equipment costs	€ 198.79
	Consumables	€ 254.88
	Other costs	€ 0

	Staff time professionals	*18 minutes*
	Staff time technicians	*135 minutes*
	Staff costs, monetised based on labour cost data for Germany (in brackets: based on labour cost data for the EU as a whole)	€ 76.16 (68.66)
	Total	**€ 529.83**
Bioinformatics and other analyses	*Cost type*	*Cost per sample*
	Equipment costs	€ 11.92
	Other costs	€ 0
	Staff time professionals	*30 minutes*
	Staff time technicians	*0 minute*
	Staff costs, based on labour cost data for Germany (for EU)	€ 26.63 (22.56)
	Total	**€ 38.54**
b) Costs of conventional method (based on previous experiences with the listed method)		
Sanger Sequencing of an entire genome (assuming a use for 100% of avian influenza samples)	*Cost type*	*Cost per sample*
	Equipment costs	€ 137.35
	Consumables	€ 360.88
	Other costs	€ 0
	Staff time professionals	*260 minutes*
	Staff time technicians	*240 minutes*
	Staff costs, based on labour cost data for Germany (for EU)	€ 337.75 (293.54)
	Total	**€ 835.98**

IV. Costs of using WGS compared to the costs of conventional methods

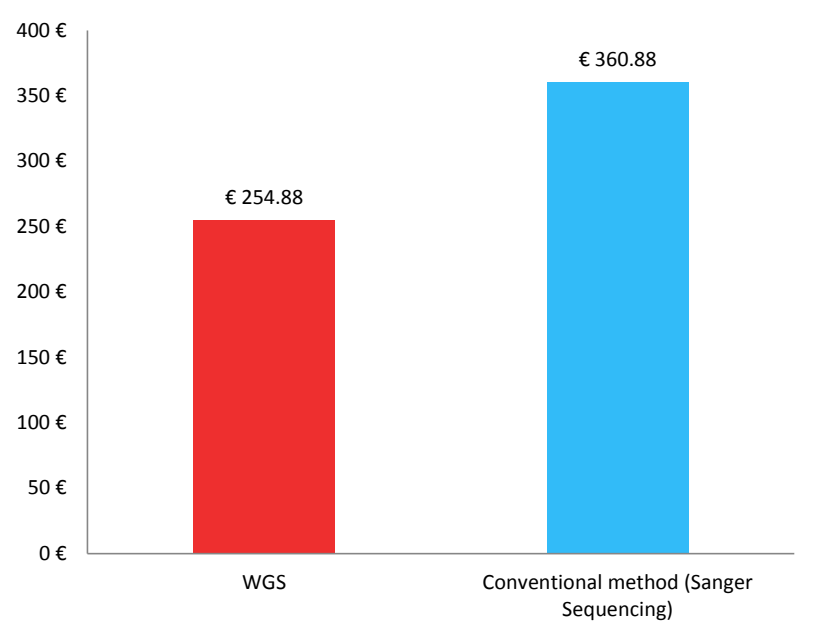
The following provides a comparison of costs per sample using WGS compared to the costs of conventional methods. See Annex I for more details.

Comparison of equipment costs



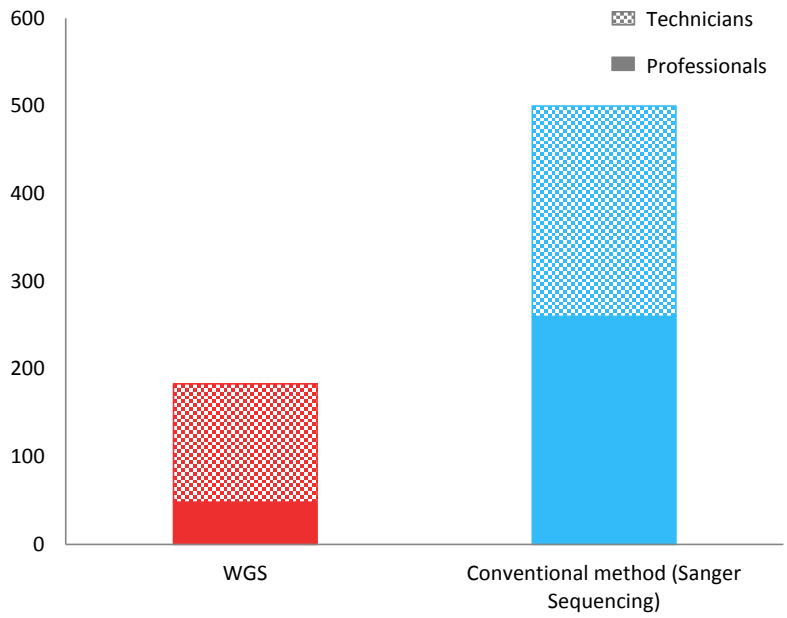
Equipment costs are significantly higher for WGS than for Sanger sequencing of an entire genome (€ 210.71 vs. € 137.35 per sample), mostly due to the purchase and maintenance costs of the IonTorrent sequencer itself.

Comparison of costs of consumables



In contrast, costs of consumables for WGS are lower than for Sanger sequencing of an entire genome (€ 254.88 vs. € 360.88 per sample). This is mostly attributable to the cost of consumables used for library preparation and sequencing, which are higher for Sanger sequencing of an entire genome.

Comparison of staff time used



The amount of staff time needed for WGS is considerably lower than for Sanger sequencing of an entire genome; however, comparatively more professional time is required for WGS, especially at the bioinformatics stage, which is exclusively conducted by professionals. Nevertheless, after monetising staff time, staff costs per sample are still more than three times higher for Sanger sequencing of an entire genome (see table below).

Comparison of overall costs	*Cost type*	*Cost per sample (WGS)*	*Cost per sample (Sanger Sequencing)*
	Equipment costs	€ 210.71	€ 137.35
	Consumables	€ 254.88	€ 360.88
	Other costs	€ 0	€ 0
	Staff time professionals	*48 minutes*	*260 minutes*
	Staff time technicians	*135 minutes*	*240 minutes*
	Staff costs, based on labour cost data for Germany (for EU)	€ 102.79 (91.23)	€ 337.75 (293.54)
	Total	**€ 568.37**	**€ 835.98**

Summary of differential costs	**A sample analysed with the use of WGS costs less than the cost of analysis with the conventional method (Sanger sequencing of an entire genome), with a cost difference of € 267.61 per sample** (€ 568.37 vs € 835.98). As indicated in the figures above, major differences in costs were found to exist in all cost categories, but especially regarding staff time.

V. Effects of using WGS results	
a) Turnaround time. Turnaround time is defined as the usual number of days of work from receipt and opening of an incoming sample until the reporting of results. Turnaround time does not include weekends and holidays, except in case that work has been conducted on these days, e.g. for a sequencing run or other analyses.	
Turnaround time	The turnaround time for the analysis of an avian influenza sample is: ▸ 4 days of work using WGS (sequencing of the full genome), compared to ▸ 8 days of work for pathogen whole genome sequencing using Sanger Sequencing. While conventional methods are therefore able to provide a fast identification of high vs. low pathogenicity of a given AI sample, WGS provides additional information on virus reassortment as well as the phylogenetic relationships. (FLI also provided the hypothetical turnaround time, if Sanger Sequencing was used to only analyse the HA segment for HPAI LPAI discrimination: This would take 2 days of work.)
b) Positive effects of using WGS for pathogen identification and surveillance during the reference period	
Sampling and sampling strategies	▸ Little or no positive effects on sampling and sampling strategies are expected from FLI's perspective despite the fact that less material is needed in terms of starting material from the extracted nucleic acids.
Analytical results and processes	▸ Overall FLI sees little evidence so far of positive effects of WGS on analytical results and processes (e.g. on the simplification of laboratory flows or consumables needed for the analysis), although it did report a clear reduction in the necessary staff time, especially when comparing WGS with Sanger sequencing of complete genomes. ▸ The institution nonetheless reported very significant positive effects of WGS on the level of detail of results produced, as well as moderately positive effects on the sensitivity of the results and reduction of overall costs for the analysis.
Outbreak identification and response	▸ Significant improvements were reported regarding the ability to detect that outbreaks are related, improved information on outbreak epidemiology (e.g. the ability to link cases to the source of infection), and a reduction in the number of secondary outbreaks. In particular, the use of WGS was able to confirm that transmission in the relevant outbreak occurred not just through wild birds but also through secondary infections between farms, highlighting potential gaps in biosecurity measures.[c),d)] Accordingly, FLI also identified positive effects regarding improved information for imposing additional control/biosecurity measures, as well as a reduction in the duration of outbreaks. ▸ FLI indicated that the genetic data provided a lot of information (on waves, clusters, and possible sources) and therefore provided hints towards certain transmission routes, allowing for some possibilities to be clearly ruled out. For example, in the present case study, FLI indicated that there were two consecutive outbreaks on one farm, raising questions regarding the effectiveness of the cleaning measures performed after the first outbreak; however, WGS analysis showed that the second outbreak on the same farm was caused by a later strain of the virus and was therefore the result of a separate introduction. ▸ Fewer benefits of WGS were reported with respect to earlier detection of the initial outbreak, given that FLI worked with samples that had already been positively identified through conventional methods. Fewer benefits were also noted with respect to a reduction in the disease burden and reduction in overall costs for outbreak identification and response.
Research and methods	▸ Regarding the positive effects on research and methods applied, FLI

applied	reported very significant improvement in the understanding of disease transmission and in epidemiological methods. FLI indicated that the same results could not be achieved with Sanger sequencing due to the level of sensitivity required.
Effects on wider society	▸ The institution considered that the use of WGS leads to positive effects for the wider society especially in relation to a reduction in the costs of outbreak(s), including through the reduction of compensation payments, and also a reduction in negative effects of the outbreak on trade (although only to a moderate extent).
c) Negative effects of using WGS	
Negative effects of using WGS	There are concerns from the industry perspective that WGS can uncover suboptimal practices e.g. in trade, biosecurity, diagnostics etc. In the present case study, for example, WGS was able to identify substantial gaps in farm biosecurity measures that contributed to the farm-to-farm transmission of avian influenza within Lower Saxony.[c),f)] Such findings could contribute e.g. to lower compensation payments or other questions of liability where secondary infections result in large economic losses. FLI indicated that to avoid a reduction in cooperation, the use of very detailed techniques and data analyses needs a proactive and careful communication strategy.
VI. Outlook	
Balance of costs and benefits achieved	▸ The efforts currently required for WGS analysis as well as the associated costs (especially equipment) are high, but it is expected that the costs of sequencing and analysis will come down, driven by the demand for sequencing. This is already the case to some extent (e.g. the cost of sequencers have already come down significantly) and the balance of costs and benefits is expected to improve in the mid- to long term.
Potential for cost reductions	▸ FLI is in the process of introducing further automation for sample preparation, which is expected to lead to a substantial reduction in hands-on staff time. ▸ In the study of the Influenza outbreak considered here, the only significant cost reduction could have been achieved by higher multiplexing in the sequencing run. This, however, would have resulted in extended turnaround times, and was therefore in this case avoided. With regard to cross-pathogen detection, FLI indicated that sample preparation was the most expensive stage and that therefore further cost reductions at the lab level could be possible with the use of different methods. This is however not feasible at the moment. ▸ Using such new methods, the costs of consumables would also be expected to decrease.
Future opportunities and challenges	▸ In the veterinary field (with a strong focus on notifiable diseases, which are well-known and for which PCR tests are available) WGS would only be used as a first step in rare cases where a diagnosis is unclear or where a novel or unknown pathogen is concerned, as WGS is much more expensive overall. Especially in case of an outbreak, under the current cost conditions, PCR would be the method of choice for initial identification of the pathogen. ▸ In the institution's perspective, the most relevant use of the cross-pathogen potential of WGS at this stage is human diagnostics in a clinical context, often through a national reference centre. For instance, FLI often receives requests regarding cases in the human field, where a hospital has an urgent case in which the pathogen could not be identified after running 30-60 PCRs (e.g. for cases of Encephalitis). These cases show most clearly the benefits of WGS and may be more economical to investigate with WGS

	rather than with multiple disease specific tests. The difficult nature of WGS for diagnostics nonetheless remains a challenge. It is expected to take at least 5-10 years before it is so simple that it can be used broadly (similarly to the past development regarding PCR diagnostics). ▸ The institution considered that metagenomics is still more of a niche topic. The analysis of an unknown pathogen for a metagenomic analysis would require more preparation, and more sequencing runs with fewer samples per run and more depth. ▸ Data accuracy is an area of concern with respect to the use of public databases, where there is a need for greater curation and validation by specialists. Data security will also be an emerging concern that will slow down the pace of analysis.

VII. Key sources/references	
Cost questionnaire	Cost questionnaire completed by FLI
Preparatory phone interview	a) Background information and description of activities
Case study visit and follow up	b) Additional data and clarifications provided
Scientific literature	c) Conraths, F. J. (2017). Making worst case scenarios real: The introduction of highly pathogenic avian influenza of subtype H5N8 led to the largest fowl plague outbreak ever recorded in Germany. *Lohmann Information*, 51(1), 36–41. d) Conraths, F. J., et al. (2017). *Epidemiologie des aktuellen Geflügelpestgeschehens in Deutschland* [Epidemiology of the current incidence of avian influenza in Germany], presentation given at the meeting of the Gesellschaft der Förderer und Freunde für Geflügel- und Kleintierforschung e.V. at the Institut für Tierschutz und Tierhaltung in Celle on 3 May 2017. e) Friedrich-Loeffler-Institut. (2017). *Qualitative Risikobewertung zur Einschleppung sowie zum Auftreten von hochpathogenem aviären Influenzavirus H5 in Hausgeflügelbestände in Deutschland*. f) Globig, A., et al (2018). Highly Pathogenic Avian Influenza H5N8 Clade 2.3.4.4b in Germany in 2016/2017. *Frontiers in Veterinary Science*, 4(January), 2–9. http://doi.org/10.3389/fvets.2017.00240 g) Grund, C., et al. (2018). A novel European H5N8 influenza A virus has increased virulence in ducks but low zoonotic potential. *Emerging Microbes and Infections*, 7(1), 1–14. http://doi.org/10.1038/s41426-018-0130-1 h) Pohlmann, A., et al. (2018). Swarm incursions of reassortants of highly pathogenic avian influenza virus strains H5N8 and H5N5, clade 2.3.4.4b, Germany, winter 2016/17. *Scientific Reports*, 8(1), 8–13. http://doi.org/10.1038/s41598-017-16936-8 i) Pohlmann, A., et al (2017). Outbreaks among Wild Birds and Domestic Poulty Caused by Reassorted Influenza A(H5N8) Clade 2.3.4.4 Viruses, Germany, 2016. *Emerging Infectious Diseases*, 23(4), 633–636. http://doi.org/http://dx.doi.org/10.3201/eid2304.161949
Other	j) FLI website, https://www.fli.de/en

3.3. Erasmus Medical Centre (EMC)

Influenza surveillance – Erasmus MC, NL			
I. Institution			
Name of institution	Erasmus University Medical Centre (Erasmus MC)		
Type of institution	University hospital		
Description [c)]	Erasmus MC is the largest university hospital in the Netherlands. It conducts research in various fields, studying fundamental and clinical domains as well as public health and prevention. The Department of Viroscience at Erasmus MC has expertise ranging from basic virology to clinical virology, connecting medical and veterinary health, public health and ecology. The Department of Viroscience at Erasmus MC is the national reference centre for influenza and emerging infections in the Netherlands, as well as a WHO Collaborating Centre on viral infections.		
Location	Rotterdam, NL		
II. Surveillance activities covered by case study			
Activity	Routine laboratory surveillance		
Reference period	12/2018 – 04/2019		
Pathogen(s) covered	Influenza virus A & B		
Summary of routine surveillance activities using WGS	Nanopore sequencing with the use of the GridION platform, a third generation sequencing approach, was introduced for routine surveillance of influenza at Erasmus MC at the beginning of the influenza virus season in November 2018. Nanopore sequencing largely replaced conventional virus culture and characterization plus Sanger sequencing for the 2018/2019 influenza virus season.		
Type of sample	Clinical samples		
Region covered by laboratory surveillance	The Netherlands		
Number of samples analysed in reference period	*Pathogen*	*Samples analysed by conventional methods*	*Samples sequenced using WGS*
	Influenza A (H1N1, H3N2) and B	The cost calculation is based on previous experiences with the listed conventional methods, assuming the same number of samples as with WGS	630
Conventional methods used as reference for costing	▸ Average for an influenza season: Real Time PCR (N= 630; 100%), virus isolation for 108 samples with high virus load (17%), phenotyping of virus isolates - Hemagglutination inhibition (34 samples, 5%) and/or Virus neutralization (20 samples, 3%) and/or NA-Star (25 samples, 4%) - and Sanger Sequencing of a representative subset (27 samples, 4%), The numbers listed here are the averages over four recent influenza seasons (2014-2018).		
Sample preparation WGS	▸ Manual sample and library preparation		
Sequencer used for WGS	▸ Nanopore GridION		
Batch size for WGS analysis	▸ The typical batch size increased over the flu season from 10 to 40, with an average batch size of 30 samples		

Reference dataset used for WGS	▸ Erasmus MC does not maintain its own internal reference database, but downloads data as needed from public databases (notably GISAID). It uses the new vaccine strains as reference strains each season.
Additional information	▸ Originally, the National Influenza Centre attempted to isolate the influenza virus from influenza cases and then characterised these viruses by hemagglutination inhibition (HI) assay or focus-reduction assay (FRA) and NA-star assay. Sanger sequencing was then used for a subset of representative viruses. In the last season, this process was reversed; samples were first subjected to WGS using the GridION and the virus was isolated and characterised for a subset of representative viruses. ▸ Consequently, for the 2018-2019 flu season, regular conventional testing was carried out in parallel to WGS, although at a lower intensity than in previous flu seasons. In the 2018-2019 flu season, 50 samples (8%) were subject to virus isolation, 15 (2%) to Hemagglutination inhibition, 8 (1%) to virus neutralisation, and 10 (2%) to NA-star. These methods have been costed into the WGS workflow below as 'supplementary conventional tests'.

III. Detailed overview of costs of WGS and conventional methods

In the following, all costs are provided on a per-sample basis. Equipment costs are annualised and incorporate the annual maintenance costs as reported by the institution. They are adjusted for the percentage use of the equipment for the listed pathogens samples during the reference period (i.e. if a sequencer was also used for other purposes, this is taken into account). Consumables costs are adjusted for the failure rate (i.e. the percentage of consumables wasted, e.g. due to failed runs). Staff time is provided in terms of the minutes of hands-on staff time per sample, for both professionals and technicians. For the calculation of total costs, staff time is then monetised based on Eurostat data on country-specific labour costs for 2017 (by staff category), plus a 25% surcharge for overheads. For comparison purposes only, we have also provided staff costs monetised based on EU average labour costs. More detailed cost data is provided in Annex I.

a) Costs of using WGS

Sample preparation and sequencing	*Cost type*	*Cost per sample*
	Equipment costs	€ 1.74
	Consumables	€ 33.52
	Supplementary conventional tests	€ 3.68
	Staff time professionals	*6 minutes*
	Staff time technicians	*67 minutes*
	Staff costs, monetised based on labour cost data for the Netherlands (in brackets: based on labour cost data for the EU as a whole)	€ 36.85 (€ 31.87)
	Total	**€ 75.78**

Bioinformatics and other analyses	*Cost type*	*Cost per sample*
	Equipment costs	€ 0.76
	Other costs	€ 0
	Staff time professionals	*12 minutes*
	Staff time technicians	*24 minutes*
	Staff costs, based on labour cost data for the Netherlands (for EU)	€ 21.93 (€ 18.83)

	Total	**€ 22.69**
b) Costs of conventional methods		
Method A: Real Time PCR (plus sample preparation)	*Cost type*	*Cost per sample*
	Equipment costs	€ 0.98
	Consumables	€ 31.00
	Other costs	€ 0
	Staff time professionals	*0 minutes*
	Staff time technicians	*84 minutes*
	Staff costs, based on labour cost data for the Netherlands (for EU)	€ 39.53 (€ 34.30)
	Total	**€ 71.51**
Method B: Sanger Sequencing	*Cost type*	*Cost per sample*
	Equipment costs	€ 14.00
	Consumables	€ 23.75
	Other costs	€ 0
	Staff time professionals	*0 minutes*
	Staff time technicians	*60 minutes*
	Staff costs, based on labour cost data for the Netherlands (for EU)	€ 28.24 (€ 24.50)
	Total	**€ 65.98**
Method C: Virus isolation	*Cost type*	*Cost per sample*
	Equipment costs	€ 2.78
	Consumables	€ 10.00
	Other costs	€ 0
	Staff time professionals	*0 minutes*
	Staff time technicians	*30 minutes*
	Staff costs, based on labour cost data for the Netherlands (for EU)	€ 14.12 (€ 12.25)
	Total	**€ 26.90**
Method D: Hemagglutination inhibition	*Cost type*	*Cost per sample*
	Equipment costs	€ 6.04
	Consumables	€ 3.00
	Other costs	€ 0
	Staff time professionals	*5 minutes*
	Staff time technicians	*18 minutes*
	Staff costs, based on labour cost data for the Netherlands (for EU)	€ 12.90 (€ 11.11)
	Total	**€ 21.95**

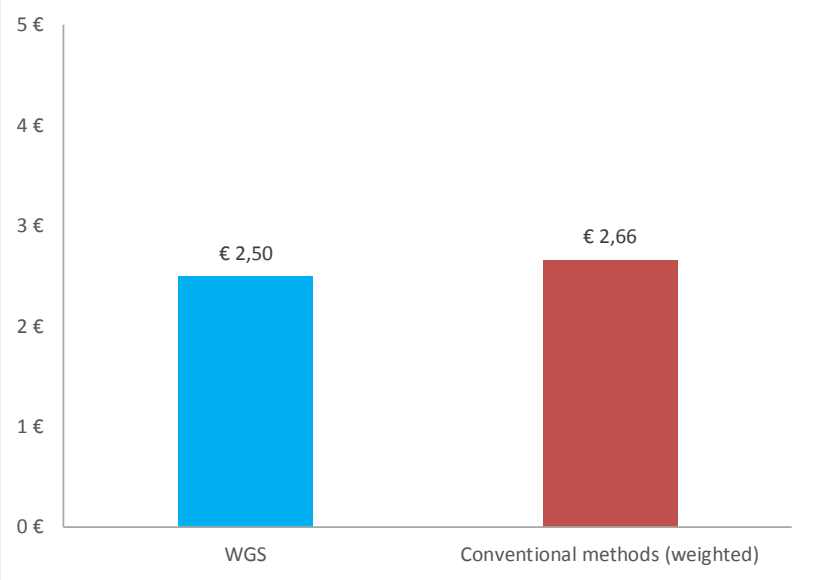
Method E: Virus neutralisation	*Cost type*	*Cost per sample*
	Equipment costs	€ 6.21
	Consumables	€ 13.00
	Other costs	€ 0
	Staff time professionals	*5 minutes*
	Staff time technicians	*102 minutes*
	Staff costs, based on labour cost data for the Netherlands (for EU)	€ 52.43 (€ 45.41)
	Total	**€ 71.64**

Method F: NA Star	*Cost type*	*Cost per sample*
	Equipment costs	€ 2.07
	Consumables	€ 2.00
	Other costs	€ 0.00
	Staff time professionals	*0 minutes*
	Staff time technicians	*42 minutes*
	Staff costs, based on labour cost data for the Netherlands (for EU)	€ 19.77 (€ 17.15)
	Total	**€ 23.83**

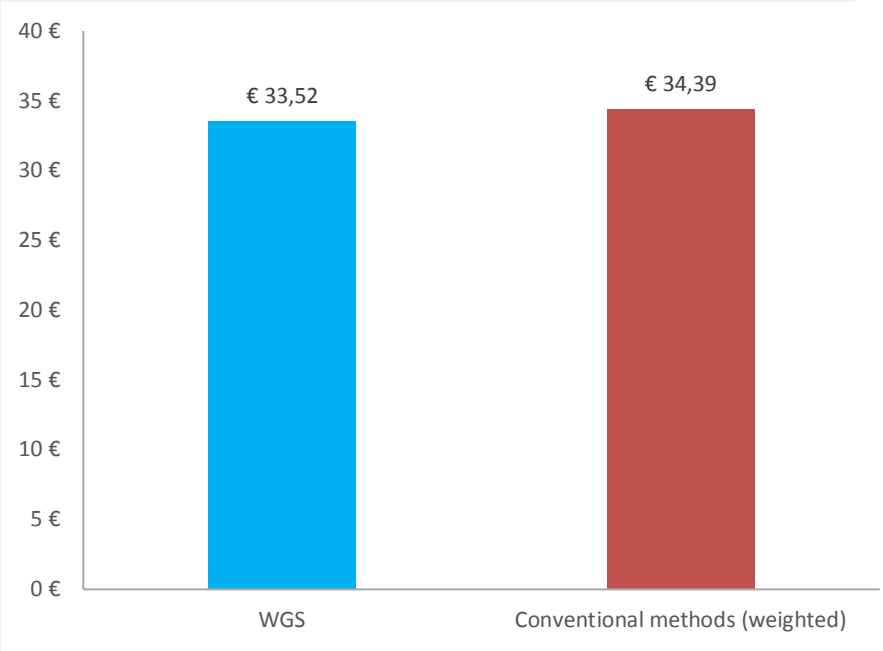
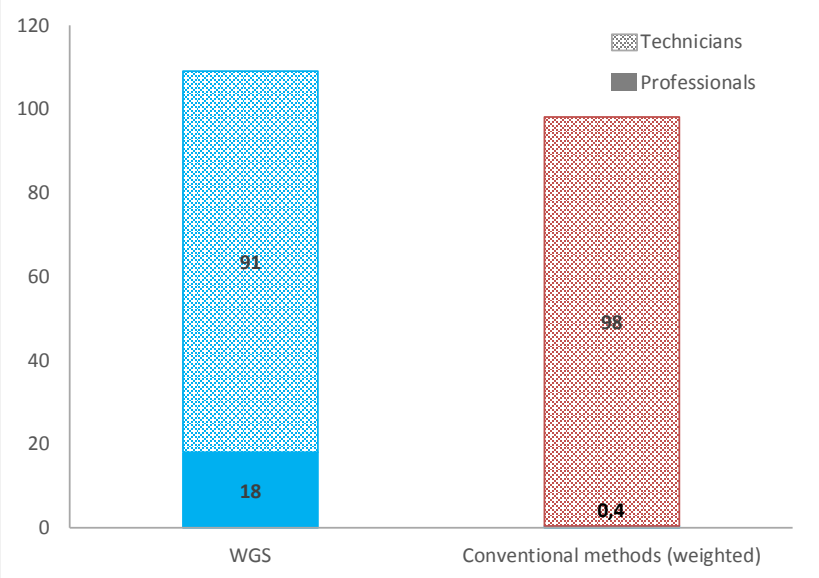
IV. Costs of using WGS compared to the costs of conventional methods

The following comparison of costs per sample using WGS compared to the costs of conventional methods considers that the number of samples processed differed for the different conventional methods. The weighted cost of the conventional methods provided here is therefore a weighted figure which accounts for the use rate of the various methods across the different pathogens. See Annex I for more details.

Comparison of equipment costs



Equipment costs per sample at Erasmus MC are slightly lower for WGS than for the weighted conventional methods (€ 2.50 vs € 2.66), although the absolute per-sample cost difference between the two methods is quite low (€ 0.16). The lower cost of the GridION platform (about half the cost of second-generation sequencers like the MiSeq or IonTorrent) is one of the

	main factors keeping down WGS costs.
Comparison of costs of consumables	 Consumables costs for WGS lie slightly below those for conventional methods (€ 33.52 vs € 34.39). The largest cost elements for WGS are the flowcells used for Nanopore sequencing (€ 11.22 per sample, for an average batch size of 30).
Comparison of staff time used (in minutes)	 WGS requires slightly less technician staff time than conventional methods (91 minutes vs 98 minutes). It also requires an additional 18 minutes of professional time, mostly at the bioinformatics stage, whereas conventional methods on average require less than 1 minute of professional staff time – although this was noted to be due to troubleshooting required. Once monetised, staff costs are therefore still higher for WGS (€ 58.78) than for conventional methods (€ 46.31), and make up the most expensive cost item for WGS overall.
Comparison of other costs	As described above under 'Additional Information', a subset of samples continued to be subject to virus isolation, HI, virus neutralisation and NA star (conventional methods C-F) in parallel to WGS during the reference period. These have been accounted for in the WGS workflow as 'supplementary conventional tests', totalling € 3.68 per sample (note that this is the average

	cost across all 630 samples, which reflects the low intensity of the conventional testing that was carried out in parallel to WGS). No other costs were reported for the conventional methods workflow.		
Comparison of overall costs	*Cost type*	*Cost per sample (WGS)*	*Cost per sample (conventional methods)*
	Equipment costs	€ 2.50	€ 2.66
	Consumables	€ 33.52	€ 34.39
	Other costs	€ 3.68 (for supplementary conventional tests in parallel to WGS)	€ 0
	Staff time professionals	*18 minutes*	*0.4 minutes*
	Staff time technicians	*91 minutes*	*98 minutes*
	Staff costs, based on labour cost data for the Netherlands (for EU)	*€ 58.78 (€ 50.70)*	€ 46.31 (€ 40.17)
	Total	**€ 98.48**	**€ 83.36**
Differential costs	**The cost difference between WGS and conventional methods is € 15.12 per sample**. A sample analysed with WGS costs approximately 18% more than analysis with conventional methods (when taking into account the use rate of the various methods). As indicated in the figures above, the largest differences are in staff costs.		
V. Effects of using WGS results			
a) Turnaround time. Turnaround time is defined as the usual number of days of work from receipt and opening of an incoming sample until the reporting of results. Turnaround time does not include weekends and holidays, except in case that work has been conducted on these days, e.g. for a sequencing run or other analyses.			
Turnaround time	The turnaround time using the GridION is typically 2 days of work. This can be compressed to just 8-10 hours in an outbreak context, with some basic information about the sample available within the first 2-3 hours. In contrast, the turnaround time for conventional methods (PCR and Sanger sequencing) is approximately 3 days of work. In an outbreak context, this can be brought down to about 20 hours with Sanger sequencing directly on clinical material, which is performed in parallel to cultivation of the virus (which still takes 3 days). In an outbreak context, the average one day reduction in turnaround time due to WGS is reported to be very significant.		
b) Positive effects of using WGS for pathogen identification and surveillance during the reference period			
Sampling and sampling strategies	▸ No effects on sampling or sampling strategies were reported by Erasmus MC for 2018-2019, as they receive clinical samples submitted by hospitals. However, Erasmus MC considered that better sampling methods could be expected in the future as a result of WGS. Erasmus MC anticipates that the NGS-first surveillance will allow for the specific identification of samples that are worthy of further phenotypic characterisation, reducing this pipeline to a maximum of 12 samples annually (i.e. down from the 50 samples that were complementing the WGS workflow considered in this case study, see 'additional information', above).		

Analytical results and processes	▸ Very significant positive effects were observed by Erasmus MC with respect to more detailed results produced due to NGS technology. This is due to the fact that all virus samples were now being sequenced, whereas prior to the introduction of the GridION only ~5% would have undergone further analysis using Sanger sequencing. ▸ Erasmus MC reported no effects on the accuracy or specificity of results, and in fact reported negative effects on the specificity of results (see 'Negative effects of WGS' below). ▸ Moderate effects were reported with respect to a reduction in time needed for analysis. While the hands-on staff time needed increased for WGS compared to conventional methods, overall a reduction in turnaround time was reported for WGS (see above). This is due to the fact that more waiting periods (e.g. for viral amplification) are required for conventional methods compared to WGS. No effects were observed with respect to simplified workflows or a reduction in consumables.
Outbreak identification and response	▸ Erasmus MC reported very significant positive effects for the earlier detection of an initial outbreak and for improved detection that outbreaks are related. However, it specified that in an international context, the benefits from improved detection that outbreaks are related depended on whether partner institutions had also adopted WGS. It indicated that the benefits of WGS for detection of international outbreaks were limited if the partners still relied on conventional methods, as the results from these methods were often not comparable with results from WGS. ▸ Erasmus MC indicated that it had insufficient information with respect to possible effects on improved information through WGS for imposing additional control measures or reductions in the duration of an outbreak, in the number of secondary outbreaks, or in overall costs for outbreak identification and response. However, such effects were considered very likely to materialise in the long run (especially for other pathogens). For example, it indicated that the faster turnaround time with Nanopore sequencing could allow patients to be isolated earlier or receive more personalised medical treatment (however, this was not considered to be relevant with respect to the case study pathogen).
Research and methods applied	▸ No concrete effects on research or methods applied were reported by Erasmus MC.
Effects on wider society	▸ No concrete effects on wider society were observed by Erasmus MC during the case study period, although it was considered that such effects would likely emerge over time.
c) Negative effects of using WGS	
Negative effects of using WGS	▸ Erasmus MC reported negative effects on the sensitivity of results with WGS due to the fact that it now skips the viral cultivation step and uses a PCR approach directly on clinical samples. This is reported to save time, but results in slightly less sensitivity (535 test results on 630 samples). Erasmus MC clarified that this is a 'problem' of internal workflow, however, not of the technology, and that the problem is not limited to Nanopore sequencing but concerns WGS in general. ▸ Erasmus MC reported limitations of Nanopore sequencing related to a failure of basecalling for homopolymeric regions in the sequences (i.e. errors in reading multiples of the same nucleotide base appearing consecutively in the DNA sequences). Erasmus MC indicated that this is a known problem specific to Nanopore sequencing and that the technology is expected to improve in the near future.

VI. Outlook	
Balance of costs and benefits achieved	▸ Erasmus MC indicated that Nanopore sequencing is a 'game changer', yet not as much as they would like due to the high prices of the required flowcells. While the costs are lower compared to e.g. Illumina sequencing, the costs are still significant. However, it was also noted that in an outbreak context 'time is more important than money', and the reduction in turnaround time was therefore considered to be very valuable.
Potential for cost reductions	▸ Erasmus MC considered that current prices (e.g. for flowcells) were relatively high, and that substantial cost reductions could be achieved through negotiation with suppliers, or increased competitive pressure. ▸ Erasmus MC indicated that the 2018-2019 season included professional staff time spent troubleshooting issues with the WGS workflow, and that this would likely be substantially less in future seasons. ▸ Erasmus MC reported that costs could be further reduced by automation of the RNA isolation process during library preparation, and by loading higher sample volumes (e.g. up to 40 samples) on a single flowcell.
Future opportunities and challenges	▸ Erasmus MC considered that Nanopore sequencing technology was constantly improving, with the above mentioned failure of basecalling for homopolymeric regions likely to be fixed in the very near future. ▸ The high price of the flowcells, which are only provided by one company (Oxford Nanopore), was noted as a challenge by Erasmus MC. The company also places contractual restrictions on the use of the flowcells purchased through the institutional contract between Erasmus MC and Oxford Nanopore, e.g. regarding their use outside the premises of Erasmus MC, and thereby limiting usefulness for field research and real-time analysis of outbreaks by Erasmus MC staff visiting other countries, such as China (however, the contract is in the process of being re-negotiated to remove these geographical restrictions at least partly). ▸ Erasmus MC reported that better communication was needed with hospitals to ensure that the hospitals send samples with higher viral loads in the future in order to counteract the lower sensitivity that can result from the use of metagenomic analysis without viral amplification.

VII. Key sources/references	
Cost questionnaire	Cost questionnaire completed by Erasmus MC
Preparatory phone interview	a) Background information and description of activities
Case study visit and follow up	b) Additional data and clarifications provided by the institution.
Scientific literature	As Nanopore sequencing was introduced for routine influenza surveillance at Erasmus MC for the first time during the case study period, no scientific literature related to the case study has been published yet by Erasmus MC.
Other	c) Erasmus MC Department of Viroscience website, https://www6.erasmusmc.nl/viroscience/

3.4. Istituto Zooprofilattico Sperimentale della Lombardia e dell'Emilia-Romagna (IZSLER)

Salmonella and Listeria surveillance – IZSLER, Italy	
I. Institution	
Name of institution	Istituto Zooprofilattico Sperimentale della Lombardia e dell'Emilia-Romagna (IZSLER)
Type of institution	Public veterinary institution
Description[17]	The Lombardy and Emilia-Romagna Experimental Zooprophylaxis Institute (IZSLER) is a public body entrusted with independent management, administrative and technical powers. It operates as a technical scientific institution of the state, the regions and the autonomous provinces. IZSLER's territory of jurisdiction comprises the regions of Lombardy and Emilia-Romagna in northern Italy and it is part of a network of regional institutes that covers all of Italy. The Institute's main tasks are the following: ▸ Animal diseases and zoonoses diagnostic service; ▸ Laboratory control on foodstuffs for human and animal consumption; ▸ Epidemiological monitoring in the ambit of animal health and in that of hygiene of zootechnic and foodstuff production; ▸ Analytic and advisory support to the carrying out of epidemic prevention, sanitation and eradication plans; ▸ Applied research in the field of breeding hygiene and improvement of zootechnic production and animal wellbeing; ▸ Applied and basic experimental research in the veterinary and food area. IZSLER's High Specialisation Centres carry out highly specialised activities in the field of animal health, food hygiene and zootechnic hygiene. In particular, IZSLER was appointed as the National Reference Centre for numerous diseases by the Ministry of Health, as the OIE Reference Laboratory for Foot-and-Mouth Disease, Swine Influenza, Myxomatosis, and Haemorrhagic Diseases of Lagomorphs, and as the FAO collaboration centre for Foot-and-Mouth Disease.
Location	While IZSLER's main office is located in Brescia, Italy, units are distributed on a provincial basis to cover the Lombardy Territorial Area and the Emilia-Romagna Territorial Area.
II. Surveillance activities covered by case study	
Activity	Routine laboratory surveillance
Reference period	01/2017 – 12/2017
Pathogen(s) covered	Salmonella, Listeria
Summary of routine surveillance activities using WGS	Since 2012, IZSLER routinely processes isolates of *Salmonella enterica* from human, animal and food sources as part of the One Health surveillance of foodborne infections based on PFGE, MLVA and serotyping. Isolates belonging to significant outbreaks have been sequenced and compared with SNPs and Gene-by-Gene approaches to highlight phylogenetic relationships and attribute source of infections. The same workflow is applied to isolates

[17] Source: http://www.izsler.it/izs_home_page/who_we_are_/00000047_English.html

	of *Listeria monocytogenes*. WGS is currently used as a confirmation method, and has also been used to retrospectively study past outbreaks.[c)-f)] The reference period of 2017 was a transition year, which extended to include 2018; the institute will switch to the full routine use of WGS in 2019, thereby stopping the use of conventional methods in parallel. The main reason for this is the information potential of whole genome sequencing and the potential for improving surveillance/public health. According to IZSLER, this was also requested by the industry, as major food producers, including export industries, are located in the region, e.g. in Parma.		
Type of sample	Isolates		
Region covered by sampling	Emilia-Romagna, Italy		
Number of samples analysed in reference period	*Pathogen*	*Samples analysed by conventional methods*	*Samples sequenced using WGS*
	Salmonella	1500	110 (7.3% of samples)
	Listeria	65	65 (100% of samples)
Conventional methods used	▸ Salmonella: Serotyping (100% of samples), PFGE (100%), PCR Verification for Typhimurium (50%), MLVA (60%) ▸ Listeria: PFGE (100%)		
Sample preparation WGS	▸ Manual		
Sequencer used for WGS	▸ MiSeq (Illumina)		
Batch size for WGS analysis	▸ The typical batch size for WGS analysis during the reference period was 24.		
Reference dataset used for WGS	▸ IZSLER uses its own reference dataset based on the analyses conducted, and regularly checks international databases for relevant new entries, which are then included into the database if necessary. The institution indicated that public databases have the advantage that data is available and can always be re-analysed, but noted that issues remain regarding data and metadata quality in such public databases.		
Additional information	▸ In the reference year, the institute had not used WGS to identify outbreaks but only to confirm or further analyse outbreaks that had already been identified through the use of conventional methods. Therefore, all sequenced isolates had already been typed using conventional methods. ▸ As indicated above, IZSLER has responsibilities with regard to both animal health and food safety. For the two pathogens covered by this case study, the institute routinely analyses isolates originating from animal infections, food samples, and human cases of infection, as part of a One Health approach to surveillance.		

III. Detailed overview of costs of WGS and conventional methods		
In the following, all costs are provided on a per-sample basis. Equipment costs are annualised and incorporate the annual maintenance costs as reported by the institution. They are adjusted for the percentage use of the equipment for the listed pathogens samples during the reference period (i.e. if a sequencer was also used for other purposes, this is taken into account). Consumables costs are adjusted for the failure rate (i.e. the percentage of consumables wasted, e.g. due to failed runs). Staff time is provided in terms of the minutes of hands-on staff time per sample, for both professionals and technicians. For the calculation of total costs, staff time is then monetised based on Eurostat data on country-specific labour costs for 2017 (by staff category), plus a 25% surcharge for overheads. For comparison purposes only, we have also provided staff costs monetised based on EU average labour costs. *More detailed cost data is provided in Annex I.*		
a) Costs of using WGS		
Sample preparation and sequencing	*Cost type*	*Cost per sample*
	Equipment costs	€ 123.07
	Consumables	€ 165.37
	Other costs	€ 0
	Staff time professionals	*0 minutes*
	Staff time technicians	*35 minutes*
	Staff costs, monetised based on labour cost data for Italy (in brackets: based on labour cost data for the EU as a whole)	€ 13.93 (14.29)
	Total	**€ 302.38**
Bioinformatics and other analyses	*Cost type*	*Cost per sample*
	Equipment costs	€ 40.41
	Other costs	€ 0
	Staff time professionals	*70 minutes*
	Staff time technicians	*0 minutes*
	Staff costs, based on labour cost data for Italy (for EU)	€ 52.35 (52.65)
	Total	**€ 92.77**
b) Costs of conventional methods		
Serotyping (used for 100% of Salmonella samples)	*Cost type*	*Cost per sample*
	Equipment costs	€ 0
	Consumables	€ 7.76
	Other costs	€ 0
	Staff time professionals	*3 minutes*
	Staff time technicians	*38 minutes*
	Staff costs, based on labour cost data for Italy (for EU)	€ 17.36 (17.77)
	Total	**€ 25.12**

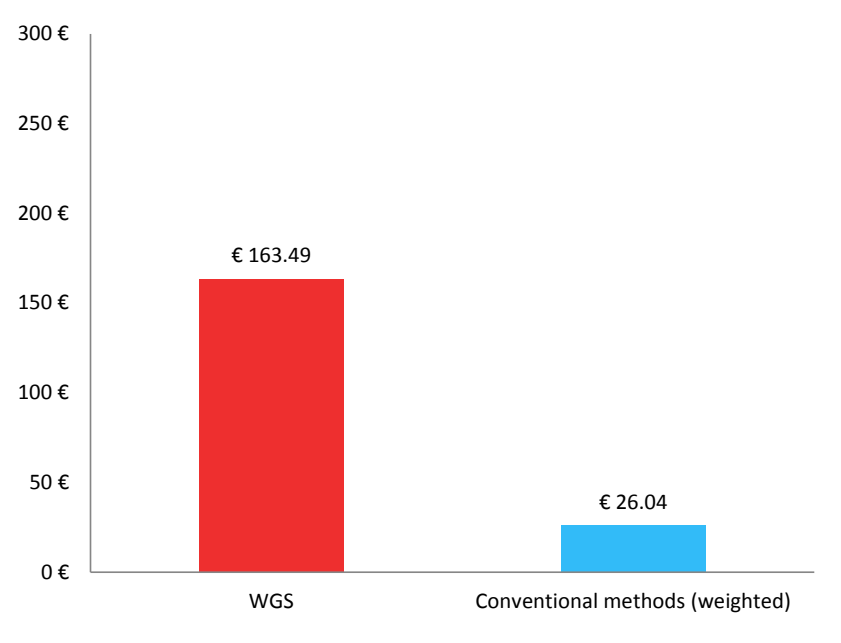
PFGE (100% of Salmonella and Listeria samples)	*Cost type*	*Cost per sample*
	Equipment costs	€ 22.84
	Consumables	€ 14.42
	Other costs	€ 0.00
	Staff time professionals	*2.5 minutes*
	Staff time technicians	*38 minutes*
	Staff costs, based on labour cost data for Italy (for EU)	€ 16.99 (17.40)
	Total	**€ 54.25**
PCR Verification for Typhimurium (50% of Salmonella samples)	*Cost type*	*Cost per sample*
	Equipment costs	€ 10.18
	Consumables	€ 2.78
	Other costs	€ 0
	Staff time professionals	*1 minute*
	Staff time technicians	*11 minutes*
	Staff costs, based on labour cost data for Italy (for EU)	€ 4.73 (4.84)
	Total	**€ 17.68**
MLVA (60% of Salmonella samples)[18]	*Cost type*	*Cost per sample*
	Equipment costs	€ 0
	Consumables	€ 0
	Other costs	€ 43.13
	Staff time professionals	*0 minute*
	Staff time technicians	*0 minute*
	Staff costs, based on labour cost data for Italy (for EU)	€ 0 (0)
	Total	**€ 43.13**

[18] Note that ISZLER has MLVA conducted externally by another lab in the network and therefore incurs no staff, consumables, or equipment costs of its own. The cost shown here is the estimated cost price.

IV. Costs of using WGS compared to the costs of conventional methods

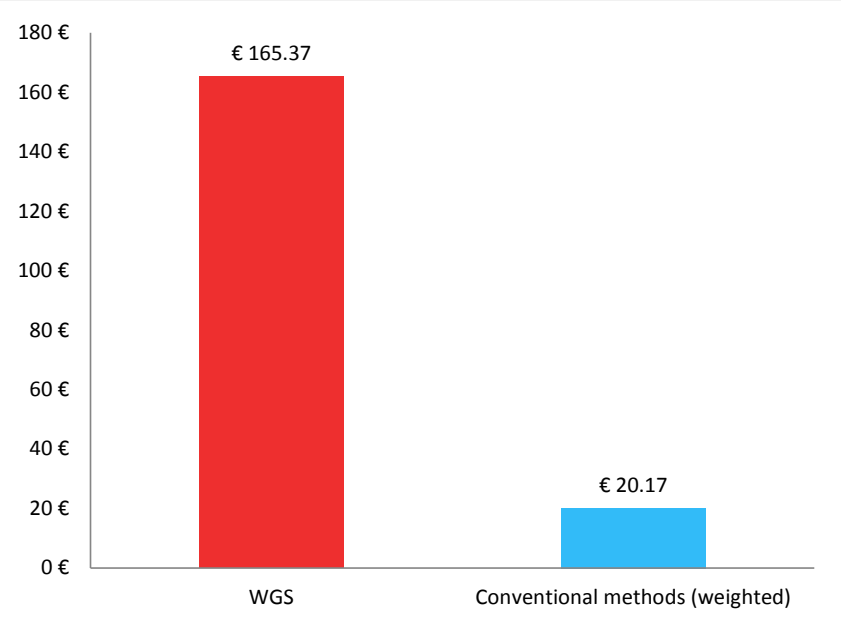
The following comparison of costs per sample using WGS compared to conventional methods takes into account the fact that the number of samples processed differed between conventional methods, e.g. serotyping is used for 100% of Salmonella samples, but MLVA is only used for 60% of Salmonella samples. The average cost of the conventional methods provided here is therefore a weighted figure which accounts for the use rate of the various methods. See Annex I for more details.

Comparison of equipment costs



Equipment costs are significantly higher for WGS (€ 163.49 vs. € 26.04 per sample), mostly due to purchase and maintenance costs of the sequencer itself. IZSLER indicated during the case study visit that larger sequencers were generally better from a cost perspective, but require a large batch size to be cost-effective. However, in a surveillance context it is not always possible to postpone analysis until a certain number of samples have accumulated.

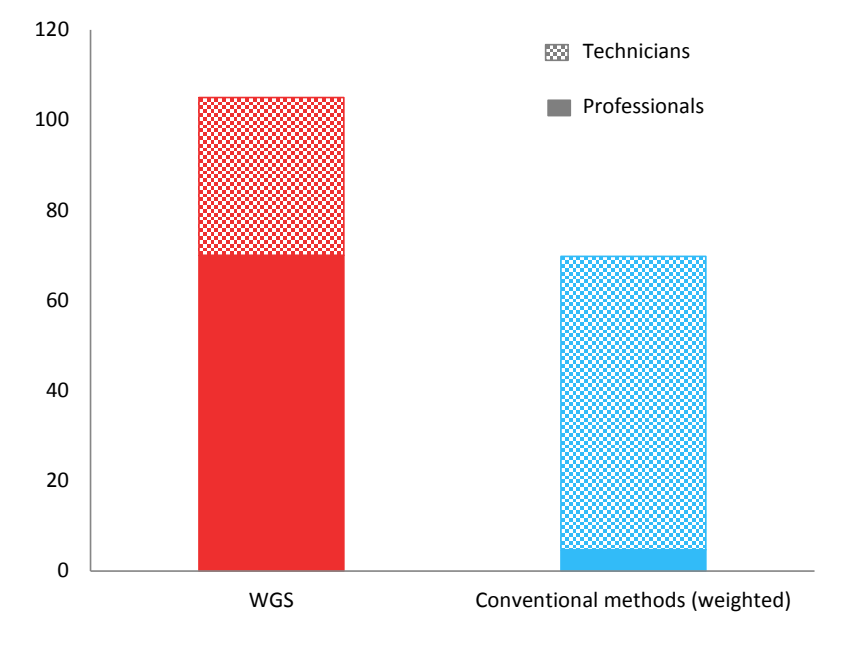
Comparison of costs of consumables



Costs of consumables for WGS are also higher than the weighted average of

conventional methods (€ 165.37 vs. € 20.17 per sample), due to the cost of consumables used for library preparation (€ 46.85 per sample using WGS) and even more importantly the cost of consumables used for sequencing (€ 114.20 per sample using WGS).

Comparison of staff time used



The amount of staff time needed for WGS is higher than for conventional methods, and the proportion of professionals' time to technicians' time is much larger for WGS. This is entirely due to the bioinformatics analysis required for WGS, as this stage is performed exclusively by professional staff, while sample preparation and sequencing are conducted exclusively by technicians. However, IZSLER indicated during the case study visit that they anticipated the bioinformatics stage to be automated for routine surveillance in the future.

Taking the different staff categories into account, monetised staff costs per sample for WGS are approximately two times the amount required for conventional methods (see table below).

Comparison of overall costs

Cost type	*Cost per sample (WGS)*	*Cost per sample (conventional methods)*
Equipment costs	€ 163.49	€ 26.04
Consumables	€ 165.37	€ 20.17
Other costs	€ 0	€ 16.27
Staff time professionals	*70 minutes*	*5 minutes*
Staff time technicians	*35 minutes*	*65 minutes*
Staff costs (monetisation based on labour cost data for Italy)	€ 66.28	€ 29.39
Staff costs (monetisation based on labour cost data for the EU)	*€ 66.94*	*€ 30.09*

	Total	**€ 395.14**	**€ 91.87**

Summary of differential costs	**The cost difference between WGS and conventional methods is € 303.27 per sample**. A sample analysed with WGS costs more than four times the amount of conventional methods (**€** 395.14 vs **€** 91.87). As indicated in the figures above, this difference is mainly due to consumables costs and equipment costs.

V. Effects of using WGS results

a) Turnaround time. Turnaround time is defined as the usual number of days of work from receipt and opening of an incoming sample until the reporting of results. Turnaround time does not include weekends and holidays, except in case that work has been conducted on these days, e.g. for a sequencing run or other analyses.

Turnaround time	▸ The turnaround time for the analysis of a sample using WGS for pathogen identification is 7 days of work, compared to 10 days of work for using the specified conventional method(s) for pathogen identification.

b) Positive effects of using WGS for pathogen identification and surveillance during the reference period

Sampling and sampling strategies	▸ Little or no positive effects of using WGS on sampling and sampling strategies are expected from IZSLER's perspective as these are not the institution's responsibility and are independent from the institution's laboratory function. In addition, the number of samples is largely independent from the method used for analysis.
Analytical results and processes	▸ IZSLER considered that the use of WGS for pathogen identification and surveillance has led to very significant positive effects on analytical results and processes. It reported significant improvement regarding the accuracy, sensitivity and specificity of results produced. ▸ IZSLER also indicated that WGS had led to simplified laboratory work flows, *inter alia* through the reduction of the number of hands-on steps. It also considered that WGS had led to a reduction in the amount of consumables needed for analysis and in staff time required.
Outbreak identification and response	▸ IZSLER considered that the use of WGS for pathogen identification and surveillance has led to very significant positive effects for outbreak identification and response, and sees a reduction in the related overall costs. ▸ IZSLER reported significant improvements regarding earlier detection of initial outbreaks, detection that isolates are related, and information on outbreak epidemiology (e.g. linking cases to the source). In the institution's experience, the high resolution power of WGS is making a striking difference in pathogen typing and source attribution; this was the finding of several scientific papers published by IZSLER retrospectively examining past salmonella and listeria outbreaks using WGS.[c)-f)] In particular, a 2018 paper published by IZSLER using WGS to examine an outbreak of salmonella in 2013 concluded that PFGE and MLVA did not have the necessary resolution or accuracy, respectively, to reliably link isolates to the outbreak source, and could in fact produce misleading results.[c)-f)] ▸ Substantial advantages of WGS were therefore found to derive from the superior accuracy in the attribution of contamination responsibilities along the food chain. For example, during the above mentioned outbreak in 2013, the PFGE based surveillance system identified an outbreak of monophasic *Salmonella Typhimurium* with the potential involvement of a salami producer, a specific abattoir and a farmer. WGS and phylogenetic analyses were able to confirm the salami producer involvement in the case

	but cleared both the farmer and the abattoir of any responsibility.[d)] ▸ IZSLER considered that WGS has also led to significant improvements regarding the information for imposing additional control/biosecurity measures. For instance, the nature (monoclonal vs polyclonal) and distribution of contamination inside food-processing facilities can be finely reconstructed by WGS. As a consequence, de-contamination of facilities can be managed and verified with high confidence. ▸ As regards the surveillance of human infections, IZSLER also considered that WGS helps identify true outbreaks, thus preventing false alerts to public health officials, and reducing the number of infections. The above quoted scientific paper concluded that, had WGS been in routine use at the time of the 2013 outbreak, the source of the outbreak could have potentially been identified up to two months earlier, possibly preventing dozens of infections if the correct mitigation measures had been taken in time. IZSLER considered that this is improving consumers' confidence in the competent authorities and in food business operators.
Research and methods applied	▸ Regarding the positive effects on research and methods applied, the institution reported very significant improvement in the understanding of disease transmission and a positive impact on epidemiological investigations.
Effects on wider society	▸ IZSLER indicated that the use of WGS has led to a significant reduction in the negative effects of food chain contamination on industry and trade relationships, and provided the example of a controversy between two operators of the Parma Ham industry following the finding of *Listeria monocytogenes* with the same PFGE type in their plants. The plants operated sequentially along the same processing chain; one was the ham producer and the second was the deboner. Considering the apparently identical contamination (based on PFGE), the operators blamed each other as the source of the contamination. WGS was able to clearly demonstrate that the isolates from the deboner and producer were unrelated despite identical having an identical PFGE type. As a result, not only were both required to improve their own hygiene procedures, but also no further commercial or legal controversy was justified. ▸ The positive impact on the food industry is also evidenced by the interest of operators in WGS and the fact that major operators have started doing their own in-house testing with WGS.
c) Negative effects of using WGS	
Negative effects of using WGS	So far, the use of WGS for pathogen identification and surveillance has not had negative effects for IZSLER, other than the currently higher costs compared to conventional methods. However, IZSLER indicates that the high resolution power of WGS might lead to the identification of a high number of smaller outbreaks which may strain existing (staff and analytical) capacities.
VI. Outlook	
Balance of costs and benefits achieved	▸ IZSLER noted that in comparison with conventional methods, using WGS is currently more expensive but should eventually reach comparable cost levels, while providing more information.
Potential for cost reductions of using WGS for pathogen identification and surveillance in the future	▸ There is a high potential for simplification of the type of samples needed for WGS with the use of metagenomics. However, IZSLER indicated that this is not expected to materialise for another 5 to 10 years. ▸ It is also expected that significant cost reduction for WGS could be achieved by scaling-up the analytical process through automation of the

(through e.g. techno-logical advances)	DNA extraction and library preparation steps. IZSLER considered that the process could eventually be almost entirely automated. ▸ Savings in the number of required staff are expected: the number of required staff for Salmonella analysis is expected to be at least halved, while maintaining the same staff categories. ▸ Technological developments might have an impact on equipment costs, although the institution noted that it is difficult to foresee how the situation will develop regarding sequencers and related equipment in the coming years.
Future opportunities and challenges	▸ The cross-pathogen potential of WGS technology is a very important advantage from IZSLER's perspective. While many conventional typing methods are pathogen-specific, using WGS can reduce the variety of methods to a single technique or to a single process. The institution noted that it is very confident that using WGS will simplify the analytical process and will improve the overall management of the laboratory. ▸ With WGS, IZSLER indicated that it will be able to satisfy a broader range of requests from public health labs, e.g. on Campylobacter, as WGS would allow them to easily switch to another pathogen in cases where there is ad hoc need to support an outbreak investigation. ▸ As indicated above, the use of WGS may lead to the identification of a high numbers of matches, i.e. potential outbreaks, which raises the question of whether they would have capacity to investigate these potential outbreaks and of the definition of an outbreak. There could also be a need for further standardisation on the approach for outbreak investigation. ▸ IZSLER noted that with the current uptake of and growing interest in WGS there is a potential for fragmentation of the system, and emphasised the importance of standards for sequencing and sharing of results. According to IZSLER quality issues with respect to public databases also indicate a need for further standards and quality assurance in this respect.

VII. Key sources/references	
Cost questionnaire	Cost questionnaire completed by IZLER
Preparatory phone interview	a) Background information and description of activities
Case study visit and follow up	b) Additional data and clarifications provided
Scientific literature	c) Comandatore, F., et al (2017). Genomic Characterization Helps Dissecting an Outbreak of Listeriosis in Northern Italy. *PLoS Currents*, 9, 1–21. http://doi.org/10.1371/currents.outbreaks.633fd8994e9f06f31b3494567c7e504c d) Morganti, M., et al. (2018). Rise and fall of outbreak-specific clone inside endemic pulsotype of salmonella 4,[5],12:i:-; insights from high resolution molecular surveillance in Emilia-Romagna, Italy, 2012 to 2015. *Eurosurveillance*, 23(13), 1–11. http://doi.org/10.2807/1560-7917.ES.2018.23.13.17-00375 e) Morganti, M., et al. (2015). Processing-dependent and clonal contamination patterns of Listeria monocytogenes in the cured ham food chain revealed by genetic analysis. *Applied and Environmental Microbiology*, 82(3), 822–831. http://doi.org/10.1128/AEM.03103-15 f) Scaltriti, E., et al. (2015). Differential single nucleotide polymorphism-based analysis of an outbreak caused by Salmonella enterica serovar Manhattan reveals epidemiological details missed by standard pulsed-field gel electrophoresis. *Journal of Clinical Microbiology*, 53(4), 1227–1238. http://doi.org/10.1128/JCM.02930-14

3.5. Administración Nacional de Laboratorios e Institutos de Salud (ANLIS)

Salmonella and E. coli surveillance – ANLIS, Argentina	
I. Institution	
Name of institution	Instituto Nacional de Enfermedades Infecciosas - Administración Nacional de Laboratorios e Institutos de Salud (INEI-ANLIS)
Type of institution	Public institution under the Ministry of Health
Description	The National Administration of Laboratories and Health Institutes is an organisation that implements the policies of the Argentinian Ministry of Health with respect to the prevention, referential diagnostics, research, and treatment of infectious, genetic, nutrition-based and non-transmissible diseases. It is also responsible for the production and quality control of immunobiological products, for the execution of health programs related to its areas of responsibility, for the coordination of laboratory networks in the country, and in the conduct of epidemiological studies. The National Institute for Infectious Diseases at ANLIS conducts and collaborates in research and methodological development concerning infectious diseases including zoonoses, foodborne infections, water infections and new microbial etiologies. It acts as the national reference laboratory for the diagnosis of viral, bacterial, fungal, and parasitic diseases.
Location	Buenos Aires, Argentina
II. Surveillance activities covered by case study	
Activity	Routine laboratory surveillance
Reference period	06/2017 – 05/2018
Pathogen(s) covered	Salmonella, E. coli
Summary of routine surveillance activities using WGS	WGS has been used at INEI-ANLIS for the routine surveillance of foodborne pathogens since 2015, having been introduced as part of a WHO Pilot Project in cooperation with the GenomeTrakr programme at the US Food and Drug Administration (US-FDA).[e-h)] Although WGS has been implemented on a routine basis for Salmonella, E. coli and Shigella, conventional methods are still being used in parallel for these pathogens due to concerns regarding the cost and availability of the relevant reagents. There are currently no plans to replace these conventional methods in the short-term. The surveillance of foodborne pathogens in Argentina is conducted through the National Diarrheal Network, in which food and clinical laboratories from the whole country participate. Depending on the pathogens, they send a number of the isolates identified to INEI-ANLIS. For Salmonella subspecies, local and provincial laboratories have the capacity to serotype the two most common serovars of Salmonella in Argentina (Salmonella enterica ser. Typhimurium and Salmonella enterica ser. Enteritidis). From these two serovars, local laboratories are required to send each month 20% of their isolates to INEI-ANLIS for further analysis. However, local laboratories must send all other serovars they isolate. To study circulating clones, INEI-ANLIS serotypes all isolates received and uses PFGE for all Salmonella enterica ser. Enteritidis and Typhimurium isolates received and for a selection of the other serovars, as well as all suspected outbreak isolates. For WGS surveillance a selection of all the isolates received at INEI-ANLIS is sequenced, including all suspected outbreak isolates.
Type of sample	Isolates (for E. Coli only: also samples)

Region covered by sampling	Argentina		
Number of samples analysed in reference period	*Pathogen*	*Samples analysed by conventional methods*	*Samples sequenced using WGS*
	Salmonella	The cost calculation is based on experiences with the listed conventional methods, assuming the same number of samples as with WGS	128
	E. Coli		192
Conventional methods used	▸ Salmonella: Biochemical testing (100% of samples), Serotyping (100%), MaldiTOF (5%), PFGE (70%) ▸ E. coli: Biochemical testing (100% of samples), PCR typing (100%), MaldiTOF (5%), PFGE (100%)		
Sample preparation WGS	▸ Manual preparation of isolates		
Sequencer used for WGS	▸ Illumina MiSeq		
Batch size for WGS analysis	▸ The typical batch size for WGS analysis during the reference period was 16 samples per run.		
Reference dataset used for WGS	INEI-ANLIS uses genomic data from publically available databases which is then complemented with genomic data from its own sequencing activities.		

III. Detailed overview of costs of WGS and conventional methods

In the following, all costs are provided on a per-sample basis. Equipment costs are annualised and incorporate the annual maintenance costs as reported by the institution. They are adjusted for the percentage use of the equipment for the listed pathogens samples during the reference period (i.e. if a sequencer was also used for other purposes, this is taken into account). Consumables costs are adjusted for the failure rate (i.e. the percentage of consumables wasted, e.g. due to failed runs). Staff time is provided in terms of the minutes of hands-on staff time per sample, for both professionals and technicians. For the calculation of total costs, staff time is then monetised based on estimated labour costs provided by INEI-ANLIS, plus a 25% surcharge for overheads.

More detailed cost data is provided in Annex I.

a) Costs of using WGS

Sample preparation and sequencing	*Cost type*	*Cost per sample*
	Equipment costs	€ 35.45
	Consumables	€ 104.62
	Other costs	€ 0.00
	Staff time professionals	*31 minutes*
	Staff time technicians	*0 minutes*
	Staff costs, monetised based on labour cost data for Argentina	€ 2.33
	Total	**€ 142.40**

Bioinformatics and other analyses	*Cost type*	*Cost per sample*
	Equipment costs	€ 7.57
	Other costs	€ 0.00
	Staff time professionals	*60 minutes*
	Staff time technicians	*0 minutes*

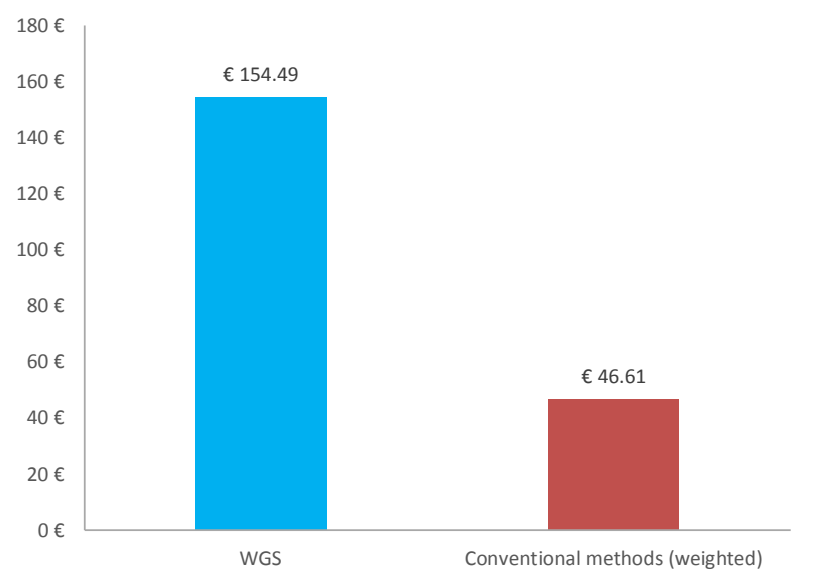
	Staff costs, based on labour cost data for Argentina	€ 4.52
	Total	**€ 12.09**
b) Costs of conventional methods[19]		
Biochemical testing and serotyping (used for 100% of Salmonella samples)	*Cost type*	*Cost per sample*
	Total	**€ 35.41**
Biochemical testing and PCR (100% of E. Coli samples)	*Cost type*	*Cost per sample*
	Total	**€ 39.83**
MaldiTOF (5% of Salmonella and 5% of E. coli samples)	*Cost type*	*Cost per sample*
	Total	**€ 61.96**
PFGE (70% of Salmonella samples and 100% of E. coli samples)	*Cost type*	*Cost per sample*
	Total	**€ 6.64**

IV. Costs of using WGS compared to the costs of conventional methods

The following comparison of costs per sample using WGS compared to conventional methods takes into account the fact that the number of samples processed differed between conventional methods, e.g. biochemical testing is used for 100% of Salmonella samples, but MaldiTOF is only used for 5% of Salmonella samples. The average cost of the conventional methods provided here is therefore a weighted figure which accounts for the use rate of the various methods. See Annex I for more details.

Comparison of overall costs	*Cost type*	*Cost per sample (WGS)*	*Cost per sample (conventional methods)*
	Equipment costs	€ 43.02	-
	Consumables	€ 104.62	-
	Other costs	€ 0.00	-
	Staff time professionals	*91 minutes*	-
	Staff time technicians	*0 minutes*	-
	Staff costs (monetisation based on labour cost data for Argentina)	€ 6.85	-
	Total	**€ 154.49**	**€ 46.61**

[19] Note that costs for conventional methods were provided as lump sum figures representing the costs that were charged to external clients for the relevant tests, including equipment, consumables and staff time.



Summary of differential costs	**The cost difference between WGS and conventional methods is € 107.88 per sample**. A sample analysed with WGS costs approximately 3.3 times the amount of conventional methods (€ 154.49 vs € 46.61).

V. Effects of using WGS results

a) Turnaround time. Turnaround time is defined as the usual number of days of work from receipt and opening of an incoming sample until the reporting of results. Turnaround time does not include weekends and holidays, except in case that work has been conducted on these days, e.g. for a sequencing run or other analyses.

Turnaround time	The turnaround time for the analysis of a sample using WGS can last 5-10 days. In the case of an outbreak where the isolates are prioritised for analysis, this can be reduced to 5-6 days. The turnaround time using conventional methods lasts: ▸ 4-7 days for pathogen identification at the species level; ▸ 5-15 days for characterisation (including the serotype and toxin profile for E. coli); and ▸ 5 days must be added for identification of clonal relationship of isolates using PFGE. In a salmonella outbreak, for example, the complete turnaround time for all three steps using conventional methods can last between 7 and 15 days.

b) Positive effects of using WGS for pathogen identification and surveillance during the reference period

Sampling and sampling strategies	▸ Little or no positive effects of using WGS on sampling and sampling strategies were identified by INEI-ANLIS, although it considered that there could be a minor effect on the simplification of sample storage or transport.
Analytical results and processes	▸ INEI-ANLIS considered that the use of WGS had significant effects on improved accuracy, sensitivity, specificity and level of detail of the results produced. Results of the WHO Pilot Project to introduce WGS in Argentina also showed that WGS could obtain additional information on virulence factors.[f)] ▸ INEI-ANLIS also indicated that WGS had led to simplified laboratory work flows and could lead to a substantial reduction in required staff numbers (if it were fully implemented and used to replace conventional methods such

	as serotyping or PFGE). However, it did not see any effects on the reduction of staff time needed for the analysis (see also above the comparison of staff time used for WGS and conventional methods), due to the increased staff time needed for the bioinformatics analysis.
Outbreak identification and response	▸ INEI-ANLIS considered that the use of WGS for pathogen identification and surveillance had significant effects with respect to improved detection that outbreaks are related and improved information on outbreak epidemiology. It cited scientific publications by its staff showing the use of WGS in retrospectively distinguishing between multiple outbreaks of Shigella sonnei in Argentina.[c-d)] The study showed that even with a lack of supporting routine data WGS was an indispensable method for the tracking and surveillance of bacterial pathogens during outbreaks and was becoming a vital tool for the monitoring of antimicrobial resistant strains of *S. sonnei*.[d)] ▸ The WHO Pilot Project concluded, however, that maximising the benefit of genomic outbreak data requires long-term contextual (i.e. routine surveillance) data from local and international sources.[g)] ▸ INEI-ANLIS did not report any effects with respect to improved information for imposing additional control or biosecurity measures, nor did it indicate any effects concerning a reduction in the duration of an outbreak or a reduction in the disease burden for humans. INEI-ANLIS reported that this was due to the delay in receiving samples (see description of surveillance system above), so that typically the outbreak is already detected at the time that samples are received from local and provincial laboratories. The lack of timely availability of WGS results means that links between isolates are usually discovered too late to be of practical relevance. It was also reported that communication between the genomics team and the epidemiological team at INEI-ANLIS, as well as with the provincial public health authorities was insufficient for effective use of the additional information provided by WGS for outbreak response.
Research and methods applied	▸ The institution reported significant positive effects related to the better understanding of disease transmission and the development of better diagnostic tests. However, it did not report any effects regarding an improvement in epidemiological methods so far.
Effects on wider society	▸ INEI-ANLIS did not identify any significant effects on the wider society. It indicated that the nature of the surveillance system, gaps in communication between different units and institutions, and a lack of implementation of public health measures in response to the available data have limited the potential impact of WGS for reducing the negative effects of outbreaks for the wider society.
c) Negative effects of using WGS	
Negative effects of using WGS	INEI-ANLIS did not identify any negative effects of using WGS.
VI. Outlook	
Balance of costs and benefits achieved	▸ On balance, the benefits of using WGS outweigh the costs, given the improvements in the accuracy of results and turnaround time (for the full analysis). With the appropriate capacity-building, WGS also brings different actors of public health together.
Potential for cost reductions of using WGS for pathogen identification and	▸ Advances in sequencing technology and increasingly automated analysis of sequencing results are expected to drive further cost reductions in using WGS for pathogen identification and surveillance.

surveillance in the future (through e.g. techno-logical advances)	▸ INEI-ANLIS considered that the cross-pathogen potential of WGS was one of the most important areas of potential cost reduction. It pointed out that at the present time, INEI-ANLIS already had a genomic platform for all pathogens in their institute with equipment, reagent and personnel costs all centralised.
Future opportunities and challenges	▸ A key challenge identified affecting present and future use of WGS is the high cost of consumables, which are significantly more expensive than in other countries, such as the US or the UK. This is aggravated by exchange rate fluctuations and import duties, which make it very difficult for INEI-ANLIS to reliably purchase consumables for conducting WGS on a routine basis. It will be difficult to fully switch to WGS as long as this reliability and affordability of supplies is not ensured (either through changes in the pricing policies of producers and distributors of consumables, or through agreements with international organisations to ensure regular supply).

VII. Key sources/references	
Cost questionnaire	Cost questionnaire completed by INEI-ANLIS
Preparatory phone interview	a) Background information and description of activities
Case study visit and follow up	b) Additional data and clarifications provided
Scientific literature	c) Baker, K. S., J. Campos, M. Pichel, A. Della Gaspera, F. Duarte-Martínez, E. Campos-Chacón, H. M. Bolaños-Acuña, et al. 2017. "Whole Genome Sequencing of Shigella Sonnei through PulseNet Latin America and Caribbean: Advancing Global Surveillance of Foodborne Illnesses." Clinical Microbiology and Infection 23 (11): 845–53. doi:10.1016/j.cmi.2017.03.021. d) Chinen, Isabel, Marcelo Galas, Ezequiel Tuduri, Maria Rosa Vinas, Carolina Carbonari, Anabella Della Gaspera, Daniela Napoli, et al. 2016. "Whole Genome Sequencing Identifies Independent Outbreaks of Shigellosis in 2010 and 2011 in La Pampa Province, Argentina." *BioRxiv*. doi:10.1101/049940. e) World Health Organisation (WHO). 2018. "Implementing Whole Genome Sequencing to Support Public Health Surveillance in Argentina." f) World Health Organization (WHO). 2018. "Annex 1. Contribution/Implementation of Whole Genome Sequencing to the National Surveillance of the Shiga Toxin Producing E. Coli O157:H7 in Argentina." WHO Pilot Project. g) World Health Organization (WHO). 2018. "Annex 2. Contribution of Whole Genome Sequencing to the National Surveillance of Shigella Sonnei in Argentina Introduction." WHO Pilot Project. h) World Health Organization (WHO). 2018. "Annex 3. Contribution/ Implementation of Whole Genome Sequencing to the National and International Surveillance of Salmonella Spp." WHO Pilot Project.
Other	i) Website, ANLIS http://www.anlis.gov.ar/

3.6. Maryland Department of Health (MDH)

Foodborne pathogen surveillance – Maryland Department of Health, USA			
I. Institution			
Name of institution	Maryland Department of Health (MDH)		
Type of institution	State department for public health		
Description[h)]	The Maryland Department of Health (MDH) is the public health department of the US state of Maryland. It is responsible for dealing with communicable diseases, tainted foods, and dangerous products. The Laboratories Administration of MDH provides diagnostic and reference services to Maryland hospitals, as well as support to local health departments. Environmental testing is also conducted. The Laboratories Administration consists of a Central Laboratory in Baltimore and Regional Laboratories in Cumberland and Salisbury. The public health laboratories perform over 10 million laboratory tests annually on human specimens and environmental samples submitted by county health departments and clinics, private physicians, hospitals, correctional facilities, private medical laboratories, and the Maryland Department of the Environment.		
Location	Maryland, USA		
II. Surveillance activities covered by case study			
Activity	Routine laboratory surveillance		
Reference period	01/2017 – 12/2017		
Pathogen(s) covered	*Salmonella spp., E. Coli, Shigella spp., Campylobacter spp., Vibrio spp., Listeria*		
Summary of routine surveillance activities using WGS	Since 2013, the MDH Laboratories Administration has routinely utilised WGS to sequence infectious agents recovered from clinical specimens and environmental samples that are submitted to the public health laboratory as part of state-wide public health infectious disease surveillance programs or as part of outbreak/case investigations.		
Type of sample	Isolates		
Region covered by laboratory surveillance	Maryland		
Number of samples analysed in reference period	*Pathogen*	*Samples analysed by conventional methods*	*Samples sequenced using WGS*
	Salmonella spp.	The cost calculation is based on experiences with the listed conventional methods, assuming the same number of samples as with WGS	1010
	E. coli		81
	Shigella spp.		134
	Campylobacter spp.		504
	Vibrio spp.		38
	Listeria spp.		35
Conventional methods used as reference for costing	▸ *Salmonella spp.*: PFGE (100% of samples) ▸ *Shigella spp.*: PFGE (100%) ▸ *E. coli*: PFGE (100%), Real-Time PCR (100%) ▸ *Campylobacter spp.*: PFGE (100%), MALDI-TOF (100%) ▸ *Vibrio spp.*: PFGE (100%), Real-Time PCR (100%) ▸ Listeria: PFGE (100%)		

	MDH reported that a two-stage approach was used for analysis of isolates during the case study period. The isolates were first analysed in another unit applying standard methods (e.g. serotyping). In the second stage, the isolates were analysed in parallel using PFGE (plus PCR and MALDI-TOF for certain pathogens) and WGS. The differential costs of the first-stage tests therefore net to zero. However, MDH indicated that it plans to switch fully to WGS in 2019 and do away with the first-stage microbiology tests. This will lead to additional cost savings which are not captured by this case study.
Sample preparation WGS	▸ DNA extraction is automated and performed by the Core Sequencing group using the Roche MagNA Pure 24 platform. Library preparation is completed manually with Illumina Nextera XT kits.
Sequencer used for WGS	▸ MiSeq (Illumina)
Batch size for WGS analysis	▸ Batch size ranged between 16 and 32, with an average batch size of 24 for automated DNA extraction and for library preparation and sequencing.
Reference dataset used for WGS	▸ No in-house reference dataset. During the case study period, MDH used CLC genomics software for denovo assembly and the Center for Genomics Epidemiology (CGE) website for sequencing analysis (http://www.genomicepidemiology.org), which is hosted by DTU, one of the project leaders of the COMPARE project. ▸ Sequences are uploaded to national and international databases maintained by the FDA (GenomeTrakr) or CDC (PulseNet) and phylogenetic analysis (e.g. cgMLST, wgMLST or SNP analysis) of the generated sequences is used to recognise genetically related clusters of bacterial isolates.

III. Detailed overview of costs of WGS and conventional methods

In the following, all costs are provided on a per-sample basis. Equipment costs are annualised and incorporate the annual maintenance costs as reported by the institution. They are adjusted for the percentage use of the equipment for the listed pathogens samples during the reference period (i.e. if a sequencer was also used for other purposes, this is taken into account). Consumables costs are adjusted for the failure rate (i.e. the percentage of consumables wasted, e.g. due to failed runs). Staff time is provided in terms of the minutes of hands-on staff time per sample, for both professionals and technicians. For the calculation of total costs, staff time is then monetised based on labour cost data provided by the institution, plus a 25% surcharge for overheads. For comparison purposes only, we have also provided staff costs monetised based on EU average labour costs. More detailed cost data is provided in Annex I.

a) Costs of using WGS

Sample preparation and sequencing	*Cost type*	*Cost per sample*
	Equipment costs	€ 28.01
	Consumables	€ 104.40
	Other costs	€ 0
	Staff time professionals	*14 minutes*
	Staff time technicians	*0 minutes*
	Staff costs, monetised based on labour cost data for the US (in brackets: based on labour cost data for the EU as a whole)	€ 9.85 (€ 10.57)
	Total	**€ 142.26**

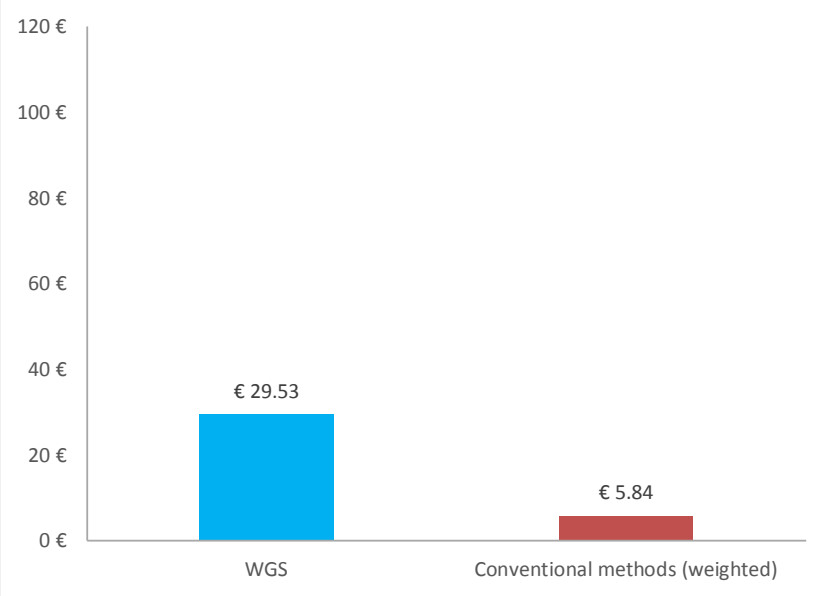
Bioinformatics and other analyses	*Cost type*	*Cost per sample*
	Equipment costs	€ 1.52

	Other costs	€ 0
	Staff time professionals	*15 minutes*
	Staff time technicians	*0 minutes*
	Staff costs, based on labour cost data for the US (for EU)	€ 10.73 (€ 11.51)
	Total	**€ 12.25**
b) Costs of conventional methods		
Method A: PFGE	*Cost type*	*Cost per sample*
	Equipment costs	€ 4.18
	Consumables	€ 31.15
	Other costs	€ 0
	Staff time professionals	*58 minutes*
	Staff time technicians	*0 minutes*
	Staff costs, based on labour cost data for the US (for EU)	€ 40.65 (€ 43.62)
	Total	**€ 75.97**
Method B: Real-Time PCR	*Cost type*	*Cost per sample*
	Equipment costs	€ 9.55
	Consumables	€ 12.55
	Other costs	€ 0
	Staff time professionals	*30 minutes*
	Staff time technicians	*0 minutes*
	Staff costs, based on labour cost data for the US (for EU)	€ 21.02 (€ 22.56)
	Total	**€ 43.13**
Method C: MALDI-TOF	*Cost type*	*Cost per sample*
	Equipment costs	€ 3.69
	Consumables	€ 3.25
	Other costs	€ 0
	Staff time professionals	*2 minutes*
	Staff time technicians	*0 minutes*
	Staff costs, based on labour cost data for the US (for EU)	€ 1.40 (€ 1.50)
	Total	**€ 8.35**

IV. Costs of using WGS compared to the costs of conventional methods

The following comparison of costs per sample using WGS compared to the costs of conventional methods considers that the number of samples processed differed for the different conventional methods. The weighted cost of the conventional methods provided here is therefore a weighted figure which accounts for the use rate of the various methods across the different pathogens. See Annex I for more details.

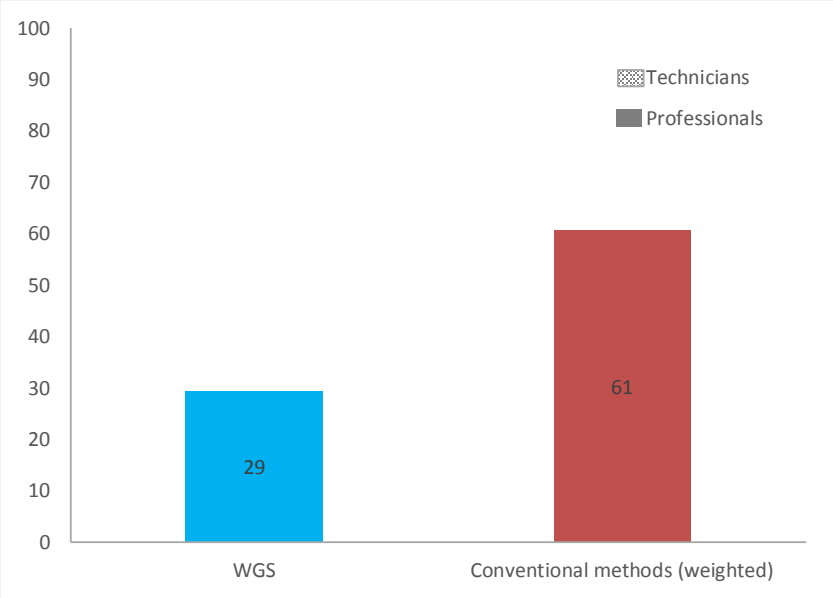
Comparison of equipment costs



Equipment costs per sample are higher for WGS than for the weighted average of conventional methods (€ 29.53 vs € 5.84). However, the total purchase costs of all equipment for conventional methods (approx. € 302 000) exceeds the total purchase costs of equipment for WGS (approx. € 209 000), indicating that the cost difference is rather due to the lower use rates (5-9%) for some of the conventional equipment. The most expensive equipment cost elements for WGS are the two Illumina MiSeq sequencers, which cost a combined total of € 155 624.

Comparison of costs of consumables

The cost of consumables for WGS is more than three times the cost of consumables for conventional methods (€ 104.40 vs € 32.89), and is also the most expensive cost type for WGS overall. The most expensive consumables cost elements for WGS are the sequencing kits used for the Illumina MiSeq, with per-sample costs ranging from € 20.20 to € 28.56.

Comparison of staff time used (in minutes)	 Staff time required for WGS analysis is less than half the staff time required for conventional methods (29 minutes vs 61 minutes). No technician time was reported for either WGS or conventional methods, as no staff member of the MDH lab falls under the case study definition for the 'technician' category. When monetised on the basis of average labour costs, staff costs are considerably cheaper for WGS than for conventional methods (€ 20.58 vs € 42.43).

Comparison of overall costs	*Cost type*	*Cost per sample (WGS)*	*Cost per sample (conventional methods)*
	Equipment costs	€ 29.53	€ 5.84
	Consumables	€ 104.40	€ 32.89
	Other costs	€ 0	€ 0
	Staff time professionals	*29 minutes*	*61 minutes*
	Staff time technicians	*0 minutes*	*0 minutes*
	Staff costs, based on labour cost data for the US (for EU)	€ 20.58 (€ 22.09)	€ 42.43 (€ 45.53)
	Total	**€ 154.51**	**€ 81.16**

Differential costs	**The cost difference between WGS and conventional methods is € 73.35 per sample.** A sample analysed with WGS costs approximately twice the amount of an analysis using conventional methods. As indicated in the figures above, this cost difference is due to equipment and consumables, as staff costs are in fact lower for WGS than for conventional methods.

V. Effects of using WGS results

a) Turnaround time. Turnaround time is defined as the usual number of days of work from receipt and opening of an incoming sample until the reporting of results. Turnaround time does not include weekends and holidays, except in case that work has been conducted on these days, e.g. for a sequencing run or other analyses.

Turnaround time	▸ The turnaround time for WGS analysis from the time the isolate is received by the Sequencing laboratory to the sharing of WGS results with the CDC and FDA takes 7 working days.

	▸ For PFGE, the time between receiving an isolate by the PFGE laboratory and uploading the PFGE pattern to the national database is about 4 working days. All *E. coli* and Listeria are processed within a 4-day turnaround time. The turnaround time for other non-priority routine surveillance organisms such as Salmonella and Campylobacter varies from 4-10 work days or even longer depending upon situational factors such as sample load, work priorities, repeats, etc.
b) Positive effects of using WGS for pathogen identification and surveillance during the reference period	
Sampling and sampling strategies	▸ Effects on sampling and sampling strategies were considered to be not applicable to MDH, as it receives clinical isolates from partners.
Analytical results and processes	▸ MDH observed very significant effects of WGS with respect to the improved accuracy, sensitivity, specificity and detail of the results produced. Retrospective analyses of past outbreaks with WGS conducted by MDH, e.g. related to Vibrio outbreaks in 2010[d)] and in 2012-13,[e-f)] also demonstrate the value of the higher-resolution data provided by WGS and show how this data can provide new analytical insights (e.g. differentiating between west coast and east coast strains of the same sequence type). The higher-quality data available through WGS has also helped to identify emerging threats to public health, e.g. by allowing public health authorities to identify new sequence types that are becoming more prevalent, as was the case with ST361 *Vibrio parahaemolyticus* in 2016.[g)] ▸ MDH considered that there had been a significant effect of WGS on the simplification of laboratory workflows. In particular, it reported that specific instruments settings, methods, and or protocols are needed for PFGE that are organism specific, while this is not the case for WGS. ▸ No positive effects were reported regarding reductions in time needed for the analysis, in consumables needed for the analysis, or in overall costs of the analysis. MDH reported that WGS in fact takes more time than PFGE and is more expensive.
Outbreak identification and response	▸ Significant or very significant effects were reported with respect to improved detection that outbreaks are related, improved information on outbreak epidemiology, and a reduction in the duration of an outbreak. MDH reported that these benefits had been particularly well-observed in a multi-state outbreak of Salmonella in Mexican papayas in 2017.[c)] Based on the information provided by WGS, the product was pulled from the market, leading MDH to consider that there had also potentially been a slightly positive effect on the disease burden. ▸ With respect to the earlier detection of an outbreak, MDH reported that both PFGE and WGS were carried out in parallel during this period, so this effect was not applicable. ▸ MDH reported that it had no regulatory authority for imposing control measures, and therefore indicated that effects on improved information for imposing additional control or biosecurity measures were not applicable. ▸ No effects were reported by MDH with respect to a reduction in overall costs for outbreak identification and response.
Research and methods applied	▸ MDH reported significant effects of WGS regarding a better understanding of disease transmission due to the additional information provided. ▸ No effects were reported by MDH regarding an improvement in epidemiological methods or other research benefits. Effects related to the development of better diagnostic tests were considered non-applicable.
Effects on wider society	▸ MDH indicated that it was not able to provide assessments of the concrete effects of WGS on the wider society during the case study period.

c) Negative effects of using WGS	
Negative effects of using WGS	No negative effects of WGS were reported during the case study period.

VI. Outlook	
Balance of costs and benefits achieved	▸ MDH indicated that WGS was still on the whole more expensive than conventional methods, which is confirmed by the case study results. However, the cost difference is expected to be reduced once the application of standard conventional methods (e.g. serotyping) during the first stage of the analysis (not covered by this case study, see above) is discontinued (as it becomes redundant due to WGS).
Potential for cost reductions	▸ MDH considered that costs might come down as WGS technologies are more widely utilized for national or international laboratory surveillance, but did not believe that these cost reductions would be significant in the near future.
Future opportunities and challenges	▸ MDH indicated that the CDC and FDA are currently moving the workflow of WGS analysis to BioNumerics and transitioning pathogen surveillance from using PFGE to WGS. As a result, a national database of genomic data will be available as a data source to all State Public Health Laboratories including MDH to analyse and determine pathogen clusters for outbreaks. While this will help to identify outbreaks more effectively, this could put an extra burden on state public health laboratories through the need to re-train the workforce and add or change existing infrastructure.

VII. Key sources/references	
Cost questionnaire	Cost questionnaire completed by Maryland Department of Health
Preparatory phone interview	a) Background information and description of activities
Case study visit and follow up	b) Additional data and clarifications provided
Scientific literature	c) Centers for Disease Control and Prevention (2017) Multistate Outbreak of Salmonella Infections Linked to Imported Maradol Papayas (Final Update). https://www.cdc.gov/salmonella/kiambu-07-17/index.html d) Haendiges, J. et al. (2016) 'A Nonautochthonous U.S. Strain of Vibrio parahaemolyticus Isolated from Chesapeake Bay Oysters Caused the Outbreak in Maryland in 2010', Applied and Environmental Microbiology, 82(11), pp. 3208–3216. doi: 10.1128/aem.00096-16. e) Haendiges, J. et al. (2014) 'Pandemic Vibrio parahaemolyticus, Maryland, USA, 2012', Emerging Infectious Diseases, 20(4), pp. 718–720. f) Haendiges, J. et al. (2015) 'Characterization of Vibrio parahaemolyticus clinical strains from Maryland (2012-2013) and comparisons to a locally and globally diverse V. parahaemolyticus strains by whole-genome sequence analysis', Frontiers in Microbiology, 6(FEB), pp. 1–11. doi: 10.3389/fmicb.2015.00125. g) Xu, F. et al. (2017) 'Sequence Type 631 Vibrio parahaemolyticus, an Emerging Foodborne Pathogen in North America', Journal of Clinical Microbiology, 55(2), pp. 645–648.
Other	h) Maryland Department of Health website, https://health.maryland.gov/laboratories/Pages/-About-The-Labs.aspx

3.7. Public Health Agency Canada (PHAC)

Foodborne pathogen surveillance – Public Health Agency of Canada			
I. Institution			
Name of institution	Public Health Agency of Canada / Agence de la santé publique du Canada		
Type of institution	Federal agency for public health		
Description[e-i)]	The Public Health Agency of Canada (PHAC) is a federal agency with the mandate to promote health; prevent and control chronic diseases, injuries, and infectious diseases; prepare for and respond to public health emergencies; and strengthen intergovernmental collaboration on public health. PHAC's National Microbiology Laboratory conducts research and lab-based surveillance as well as coordinate emergency preparedness and response activities in the area of public health. The National Microbiology Laboratory is also responsible for coordinating PulseNet Canada, the national surveillance system for foodborne disease outbreaks.		
Location	Winnipeg, Manitoba, Canada		
II. Surveillance activities covered by case study			
Activity	Routine laboratory surveillance		
Reference period	05/2017 – 05/2018		
Pathogen(s) covered	Salmonella, Listeria		
Summary of routine surveillance activities using WGS	All cases of listeriosis in Canada have been characterised by WGS since February 2017, as have all cases of salmonellosis beginning in May 2017. Prior to this, WGS had been used since approximately 2014 to supplement traditional methods, but only during outbreak response for E. coli, Salmonella, and Listeria. All Listeria and Salmonella isolates from food products (as part of PHAC's integrated/targeted sampling and from its food regulatory partners) were also characterized by WGS and included within national surveillance system during the reference period. During the reference period, as part of a transitional arrangement for the implementation of WGS, all samples were collected by laboratories in Canada's ten provinces and then shipped to the National Microbiology Lab for centralised sequencing. PHAC indicated that this workflow was only temporary, and that the larger provinces would soon do their own sequencing as part of a decentralised surveillance model.		
Type of sample	Isolates		
Region covered by laboratory surveillance	Canada (all provinces and territories)		
Number of samples analysed in reference period	*Pathogen*	*Samples analysed by conventional methods*	*Samples sequenced using WGS*
	Salmonella	The cost calculation is based on experiences with the listed conventional methods, assuming the same number of samples as with WGS	8 273
	Listeria		357
Conventional methods used as reference for costing	▸ Salmonella: Biochemical testing (100% of samples), Serotyping (100%), PFGE (65%) ▸ Listeria: Biochemical testing (100%), PFGE (100%) ▸ Conventional methods were carried out in parallel to characterisation using WGS during the reference period. Since then, conventional testing has been		

	largely discontinued, and is now carried out on less than 10% of isolates.
Sample preparation WGS	▸ PHAC follows the standard PulseNet International procedures for the use of WGS on Salmonella and Listeria.
Sequencer used for WGS	▸ MiSeq (Illumina)
Batch size for WGS analysis	▸ Average batch size of 32 isolates
Reference dataset used for WGS	▸ PHAC uses reference datasets from NCBI and from the shared schemes through PulseNet International. It has developed its own highly innovative bioinformatics infrastructure with custom pipelines and a custom bioinformatics platform, Integrated Rapid Infectious Disease Analysis (IRIDA), which is entirely open-source, automatic, pathogen-neutral and adapted for a cross-pathogen approach.[f)]

III. Detailed overview of costs of WGS and conventional methods

In the following, all costs are provided on a per-sample basis. Equipment costs are annualised and incorporate the annual maintenance costs as reported by the institution. They are adjusted for the percentage use of the equipment for the listed pathogens samples during the reference period (i.e. if a sequencer was also used for other purposes, this is taken into account). Consumables costs are adjusted for the failure rate (i.e. the percentage of consumables wasted, e.g. due to failed runs). Staff time is provided in terms of the minutes of hands-on staff time per sample, for both professionals and technicians. For the calculation of total costs, staff time is then monetised based on labour cost data provided by the institution, plus a 25% surcharge for overheads. For comparison purposes only, we have also provided staff costs monetised based on EU average labour costs. More detailed cost data is provided in Annex I.

a) Costs of using WGS

Sample preparation and sequencing	*Cost type*	*Cost per sample*
	Equipment costs	€ 7.32
	Consumables	€ 69.75
	Other costs	€ 0.00
	Staff time professionals	*0 minutes*
	Staff time technicians	*19 minutes*
	Staff costs, monetised based on labour cost data for Canada (in brackets: based on labour cost data for the EU)	€ 7.89 (€ 7.85)
	Total	**€ 84.95**

Bioinformatics and other analyses	*Cost type*	*Cost per sample*
	Equipment costs	€ 68.59
	Other costs	€ 0.00
	Staff time professionals	*90 minutes*[20]
	Staff time technicians	*0 minutes*
	Staff costs, based on labour cost data for Canada (for EU)	€ 61.82 (€ 67.99)

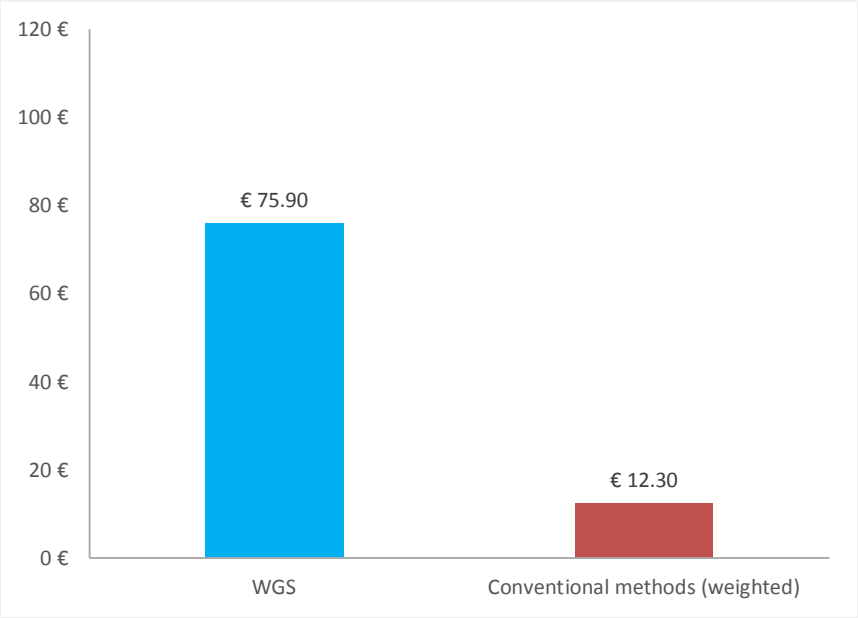
[20] Note that staff time for bioinformatics includes IT support that relates exclusively for maintenance of the database that is used for routine surveillance activities, as well as analytical time for genomic epidemiology.

	Total	**€ 130.41**
b) Costs of conventional methods		
Method A: Biochemical testing (100% of Salmonella samples, 100% of Listeria samples)	*Cost type*	*Cost per sample*
	Equipment costs	€ 0.00
	Consumables	€ 2.42
	Other costs	€ 0.00
	Staff time professionals	*0 minutes*
	Staff time technicians	*40 minutes*
	Staff costs, based on labour cost data for Canada (for EU)	€ 16.41 (€ 16.33)
	Total	**€ 18.83**
Method B: Serotyping (100% of Salmonella samples)	*Cost type*	*Cost per sample*
	Equipment costs	€ 0.00
	Consumables	€ 5.12
	Other costs	€ 0.00
	Staff time professionals	*0 minutes*
	Staff time technicians	*40 minutes*
	Staff costs, based on labour cost data for Canada (for EU)	€ 16.41 (€ 16.33)
	Total	**€ 21.53**
Method C: PFGE (65% of Salmonella samples, 100% of Listeria samples)	*Cost type*	*Cost per sample*
	Equipment costs	€ 18.51
	Consumables	€ 41.58
	Other costs	€ 0.00
	Staff time professionals	*15 minutes*
	Staff time technicians	*30 minutes*
	Staff costs, based on labour cost data for Canada (for EU)	€ 22.42 (€ 23.38)
	Total	**€ 82.51**

IV. Costs of using WGS compared to the costs of conventional methods

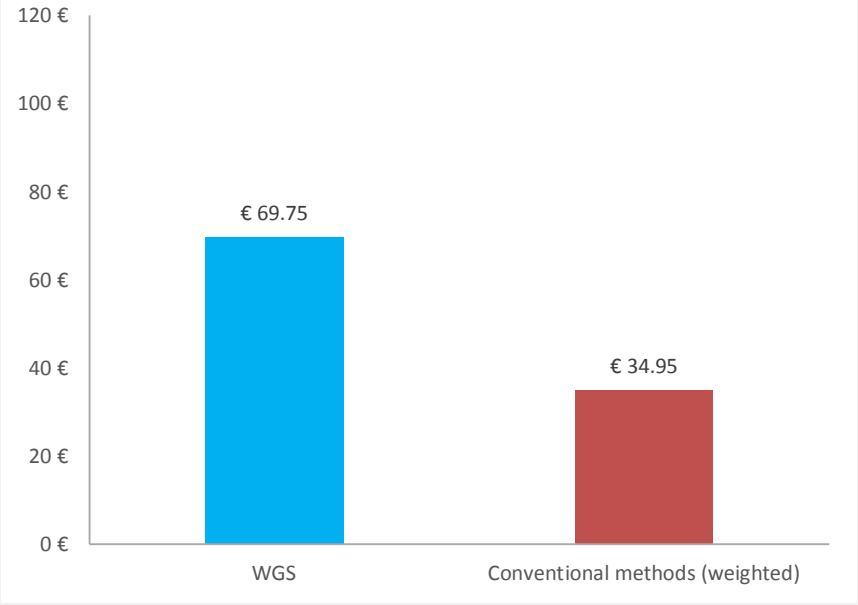
The following comparison of costs per sample using WGS compared to the costs of conventional methods considers that the number of samples processed differed for the different conventional methods. The weighted cost of the conventional methods provided here is therefore a weighted figure which accounts for the use rate of the various methods across the different pathogens. See Annex I for more details.

Comparison of equipment costs

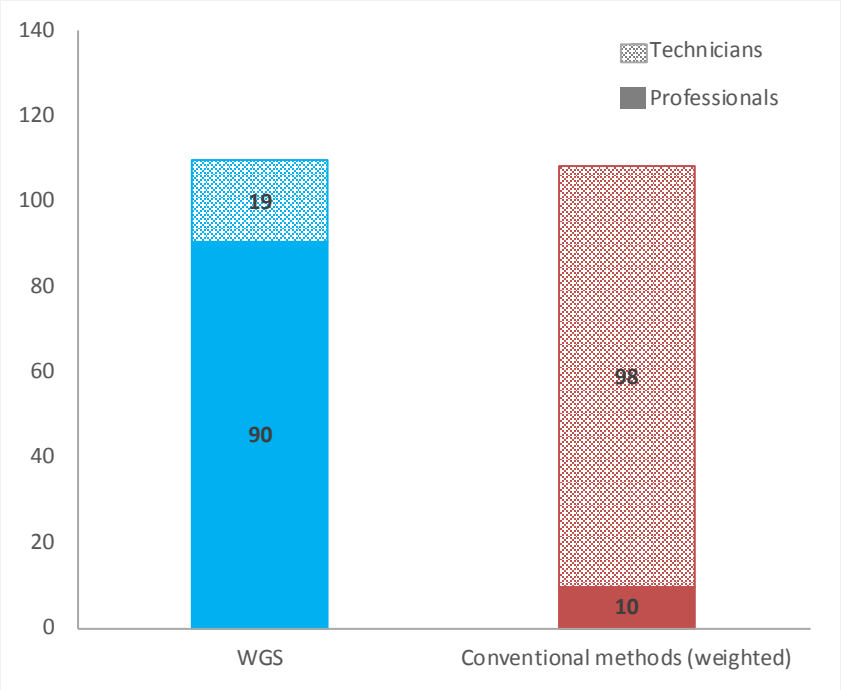


Equipment costs per sample are considerably higher for WGS than for the weighted average of conventional methods (€ 75.90 vs € 12.30). The most expensive equipment cost elements for WGS are not the sequencers themselves (three Illumina MiSeq sequencers, costing a combined total of € 264 345), but the bioinformatics infrastructure, which costs a total of € 2.9 million for the necessary high performance computing hardware (storage, network and servers) and BioNumerics software licences.

Comparison of costs of consumables



The cost of consumables for WGS is more expensive than the cost of consumables for conventional methods (€ 69.75 vs € 34.95). The most expensive consumables cost elements for WGS are the sequencing kits used for the Illumina MiSeq, costing € 33.60 per sample. The cost of conventional methods is largely driven by the consumables costs for PFGE (€ 41.58 per sample), which are significantly higher than consumables costs for either biochemical testing (€ 2.42 per sample) or serotyping (€ 5.12).

Comparison of staff time used (in minutes)	 Total staff time in minutes is roughly equal between WGS and conventional methods (a total of 110 minutes per sample versus a total of 108 minutes per sample). While the staff time for WGS largely consists of professional staff time (which all takes place at the bioinformatics stage), the staff time for conventional methods consists almost entirely of technician staff time. When monetised on the basis of average labour costs, staff time is more expensive for WGS than for conventional methods (€ 69.71 vs € 47.05).

Comparison of overall costs	*Cost type*	*Cost per sample (WGS)*	*Cost per sample (conventional methods)*
	Equipment costs	€ 75.90	€ 12.30
	Consumables	€ 69.75	€ 34.95
	Other costs	€ 0.00	€ 0.00
	Staff time professionals	*90.4 minutes*	*9.8 minutes*
	Staff time technicians	*19.2 minutes*	*108.1 minutes*
	Staff costs, based on labour cost data for Canada	€ 69.71	€ 47.05
	Total	**€ 215.36**	**€ 94.29**

Differential costs	**The cost difference between WGS and conventional methods is € 121.07 per sample.** A sample analysed with WGS costs approximately 128% more than an analysis using conventional methods. As indicated in the figures above, WGS is more expensive than conventional methods for all cost types.

V. Effects of using WGS results

a) Turnaround time. Turnaround time is defined as the usual number of days of work from receipt and opening of an incoming sample until the reporting of results. Turnaround time does not include weekends and holidays, except in case that work has been conducted on these days, e.g. for a sequencing run or other analyses.

Turnaround time	▸ The turnaround time for WGS analysis from the time the isolate is received

	to the reporting of results is 10-14 days, with potentially an additional 5-21 days for shipping time. ▸ For conventional methods, the turnaround time is 1.5-5 days of work. The higher turnaround time for WGS is primarily due to the batching required (i.e. waiting to accumulate enough samples to run the sequencers cost-efficiently) as well as the time to ship isolates from provincial labs across Canada to the central laboratory in Winnipeg for sequencing. The shipping time is unique to the WGS transition period and was not relevant for conventional methods, as conventional methods were previously done entirely at the provincial level. PHAC indicated that the turnaround time for WGS would likely be faster than for conventional methods once the transition to more decentralised model (i.e. with sequencing done in individual provinces) was complete. The difference in turnaround time in the transition to WGS is 'extremely relevant' for PHAC. All of its provincial and federal laboratory partners who rely on the surveillance data generated by PHAC have had to adjust their own workflows as a result, which was reported to be quite disruptive. The delay in turnaround time with WGS has increased concern that the recall of information when patients are questioned on their food histories may be compromised, as well as concern that outbreaks may be detected slower.
b) Positive effects of using WGS for pathogen identification and surveillance during the reference period	
Sampling and sampling strategies	▸ No effects on sampling and sampling strategies were observed by PHAC.
Analytical results and processes	▸ PHAC observed very significant effects of WGS with respect to the improved accuracy, sensitivity, specificity and detail of the results produced. ▸ PHAC considered that there had been a significant effect of WGS on the simplification of laboratory workflows. In particular, it reported that a reduction in the number of different tests had simplified workflows. At the same time, however, it indicated that the replacement workflow with WGS is significantly more complex with respect to coordination. This is due to the integration of more units in the workflow, as traditional methods had previously been handled exclusively by the enterics lab, while the WGS workflow now spans the enterics lab, the genomics core lab, and the bioinformatics section. ▸ With respect to the time needed for the analysis, PHAC reported a very significant negative effect (see turnaround time above). It also reported no effect of WGS on staff time. ▸ PHAC reported a significant effect of WGS in terms of the reduction of overall costs for the analysis, as well as a moderate effect of WGS in terms of a reduction in consumables needed for the analysis. It indicated that WGS enabled PHAC to discontinue expensive tests like PFGE and serotyping; however, these were only discontinued after the reference period.
Outbreak identification and response	▸ Significant or very significant effects were reported with respect to improved detection that outbreaks are related, improved information on outbreak epidemiology, and improved information for imposing additional control or biosecurity measures. PHAC reported, for example, that PFGE had been detecting Listeria outbreaks were none existed, diverting epidemiological resources to investigating outbreaks that were not real. PHAC noted that WGS therefore allowed them to devote more resources to investigating 'true clusters'. ▸ PHAC reported that within a few weeks of implementing WGS for Salmonella surveillance, it began to detect outbreaks of S. Enteritidis that were not discernible by PFGE. Overall, the number of S. Enteritidis outbreaks detected with laboratory data in Canada increased from less than 20 each year in 2012-2016 to more than 100 in 2017, the first year that WGS was

	introduced for routine use. ▸ Within the first 6 months of using WGS, 14 different outbreaks of S. Enteritidis were detected and solved, and led to recalls of various types of chicken products. Utilising all of the WGS data allowed PHAC to estimate the burden of illness from the products overall, and this led to a national food policy change. For example, data from WGS detected multiple S. Enteritidis outbreaks linked to raw frozen breaded chicken products, which were estimated to comprise approximately 40% of the disease burden of S. Enteritidis each year. On the basis of this evidence, the Government of Canada adopted much stricter regulations for producers of raw frozen breaded chicken products in 2018.[i)] ▸ Nevertheless, PHAC reported that it did not have specific information regarding effects of WGS on a reduction in the duration of an outbreak, reductions in the disease burdens for humans or animals, or a reduction in the overall costs for outbreak identification and response. Although PHAC could point to cases where WGS had made a difference (such as with Salmonella-contaminated chicken products), it indicated that it had not yet undertaken a 'before' and 'after' measurement in this respect. ▸ With respect to the earlier detection of an outbreak, PHAC reported a negative effect of WGS due to the lengthening of the turnaround time.
Research and methods applied	▸ PHAC reported very significant effects of WGS regarding a better understanding of disease transmission, as well as moderate effects on the development of better diagnostic tests. It indicated that WGS offers an unprecedented level of potential research questions that may help to mitigate future disease burdens. ▸ Very significant effects were reported in terms of other benefits for research. In particular, PHAC reported that data generated through WGS were being used in research for scheme development, genome-wide association studies, machine learning, and antimicrobial resistance. ▸ PHAC also indicated that there was a very significant positive effect as the infrastructure and protocols developed for WGS in the context of foodborne disease were being leveraged for other disease areas.
Effects on wider society	▸ PHAC reported moderate effects of WGS in reducing negative effects of outbreaks on consumer trust in food. ▸ No other effects on the wider society were reported. PHAC indicated that there was likely a positive effect with respect to reducing the costs of outbreaks for the wider society, but that this had not yet been measured.
c) Negative effects of using WGS	
Negative effects of using WGS	▸ The increase in turnaround time (above) was considered to be one of the most significant negative effects of using WGS, since provincial laboratories could not afford to add WGS to their services and were therefore required to ship all their samples to the National Microbiology Laboratory. ▸ Transition costs from the former PFGE-based system to a WGS-based system were reported to be considerable, since conventional methods and WGS were temporarily performed in parallel. PHAC also indicated that there were many challenges in knowledge translation so that all laboratories and epidemiologists across the country could use the results from WGS for public health and regulatory decision-making. This put a significant (cost) burden on PHAC to provide extensive and ongoing training around the country.
VI. Outlook	
Balance of costs and	▸ Despite the challenges of longer turnaround times and the transition cost,

benefits achieved	PHAC reported that the use of WGS as the primary surveillance method is widely supported in Canada due to the significant improvement in the accuracy of the data and the actions that are taken from it. It reported that the use of WGS data has significantly increased confidence in taking action (regulatory or otherwise).
Potential for cost reductions	▸ PHAC indicated that their current focus was on reducing turnaround time while keeping costs manageable, and that shorter read kits, the ability to sequence in smaller batches in the provincial labs, and (assumed future) shorter run times on the sequencers themselves would ideally contribute towards this goal. ▸ PHAC indicated that since most laboratories (and their purchasing of reagents) work on a pathogen/organism basis, there is still work to be done to realise maximum cost efficiencies through WGS.
Future opportunities and challenges	▸ PHAC considered that the information provided by WGS has the potential for substantial impacts of surveillance, outbreak detection and response, and is poised to mitigate the burden of foodborne disease with international cooperation. It considered that metagenomics was a promising area of future research. Finally, PHAC considered that with WGS technology, it was now possible to make the One Health approach a reality. ▸ However, PHAC reported that in practice, WGS is a 'severe disruption' to existing public health systems and implementation is very challenging, as illustrated by the transitional system in Canada. It considered that changes in organisational thinking (e.g. in how laboratories and surveillance systems are arranged) will be one of the largest future challenges.

VII. Key sources/references	
Cost questionnaire	Cost questionnaire completed by the National Microbiology Laboratory at the Public Health Agency of Canada
Preparatory phone interview	a) Background information and description of activities
Case study visit and follow up	b) Additional data and clarifications provided
Scientific literature	c) Remore J. et al (2018), 'Evaluation of whole-genome sequencing for outbreak detection of Verotoxigenic Escherichia coli O157:H7 from the Canadian perspective', BMC Genomics, 19(1):870. doi: 10.1186/s12864-018-5243-3. d) Yachison, C.A., et al (2017), 'The Validation and Implications of Using Whole Genome Sequencing as a Replacement for Traditional Serotyping for a National Salmonella Reference Laboratory', Front Microbiology, 8:1044. doi: 10.3389/fmicb.2017.01044.
Other	e) PHAC website, https://www.canada.ca/en/public-health.html f) National Microbiology Lab website https://www.canada.ca/en/public-health/programs/national-microbiology-laboratory.html g) PulseNet Canada website https://www.canada.ca/en/public-health/programs/pulsenet-canada.html h) IRIDA website https://www.irida.ca/ i) PHAC, Public Health Notice - Outbreaks of Salmonella infections linked to raw chicken, including frozen raw breaded chicken products https://www.canada.ca/en/public-health/services/public-health-notices/2018/outbreaks-salmonella-infections-linked-raw-chicken-including-frozen-raw-breaded-chicken-products.html

3.8. Public Health England (PHE)

Foodborne pathogen surveillance – PHE, UK			
I. Institution			
Name of institution	Public Health England (PHE)		
Type of institution	Executive agency of the Department of Health and Social Care		
Description[n)]	The Gastrointestinal Bacteria Reference Unit (GBRU) at Public Health England is the national reference laboratory for gastrointestinal bacterial pathogens for England, Wales and Northern Ireland from clinical, food and environmental samples. The GBRU also undertakes research into the genetic diversity of pathogens and the development of improved detection and characterisation techniques for food, water and environmentally borne diseases and offers expert advice, education and training on public health aspects of food microbiology and safety. In 2012, Public Health England established a central genomics service at PHE Colindale to provide sequencing capabilities for microbiology services across PHE. Whilst initially focused on a few pathogens, including Salmonella, WGS is now being used by Public Health England for routine identification, characterisation and typing of Salmonella, Listeria, E. coli & Shigella, and Campylobacter isolates from England, Wales and Northern Ireland.[f)]		
Location	Greater London, UK		
II. Surveillance activities covered by case study			
Activity	Routine laboratory surveillance		
Reference period	04/2016 – 03/2017		
Pathogen(s) covered	Salmonella, Listeria, E. coli & Shigella, Campylobacter		
Summary of routine surveillance activities using WGS	WGS has been used for routine surveillance for all referred isolates of the listed pathogens since 2015 (Campylobacter since January 2016).		
Type of sample	Bacterial isolates from clinical, food and environmental samples		
Region covered by laboratory surveillance	England, Wales and Northern Ireland		
Number of samples analysed in reference period	*Pathogen*	*Samples analysed by conventional methods*	*Samples sequenced using WGS*
	Salmonella	The cost calculation is based on previous experiences with the listed conventional methods, assuming the same number of samples as with WGS	10174
	Listeria		1000
	E. coli & Shigella		4294
	Campylo-bacter		350
Conventional methods used as reference for costing	▸ Salmonella: Taqman PCR (73% of samples), Monophasic PCR for S. Typhimurium (10%), Serotyping (98%), Phage typing (99%), D-Tartrate (3%), Glucose gas test (3%), MLVA (48%), PFGE (3%), Antimicrobial resistance (AMR) testing (68%). Use of MLVA and PFGE for Salmonella was previously based on exceedance levels for certain serotypes/phage types. ▸ Listeria: PCR (x2; 100% each), fAFLP (100%). ▸ E. coli and Shigella: Real-time PCR (100%), Serotyping (100%), Phage typing (100%), Biochemistry (100%), MLVA (100%).		

	▸ Campylobacter: Real-time PCR (100%), Serotyping (12%), Phage typing (38%), MLST (52%). PHE indicated that serotyping and phage typing would have only been done in outbreaks. ▸ Sample preparation for serotyping was partly automated through the use of a robot for the preparation of antisera plates.
Sample preparation WGS	▸ Automated laboratory processes with minimal hands-on time (for example, DNA extraction is partially automated through the use of an automated DNA extraction machine).
Sequencer used for WGS	▸ Illumina HiSeq
Batch size for WGS analysis	▸ The data provided for the reference period assumes a run of 96 samples (or batches of 40 for sample processing)
Reference dataset used for WGS	▸ PHE uses its own in-house database for SNP analysis on a routine basis as well as other public databases on an ad hoc basis as required.

III. Detailed overview of costs of WGS and conventional methods

In the following, all costs are provided on a per-sample basis. Equipment costs are annualised and incorporate the annual maintenance costs as reported by the institution. They are adjusted for the percentage use of the equipment for the listed pathogens samples during the reference period (i.e. if a sequencer was also used for other purposes, this is taken into account). Consumables costs are adjusted for the failure rate (i.e. the percentage of consumables wasted, e.g. due to failed runs). Staff time is provided in terms of the minutes of hands-on staff time per sample, for both professionals and technicians. For the calculation of total costs, staff time is then monetised based on Eurostat data on country-specific labour costs for 2017 (by staff category), plus a 25% surcharge for overheads. For comparison purposes only, we have also provided staff costs monetised based on EU average labour costs. More detailed cost data is provided in Annex I.

a) Costs of using WGS[21]

Sample preparation and sequencing	*Cost type*	*Cost per sample*
	Equipment costs	€ 30.34
	Consumables	€ 53.92
	Other costs	€ 0
	Staff time professionals	*6.85 minutes*
	Staff time technicians	*17.15 minutes*
	Staff costs, monetised based on labour cost data for the UK (in brackets: based on labour cost data for the EU as a whole)	€ 11.67 (€ 12.15)
	Total	**€ 95.93**

Bioinformatics and other analyses	*Cost type*	*Cost per sample*
	Equipment costs	€ 4.89
	Other costs	€ 0
	Staff time professionals	*36 minutes*

[21] PHE provided cost data in pounds sterling. These have been converted to Euro using the European Central Bank's yearly average reference exchange rate for the relevant year (i.e. the year of purchase for equipment, or 2017 otherwise).

	Staff time technicians	*0 minute*
	Staff costs, based on labour cost data for the UK (for EU)	€ 23.78 (€ 27.08)
	Total	**€ 28.67**

b) Costs of conventional methods

Note that detailed costing data were not available for every conventional test, as many of the conventional methods had been discontinued with the introduction of WGS. In consultation with PHE, it was decided to use similar tests for which data were available as a cost proxy. For example, as MLVA, MLST, and fAFLP are all enzyme reactions, the cost for MLVA was used as a proxy for the cost of MLST and fAFLP. Conventional tests were costed across all pathogens (e.g. the same per-sample cost calculation for Serotyping applies to Salmonella, Listeria, E. coli and Shigella, and Campylobacter).

Method A: PCR (Taqman)	*Cost type*	*Cost per sample*
	Equipment costs	€ 2.60
	Consumables	€ 2.12
	Other costs	€ 2.35
	Staff time professionals	*0 minutes*
	Staff time technicians	*5.63 minutes*
	Staff costs, based on labour cost data for the UK (for EU)	€ 2.35 (€ 2.30)
	Total	**€ 7.07**

Method B: PCR (Monophasic)	*Cost type*	*Cost per sample*
	Equipment costs	€ 2.60
	Consumables	€ 2.44
	Other costs	€ 0
	Staff time professionals	*0 minutes*
	Staff time technicians	*3.96 minutes*
	Staff costs, based on labour cost data for the UK (for EU)	€ 1.65 (€ 1.62)
	Total	**€ 6.69**

Method C: PCR (RT, other)	*Cost type*	*Cost per sample*
	Equipment costs	€ 5.12
	Consumables	€ 9.49
	Other costs	€ 0
	Staff time professionals	*2.50 minutes*
	Staff time technicians	*3.00 minutes*
	Staff costs, based on labour cost data for the UK (for EU)	€ 2.90 (€ 3.11)
	Total	**€ 17.51**

Method D: MLVA/MLST/fAFLP	*Cost type*	*Cost per sample*
	Equipment costs	€ 0
	Consumables	€ 3.87
	Other costs	€ 0
	Staff time professionals	*0 minutes*
	Staff time technicians	*7.71 minutes*
	Staff costs, based on labour cost data for the UK (for EU)	€ 3.21 (€ 3.15)
	Total	**€ 7.08**
Method E: Serotyping	*Cost type*	*Cost per sample*
	Equipment costs	€ 1.08
	Consumables	€ 13.36
	Other costs	€ 0
	Staff time professionals	*0 minutes*
	Staff time technicians	*27.25 minutes*
	Staff costs, based on labour cost data for the UK (for EU)	€ 11.35 (€ 11.13)
	Total	**€ 15.79**
Method F: Phage Typing	*Cost type*	*Cost per sample*
	Equipment costs	€ 0.08
	Consumables	€ 3.48
	Other costs	€ 0
	Staff time professionals	*2.25 minutes*
	Staff time technicians	*12.50 minutes*
	Staff costs, based on labour cost data for the UK (for EU)	€ 6.69 (€ 6.80)
	Total	**€ 10.26**
Method G: PFGE[22]	*Cost type*	*Cost per sample*
	Equipment costs	€ -
	Consumables	€ -
	Other costs	€ 97.82
	Staff time professionals	-
	Staff time technicians	-
	Staff costs, based on labour cost data for the UK (for EU)	€ - (€ -)

[22] Note that detailed cost data were not available for PFGE, so PHE's internal estimate of € 97.82 per sample was used as a unit cost.

	Total	**€ 97.82**
Method H: D-Tartrate	*Cost type*	*Cost per sample*
	Equipment costs	€ 0
	Consumables	€ 7.26
	Other costs	€ 0
	Staff time professionals	*0 minutes*
	Staff time technicians	*25.00 minutes*
	Staff costs, based on labour cost data for the UK (for EU)	€ 10.42 (€ 10.21)
	Total	**€ 17.67**
Method I: Glucose Gas	*Cost type*	*Cost per sample*
	Equipment costs	€ 0
	Consumables	€ 0.79
	Other costs	€ 0
	Staff time professionals	*0 minutes*
	Staff time technicians	*10.00 minutes*
	Staff costs, based on labour cost data for the UK (for EU)	€ 4.17 (€ 4.08)
	Total	**€ 4.96**
Method J: AMR	*Cost type*	*Cost per sample*
	Equipment costs	€ 0
	Consumables	€ 1.40
	Other costs	€ 0
	Staff time professionals	*0 minutes*
	Staff time technicians	*2.00 minutes*
	Staff costs, based on labour cost data for the UK (for EU)	€ 0.83 (€ 0.82)
	Total	**€ 2.23**
Method K: Biochemistry	*Cost type*	*Cost per sample*
	Equipment costs	€ 10.43
	Consumables	€ 25.97
	Other costs	€ 0
	Staff time professionals	*6.00 minutes*
	Staff time technicians	*36.00 minutes*
	Staff costs, based on labour cost data for the UK (for EU)	€ 18.96 (€ 19.21)
	Total	**€ 55.36**

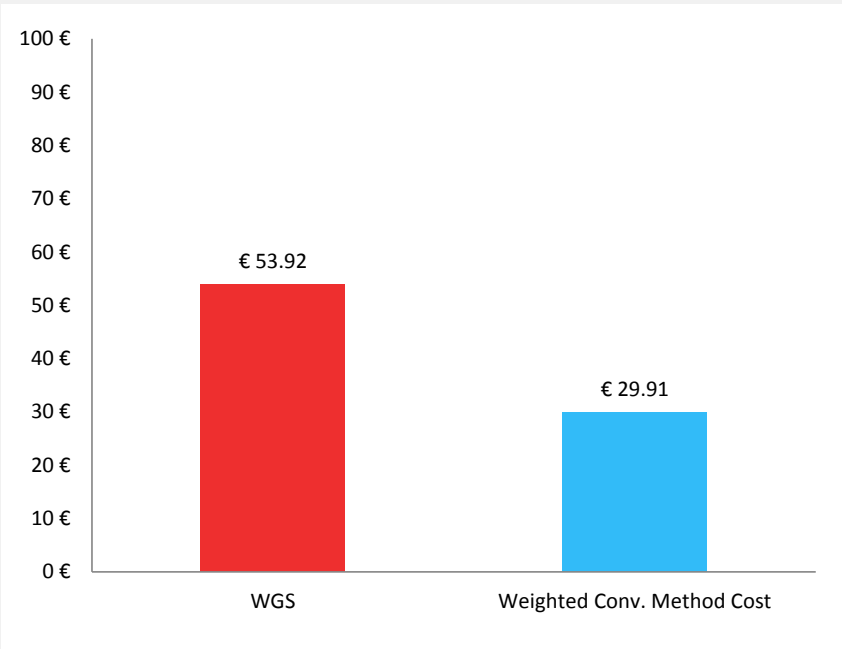
IV. Costs of using WGS compared to the costs of conventional methods

The following comparison of costs per sample using WGS compared to the costs of conventional methods considers that the number of samples processed differed for the different conventional methods. The weighted cost of the conventional methods provided here is therefore a weighted figure which accounts for the use rate of the various methods across the different pathogens. See Annex I for more details.

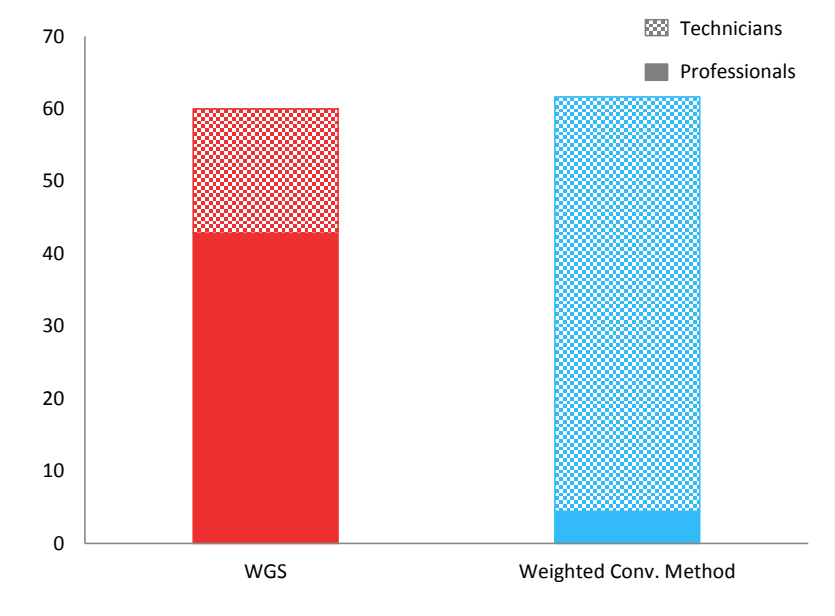
Comparison of equipment costs

Equipment costs *per sample* at PHE are higher for WGS than for the weighted conventional methods (€ 35.23 vs € 7.11), although the large volume of samples processed (15 791 during the reference period) keeps equipment costs for both WGS and conventional methods low on a per-sample basis. The large sample size and the relatively lower cost of the equipment used for the conventional methods brings the per-sample weighted cost for the conventional methods down to just € 7.11.

Comparison of costs of consumables



Consumables costs for WGS (€ 53.92) are higher than for conventional methods (€ 29.91). The higher costs for WGS result from the higher per-

	sample costs of the various kits used for library preparation, particularly the Nextera DNA Library Prep Kit for 96 samples.
Comparison of staff time used (in minutes)	 The amount of staff time needed for WGS analysis (a total of 60 minutes per sample) is slightly lower than the amount of staff time needed to carry out the various conventional methods (62 minutes). Note however that as with the other cost categories, the staff time required for conventional methods was weighted to take into account the fact that multiple tests were often performed on the same samples. The staff time required for individual conventional tests ranged from a low of 2 minutes per sample (for AMR testing) to a high of 42 minutes per sample (for the biochemistry tests). Compared to conventional methods, analysis with WGS requires a significantly larger proportion of professional staff time. As a result, once staff time has been monetised, WGS has higher staff costs (€ 35.44) than the weighted conventional methods (€ 26.77).

Comparison of overall costs

Cost type	*Cost per sample (WGS)*	*Cost per sample (conventional methods)*
Equipment costs	€ 35.23	€ 7.11
Consumables	€ 53.92	€ 29.91
Other costs	€ 0	€ 1.67
Staff time professionals	*42.85 minutes*	*4.43 minutes*
Staff time technicians	*17.15 minutes*	*57.23 minutes*
Staff costs, based on labour cost data for the UK (for EU)	€ 35.44 (€ 39.23)	€ 26.77 (€ 26.70)
Total	**€ 124.59**	**€ 65.46**

Differential costs	**The cost difference between WGS and conventional methods is € 59.13 per sample**. A sample analysed with WGS costs approximately twice the amount of analysis with conventional methods. As indicated in the figures above, the largest differences are in equipment and consumables costs.

V. Effects of using WGS results	
a) Turnaround time. Turnaround time is defined as the usual number of days of work from receipt and opening of an incoming sample until the reporting of results. Turnaround time does not include weekends and holidays, except in case that work has been conducted on these days, e.g. for a sequencing run or other analyses.	
Turnaround time	▸ The turnaround time for the analysis of a sample using WGS for pathogen identification is 10 days of work. This figure includes weekends, as machines can be set to run over the weekend. ▸ The turnaround time using the specified conventional methods for pathogen identification is dependent on the pathogen. For example, the turnaround time would be 10-15 days of work for Salmonella (14-21 days including weekends, as machines can be set to run over the weekend), or 3 days of work for L. monocytogenes (5 days including weekends). However, these estimates do not include typing, but just confirmation of identification and serotyping. ▸ PHE considered that for most pathogens there has been an improvement in turnaround times with WGS. However, this depends on the type of analysis needed: for example, some of PHE's clients only need confirmation of identity, which takes longer with WGS than using conventional methods (i.e. PCR identification). As a result, in cases where identification is required urgently, PHE still does PCR identification tests.
b) Positive effects of using WGS for pathogen identification and surveillance during the reference period	
Sampling and sampling strategies	▸ PHE reported no effects at all on sampling and sampling strategies.
Analytical results and processes	▸ PHE indicated that WGS had very significant positive effects on analytical results and processes. It considered that WGS had significantly improved the accuracy, sensitivity, specificity, and level of detail in the results produced, citing papers in which the higher resolution data from WGS was used to produce results above and beyond what would be possible with conventional methods alone.[f)-k)] For example, PHE indicated that WGS can show how strains diversify over time, allowing strains to be identified as being phylogenetically linked, while under past methods these would have been seen to be unrelated strains. ▸ PHE indicated that WGS had led to considerable streamlining in their laboratory. It reported that WGS had simplified laboratory work flows, noting that WGS was able to replace the numerous tests that had previously been performed on each pathogen with a single, unified workflow. PHE also indicated that WGS had led to a reduction in (analytical) time, staff time, and consumables. PHE reported having reduced their lab staff considerably since introducing WGS. ▸ Another benefit noted by PHE was the ability to better monitor its own laboratory processes. PHE was able to introduce processes to report on the use of WGS (e.g. related to the number of samples processed) and indicated that it used this data to track trends in WGS usage, predict future costs, and try to reduce costs in the future.
Outbreak identification and response	▸ PHE indicated that the impact of using WGS in pathogen surveillance has been 'transformational'. It stated that WGS has dramatically changed outbreak detection, namely that more outbreaks were being detected than previously;[h)] that large multinational outbreaks are being detected that would have not been detected and confirmed with certainty before;[d)] and that 'slow burn' outbreaks with few cases over several years can also now be detected. For example, WGS was able to identify an outbreak of

	Salmonella enteritidis in reptile feeder mice that had previously been continuing undetected over a period of four years with at least 162 cases identified between 2012 and 2015.[c)] ▸ PHE also indicated that one of the benefits of WGS was the ability to monitor the effectiveness of public health interventions. As an example, it cited the case of a large EU-wide Salmonella outbreak in eggs, where action was taken to address the problem but WGS was able to identify the re-emergence of human cases, indicating an ongoing issue. With previous typing methods it would not have been possible to show it was the same strain with the level of certainty provided by WGS. ▸ PHE reported that WGS can be used for more precise case definitions in outbreak investigations. It noted that WGS provided a tool to rule cases as being in or out of the outbreak far more accurately, making subsequent epidemiological investigations more powerful by not including cases that were not actually part of the outbreak. For example, WGS was used by PHE to discriminate between three separate outbreaks of Shigella in the English Orthodox Jewish community which were circulating at the same time.[i),m)] ▸ PHE noted that WGS also allowed them to identify whether an outbreak isolate was likely to have come from outside the UK through clustering with travel-related isolates or comparisons with sequence data in external databases. It considered that WGS enabled the tracking and dissemination of emerging strains at a global scale. ▸ In sum, PHE indicated that WGS had highly significant effects on the earlier detection of an initial outbreak, improved detection that outbreaks are related, improved information on outbreak epidemiology, and improved information for imposing additional control or biosecurity measures. It also considered that WGS had contributed to a reduction in the duration of outbreaks, and had likely contributed to a reduction of the disease burden in humans (although it stated that it had not observed this directly, and that this effect might take longer to see).
Research and methods applied	▸ PHE reported very significant positive effects of using WGS regarding better understanding of disease transmission. For example, PHE described a case where an E. coli O157 isolate causing an outbreak via salad leaves was matched to isolates from UK sheep, leading it to determine that the salad leaves most likely became contaminated as a result of being grown or irrigated with river water contaminated by run-off from nearby fields where sheep had been grazing. ▸ PHE also noted other benefits for research, in particular the fact that large amounts of WGS data (sequence data) are now made publicly available and can be used freely for analysis. It also noted that WGS data made it easier to collaborate internationally, since it is now possible to send sequence data instead of isolates. ▸ Moderate effects of WGS were observed by PHE with respect to improvements in epidemiological methods. PHE indicated that the use of WGS in case definitions improves the power of analytical epidemiological studies, citing the previously-mentioned study concerning a long-undetected Salmonella outbreak linked to reptile feeder mice.[c)] ▸ Moderate effects of WGS were also observed regarding the development of better diagnostic tests. For example, PHE cited a paper co-authored by its staff which demonstrates the use of WGS as a resource for the development and evaluation of molecular diagnostic assays for Campylobacter.[l)] PHE also noted that it had recently developed and implemented a PCR assay to distinguish between typhi/paratyphi and non-typhoidal strains of Salmonella, and that it had been able to design the primers and probes and carry out extensive validation of these on a panel of over 1000 WGS results from different Salmonella samples.
Effects on wider society	▸ PHE considered that it was not able to fully assess the effects of using WGS

	on the wider society. Nevertheless, it did indicate that WGS had led to a reduction of costs of outbreaks for the wider society, citing the general principle that identifying an outbreak and putting in preventative measures should lead to the prevention of further cases going forward. ▸ PHE also considered that WGS had likely reduced the negative effects of outbreaks on consumer trust in food.
c) Negative effects of using WGS	
Negative effects of using WGS	PHE indicated that since switching to WGS, it is detecting far more outbreaks than previously (particularly with respect to Salmonella), and that this has resource implications for their epidemiological investigations.[g),h)] PHE indicated that it currently doesn't have the resources to investigate all the linked cases that they see with WGS. However, it noted that if more outbreaks are resolved, then this would lead to a reduction in the disease burden overall.
VI. Outlook	
Balance of costs and benefits achieved	▸ PHE considered that their costs had increased due to an increase in the number of outbreaks detected through WGS. However, it expected that if preventative measures are successfully implemented on the basis of better outbreak detection, improved understanding, investigation and implementation of effective control measures, the overall costs should come down from both a societal and an institutional perspective.
Potential for cost reductions	▸ PHE expected costs to come down in the long term as laboratories reorganise their operations around WGS (e.g. by replacing conventional typing methods for other gastrointestinal pathogens, through streamlining processes and needing fewer staff). It considered that there would likely be future improvements in bioinformatics, i.e. in algorithm development, which could further streamline the analysis and reduce costs. ▸ PHE also expected to see a long term reduction in the costs of outbreak detection and response through the prevention of future cases.
Future opportunities and challenges	▸ PHE considered that the full potential of WGS technology has probably not yet been fully realised, and that WGS will lead to better information on transmission of gastrointestinal pathogens and improve epidemiological investigations. It reported that some effects of WGS (e.g. on staff costs and laboratory organisation, but also on wider effects such improved epidemiological investigations and the reduction of the overall disease burden) would take longer to see. ▸ PHE considered that the MinION had a lot of potential for outbreak response in the future, and could also provide a way for laboratories to diversity their technology against price increases through supplier monopolies (e.g. from supplies who are the sole producers of necessary sequencing kits). It also considered that the MinION could be a valuable tool in developing countries, and thought there was potential for these countries to 'leapfrog' previous technology and jump right into sequencing. ▸ PHE noted that back-compatibility could be a concern going forward, as the new information provided by WGS is very different from what was collected before (e.g. through phage typing). This could cause difficulties in inter-agency communication with agencies that do not yet use WGS. ▸ Training and communications were noted as a present and future challenge, since PHE noted that WGS has a steep learning curve and re-training can require significant resources. ▸ Another future challenge noted by PHE related to the availability of bioinformatics skills, since the bioinformatics analysis requires a very

	specific set of skills in computer science, statistics, biology, and epidemiology, and people with this expertise can be difficult to recruit.
VII. Key sources/references	
Cost questionnaire	Cost questionnaire completed by PHE
Preparatory phone interview	a) Background information and description of activities
Case study visit and follow up	b) Additional data and clarifications provided
Scientific literature	c) Kanagarajah, S., Waldram, A., Dolan, G., Jenkins, C., Ashton, P. M., Martin, A. I. C., ... et al. (2018). Whole genome sequencing reveals an outbreak of Salmonella Enteritidis associated with reptile feeder mice in the United Kingdom, 2012-2015. Food microbiology, 71, 32-38. d) Inns, T., Ashton, P. M., Herrera-Leon, S., Lighthill, J., Foulkes, S., Jombart, T., et al. (2017). Prospective use of whole genome sequencing (WGS) detected a multi-country outbreak of Salmonella Enteritidis. Epidemiology & Infection, 145(2), 289-298. e) Ashton, P. M., Nair, S., Peters, T. M., Bale, J. A., Powell, D. G., Painset, A.,et al. (2016). Identification of Salmonella for public health surveillance using whole genome sequencing. PeerJ, 4, e1752. f) Ashton, P., Nair, S., Peters, T., Tewolde, R., Day, M., Doumith, M., et al. (2015). Revolutionising public health reference microbiology using whole genome sequencing: Salmonella as an exemplar. bioRxiv, 033225. g) Waldram, A., Dolan, G., Ashton, P. M., Jenkins, C., & Dallman, T. J. (2018). Epidemiological analysis of Salmonella clusters identified by whole genome sequencing, England and Wales 2014. Food microbiology, 71, 39-45. h) Mook P, Gardiner D, Verlander NQ, McCormick J, Usdin M, Crook P, Jenkins C, Dallman TJ. Operational burden of implementing Salmonella Enteritidis and Typhimurium cluster detection using whole genome sequencing surveillance data in England: a retrospective assessment. Epidemiol Infect. 2018 Jul 2:1-9. i) Vanessa Rew, Piers Mook, Suzan Trienkens, Kate S Baker, Timothy J Dallman, Claire Jenkins, Paul D Crook and Nicholas R Thomson. Whole-genome sequencing revealed concurrent outbreaks of shigellosis in the English Orthodox Jewish Community caused by multiple importations of Shigella sonnei from Israel. Microbial Genomics, 2018:4. j) Butcher H, Elson R, Chattaway MA, Featherstone CA, Willis C, Jorgensen F, Dallman TJ, Jenkins C, McLauchlin J, Beck CR, Harrison S. Whole genome sequencing improved case ascertainment in an outbreak of Shiga toxin-producing Escherichia coli O157 associated with raw drinking milk. Epidemiol Infect. 2016 Oct;144(13):2812-23. Epub 2016 Mar 10 k) Timothy J. Dallman, Marie A. Chattaway, Piers Mook, Gauri Godbole, Paul D. Crook, Claire Jenkins. Use of whole-genome sequencing for the public health surveillance of Shigella sonnei in England and Wales, 2015. 2016, Journal of Medical Microbiology 65: 882-884 l) Jansen van Rensburg MJ, Swift C, Cody AJ, Jenkins C, Maiden MC. Exploiting Bacterial Whole-Genome Sequencing Data for Evaluation of Diagnostic Assays: Campylobacter Species Identification as a Case Study. J Clin Microbiol. 2016 Dec;54(12):2882-2890. Epub 2016 Oct 12 m) J. Mcdonnell, T. Dallman, S. Atkin, D. A. Turbitt, T. R. Connor, K. A. Grant, N. R. Thomson And C. Jenkins. Retrospective analysis of whole genome sequencing compared to prospective typing data in further informing the epidemiological investigation of an outbreak of Shigella sonnei in the UK Epidemiol. Infect. (2013), 141, 2568–2575. Cambridge University Press 2013
Other	n) Website, Gastrointestinal bacteria reference unit (GBRU) https://www.gov.uk/guidance/gbru-reference-and-diagnostic-services o) Pathogen Genomics Into Practice, PHG Foundation, 2015.

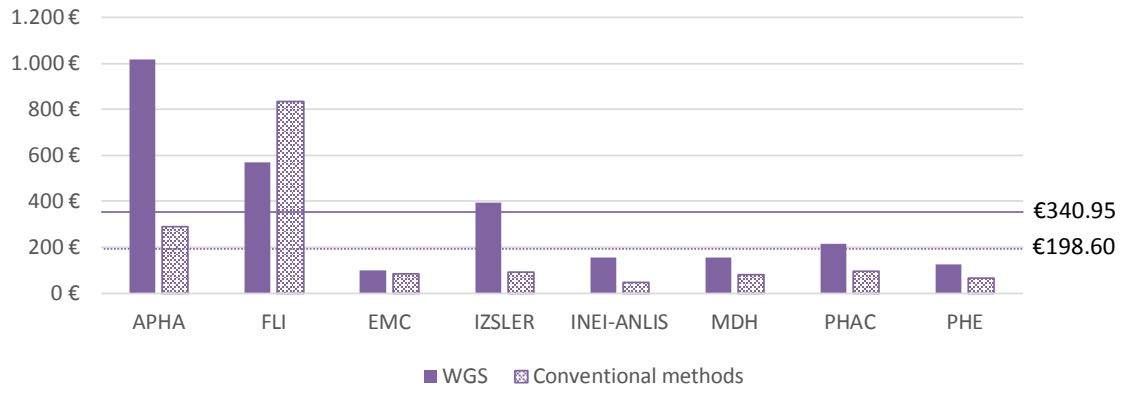
4. Results

This section presents first a summary of the final analysis of costs, and then the final analysis of benefits.

4.1. Analysis of costs

Overall per-sample costs of WGS exceed the costs of conventional methods in all reference laboratories analysed except in one (FLI), where a non-routine method - sequencing of a whole virus genome using Sanger sequencing - was chosen as comparator by the institution. Excluding this case, the use of WGS is between 1.2 and 4.3 times more expensive than the use of conventional methods, with a cost differential between EUR 15 and EUR 727 per sample. This is graphically illustrated below (average costs are indicated on the right side of this and the following figures, with the straight line representing average costs of WGS and the dotted line representing average costs of conventional methods).

Figure 2: Overall per sample costs, WGS vs conventional methods (in EUR)



The following table presents the costs of WGS and conventional methods according to cost type and indicates the additional costs of WGS for each case study. It also provides contextual information, such as the case study area (avian influenza, human influenza, foodborne pathogens), whether the samples were analysed in an outbreak or routine surveillance situation, the number of samples analysed in the reference period, and the batch size for sample processing/sequencing.

Table 3: Overview of per sample costs of WGS vs. conventional methods, by cost type

Case study area		Avian Influenza (HPAI)		Influenza A+B	Foodborne pathogens[a)]				
Institution		**APHA (UK)**	**FLI (DE)**	**EMC (NL)**	**IZSLER (IT)**	**INEI-ANLIS (ARG)**	**MDH (USA)**	**PHAC (CAN)**	**PHE (UK)**
Outbreak or routine surveillance		*Outbreak*	*Outbreak*	*Routine surveillance*	*Routine surveillance*	*Routine surveillance*	*Routine surveillance*	*Routine surveillance*	*Routine surveillance*
No. of samples in reference period		*26 (in 8 months)*	*30 (3 months)*	*630 (5 months)*	*175 (12 months)*	*320 (12 months)*	*1 767 (12 months)*	*8 630 (12 months)*	*15 791 (12 months)*
WGS									
Sequencer used		*Illumina MiSeq*	*IonTorrent PGM*	*Nanopore GridION*	*Illumina MiSeq*	*Illumina MiSeq*	*Illumina MiSeq*	*Illumina MiSeq*	*Illumina HiSeq*
Batch size for sample process./sequencing		*1-2*	*6*	*30*	*24*	*12*	*24*	*32*	*Processing: 40 Sequencing: 96*
Equipment		€ 58.53	€ 210.71	€ 2.50	€ 163.49	€ 43.02	€ 29.53	€ 75.90	€ 35.23
Consumables		€ 830.97	€ 254.88	€ 33.52	€ 165.37	€ 104.62	€ 104.40	€ 69.75	€ 53.92
Staff costs	*Prof.*	€ 39.63	€ 42.60	€ 15.95	€ 52.35	€ 6.85	€ 20.58	€ 61.82	€ 28.30
	Tech.	€ 87.50	€ 60.19	€ 42.83	€ 13.93	€ 0.00	€ 0.00	€ 7.89	€ 7.15
Other costs		€ 0.00	€ 0.00	€ 3.68[b)]	€ 0.00	€ 0.00	€ 0.00	€ 0.00	€ 0.00
Total per-sample cost WGS		**€ 1016.63**	**€ 568.37**	**€ 98.48**	**€ 395.14**	**€ 154.49**	**€ 154.51**	**€ 215.36**	**€ 124.59**
Conventional methods[c)]									
Method(s) used		*Sanger sequencing (HA/NA analysis)*	*Sanger sequencing (whole genome[d)])*	*PCR; Sanger sequencing (HA/NA); Virus isolation; HI; Virus neutra-lisation; NA STAR*	*Serotyping; PFGE; PCR; MLVA*	*Biochemical analysis; Serotyping; PCR typing; MaldiTOF; PFGE*	*PFGE; PCR; MaldiTOF*	*PFGE; Biochemical testing; Serotyping*	*PCR; MLVA; MLST; fAFLP; Serotyping; Phage typing; PFGE; D-Tartrate; Glucose gas; AMR; Biochemistry*
Equipment		€ 78.55	(€ 137.35)[d)]	€ 2.66	€ 26.04	n.a.	€ 5.84	€ 12.30	€ 7.11
Consumables		€ 21.91	(€ 360.88)[d)]	€ 34.39	€ 20.17	n.a.	€ 32.89	€ 34.95	€ 29.91
Staff costs	*Prof.*	€ 39.63	(€ 230.75)[d)]	€ 0.38	€ 3.52	n.a.	€ 42.43	€ 6.72	€ 2.92
	Tech.	€ 150.00	(€ 107.00)[d)]	€ 45.93	€ 25.88	n.a.	€ 0.00	€ 40.32	€ 23.85
Other costs		€ 0.00	(€ 0.00)[d)]	€ 0.00	€ 16.27	n.a.	n.a.	€ 0.00	€ 1.67
Total per-sample cost conventional methods		**€ 290.08**	**(€ 835.98)[d)]**	**€ 83.36**	**€ 91.87**	**€ 46.61**	**€ 81.16**	**€ 94.29**	**€ 65.46**
Cost difference between WGS and conventional methods									
Additional cost WGS		**€ 726.54**	**(- €267.61)[d)]**	**€ 15.12**	**€ 303.27**	**€ 107.88**	**€ 73.35**	**€ 121.07**	**€ 59.13**
Quotient of WGS over conventional methods		**3.5**	**(0.7)[d)]**	**1.2**	**4.3**	**3.3**	**1.9**	**2.3**	**1.9**

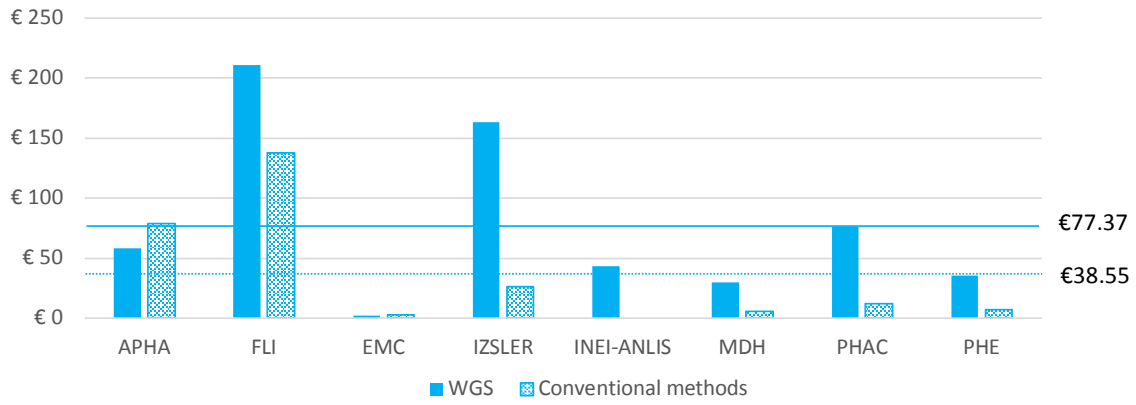
Source: Own compilation based on case study results. a) Foodborne pathogens: *Salmonella* (all), Listeria (IZSLER, PHE, PHAC, MDH), E.coli and shigella (PHE, INEI-ANLIS, MDH), Campylobacter (PHE, MDH), Vibrio (MDH). b) Costs for supplementary conventional tests that continue to be part of the WGS workflow c) Note that the cost of conventional methods is a weighted figure which accounts for the use rate of the various methods across the different pathogens. d) Sequencing of a whole genome of a virus using Sanger sequencing - as indicated by FLI as comparator method - is a resource-intensive process that has generally been replaced by next-generation sequencing, and Sanger sequencing would typically be used for the (more limited and less resource-intensive) HA/NA analysis (the comparator method used by APHA). The figures from the FLI case study are therefore placed in brackets and are provided for comparison purposes only. n.a. No further cost breakdown by cost type was available.

Table 1 gives an overview of the costs of WGS and conventional methods according to cost type, and specifies the additional costs of WGS for each reference laboratory. The total per-sample cost of WGS ranges from EUR 1 017 to EUR 98. An inverse

relationship can be observed between sample volume/batch size and total per-sample costs. Excluding the EMC case study (in which a lower-cost Nanopore sequencer was used), the total per-sample costs decrease almost uniformly across the table from left to right as the total sample volume increases. The exception to this trend is PHAC, where the more extensive bioinformatics infrastructure contributes to a substantially higher equipment and staff time cost. In general, reference laboratories with a low-throughput in (avian influenza) outbreak situations (APHA, FLI) have the highest per-sample costs for WGS, ranging between EUR 568 and EUR 1 017; reference laboratories that conduct routine surveillance of foodborne pathogens with a medium-throughput have moderate per-sample costs for WGS, ranging between EUR 154 to EUR 395; and reference laboratories that conduct routine surveillance of foodborne pathogens with a high-throughput have among the lowest per-sample costs for WGS at EUR 125 to EUR 215. The results of the case study at EMC (human influenza) suggest that lower cost per sample could also potentially be achieved at a medium batch size/sample volume through Nanopore sequencing, as the total per-sample costs in this case study (EUR 98) lie below even the costs calculated for the reference laboratory that had the highest throughput of samples and batch sizes during the reference period (PHE). The increasing returns to scale are visible to at least some extent in all major cost types (equipment, consumables and staff time). As shown in the table, other costs are only relevant in a few cases, and accrue, e.g. due to complementary tests or outsourcing of specific tests.

The case study institutions vary considerably with respect to the type and amount of **equipment** used for WGS. This is true not just for the choice of sequencer (Illumina MiSeq/HiSeq, IonTorrent PGM, or Nanopore GridION), but also for the degree of automation in sample processing and library preparation as well as for the degree of sophistication in the bioinformatics infrastructure (Supplementary Table S1 describes the type of equipment used by each of the case study institutions). The total purchase cost of equipment for the WGS workflow (not considering basic lab equipment) in the year of purchase ranges from a low of approx. EUR 75 000 for third-generation sequencing using the Nanopore GridION, including purchase of a dedicated server and other equipment, to a high of EUR 3.2 million for three Illumina MiSeqs and a top-of-the-line custom bioinformatics infrastructure. Overall, higher purchase costs tend to reflect higher throughputs (i.e. multiple sequencers, or higher-capacity sequencers such as the Illumina HiSeq) as well as greater investment in automation and/or bioinformatics capacity. As graphically depicted in the following figure, per-sample *equipment* costs are higher for WGS by a substantial margin in all but two of the case study institutions (APHA and EMC), when compared to the costs of conventional methods.

Figure 3: Per sample equipment costs, WGS vs conventional methods (in EUR)



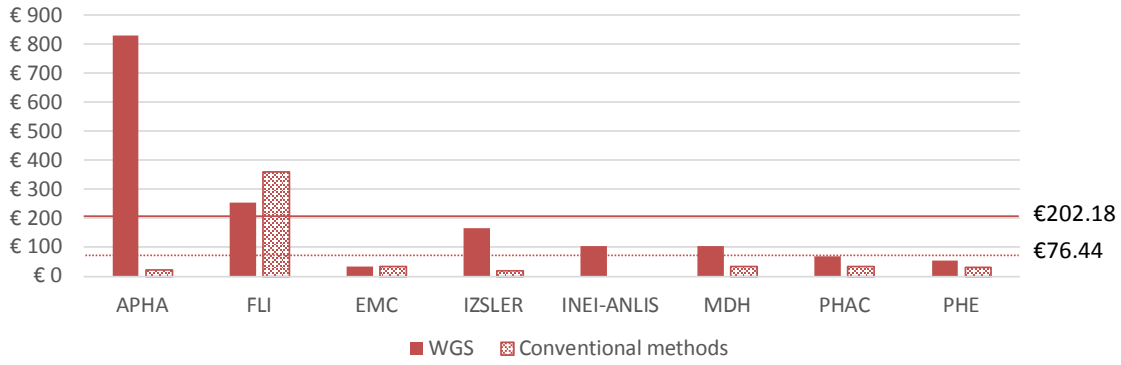
Note: For INEI-ANLIS, a breakdown by cost type was not possible for conventional methods.

This is particularly true for foodborne pathogen surveillance, where reference laboratories often rely on less costly equipment for conventional methods than in the

other areas, and therefore have a greater difference between the equipment costs for WGS and for conventional methods. For the reference laboratories dealing with avian influenza, where the alternative method (Sanger sequencing) requires the use of a sequencer comparable in original purchase price to next-generation sequencers, the difference in costs is relatively smaller (FLI) or even in favour of WGS (APHA). The difference between equipment costs for WGS and conventional methods is negligible for the case study using Nanopore sequencing (EMC). Note that these costs are also influenced by use rates of the respective equipment, which were considered in this exercise to ensure uniform cost accounting across case studies. For example, the very low per-sample equipment cost at EMC for sequencing (EUR 2.5) is due not only to the comparatively low costs of the GridION sequencer, but also to the fact that is was used only 25% of the time for the 630 samples analysed during the 5 months reference period (and 75% for other analysis).

Per-sample ***consumables*** costs are higher for WGS than for conventional methods in all but two reference laboratories (FLI, which used a non-routine method as comparator, and EMC, which used Nanopore sequencing and benefits from substantial institutional discounts, see below), and sometimes considerably so. For example, in the case of APHA, the consumables cost for WGS (EUR 831) is nearly 38 times the consumables cost for conventional methods (EUR 22), owing to the time-sensitivity of obtaining data for the index cases of an avian influenza outbreak. In addition the consumables used for Sanger sequencing are both cheaper and utilisable for larger batch sizes. This is illustrated in the following figure.

Figure 4: Per sample consumables costs, WGS vs conventional methods (in EUR)



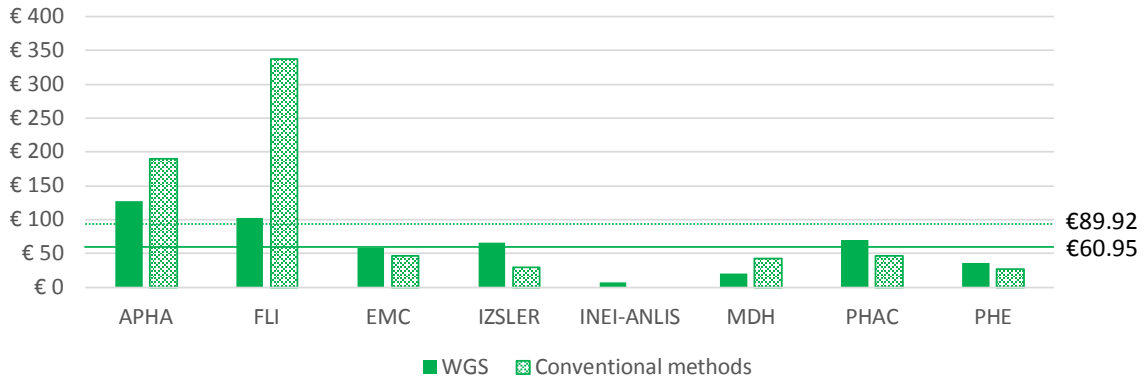
Notes: For INEI-ANLIS, a breakdown by cost type was not possible for conventional methods. FLI used a non-routine method as comparator (sequencing of a whole genome of a virus using Sanger sequencing). In contrast, APHA used the more limited and less resource-intensive HA/NA analysis, a more typical conventional method for routine analysis.

The determining factor is the higher cost of kits and reagents required for WGS, with a specific cost driver in this context being again the overall throughput in terms of number of samples and the batch size for sequencing. The total per-sample consumables cost decreases as the average throughput and batch size increases. Notably, however, the EMC case study with Nanopore sequencing and a medium-throughput shows per-sample consumables costs (EUR 34) that actually lie below the costs of reference laboratories with a much higher throughput of samples for sequencing during the reference period. However, this may also be due to other factors: EMC reported that substantial institutional discounts on consumables (as well as equipment) could be obtained through negotiation with suppliers to buy in bulk. For example, EMC was able to obtain discounts of up to 60% over the list price for key consumables and WGS equipment by joining together with other university hospitals and collectively negotiating with the suppliers. Dependency on specific consumables for sequencing was noted by several of the reference laboratories as a key factor driving costs, making WGS currently less affordable. INEI-ANLIS in particular highlighted this as a serious problem. The costs of kits and reagents were reported to

be much higher in Argentina, making it cheaper to purchase kits in the USA in the framework of an international pilot project.

With respect to **staff costs**, hands-on staff time estimates per sample differ considerably between case study institutions. Estimates of professional staff time per sample for WGS range from 18 to 90 minutes (with the costs ranging from EUR 7 to EUR 62), while estimates of technician staff time per sample for WGS range from 0 to 210 minutes (with associated costs between EUR 0 and EUR 88). The following figure provides an overview of per-sample staff costs.

Figure 5: Per sample staff costs, WGS vs conventional methods (in EUR)



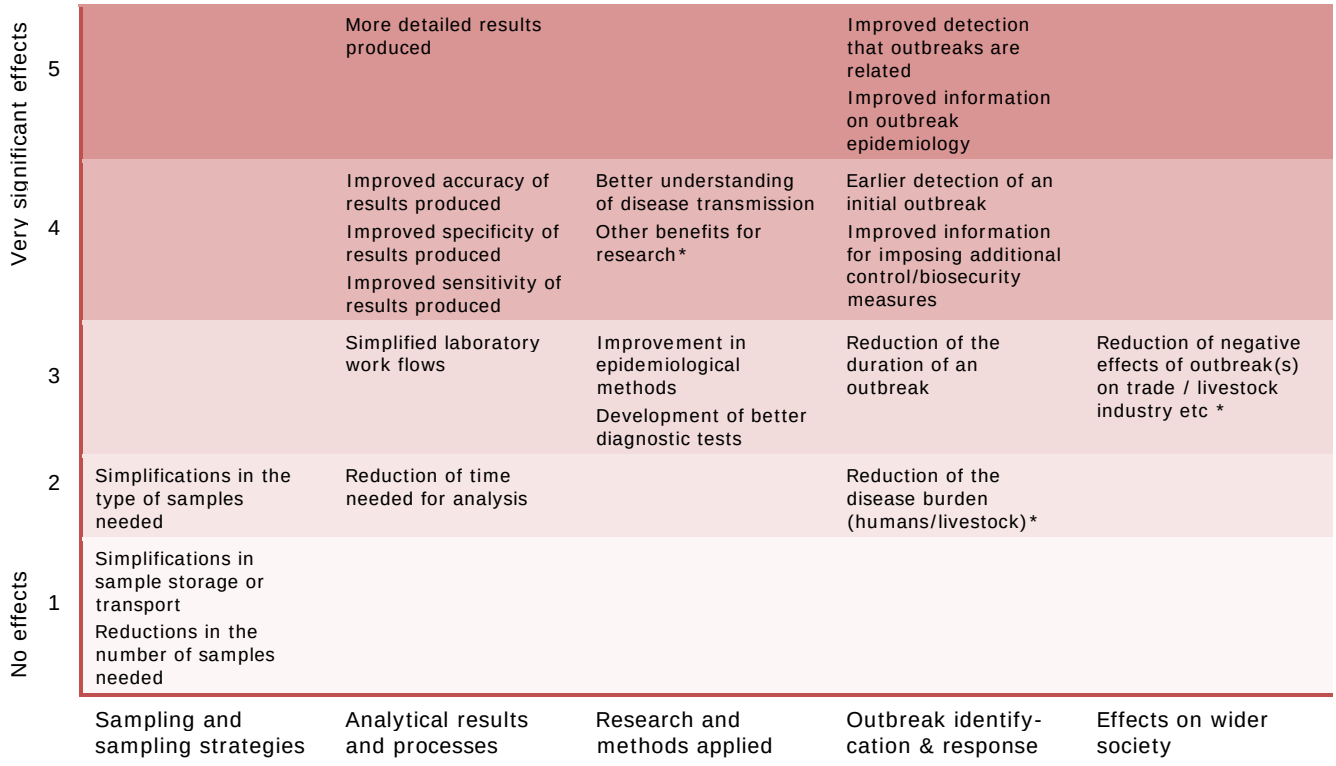
Note: For INEI-ANLIS, no breakdown by cost type was possible for conventional methods.

For four of the case study institutions, staff costs are lower for conventional methods than for WGS. They are, however, much higher for conventional methods used in the two reference laboratories dealing with avian influenza. This is most likely a consequence of the lower batch sizes due to the outbreak context, the more complex and time-intensive steps involved in Sanger sequencing (the conventional method used in these case studies) as well as the greater involvement of professional staff required. In contrast, the conventional methods used by reference laboratories for foodborne pathogen surveillance tend to be more straightforward (e.g. PCR or MLVA analysis, each requiring less than 10 minutes of staff time) and rely often entirely on technician staff rather than professional staff. In addition to the batch size, the level of automation emerges as another key cost factor with respect to staff time demands of using WGS. The lowest total staff time requirements in the pre-bioinformatics stages were consistently achieved by PHE, which also has the highest level of automation in these stages. The high level of automation at PHE appears to have the effect of generating considerable savings with respect to technician time in particular. Finally, the comparatively low staff costs for WGS in the case of MDH is due to the use of online tools for sequencing analysis (www.genomicepidemiology.org), which were partly developed through the COMPARE project. MDH reported an average professional staff time for the bioinformatics analysis of only 15 minutes per sample – markedly lower than the other case study institutions except EMC (which also reported a similarly low figure of 12 minutes).

4.2. Analysis of benefits

All eight reference laboratories reported major benefits of using WGS for pathogen identification and surveillance. Benefits were experienced in different areas, most notably with respect to analytical results/processes and outbreak identification/ response, but also related to sampling and sampling strategies, research and methods applied, and effects on wider society (see detailed discussion below). The following figure presents the extent to which key positive effects of using WGS were observed during the reference period. Effects shown towards the top of the figure were indicated by the reference laboratories to be more significant.

Figure 6: Key positive effects of using WGS as experienced by case study institutions



*Notes: Case study institutions were asked to assess specific positive effects or impacts of using WGS on a scale from 1 (no effect at all) to 5 (very significant positive effect). Effects are indicated in the above figure based on average assessments. * Only four or fewer case study institutions provided an assessment*

Effects on sampling and sampling strategies

As indicated in the figure above, most of the reference laboratories did not observe effects on sampling and sampling strategies. One of the reasons was that sampling is mostly not within their purview, as samples are independently collected by external institutional partners and sent to the case study institutions for further analysis. However, one of the reference laboratories active in foodborne pathogen surveillance reported that the introduction of WGS has resulted in changes to how food safety officials conduct sampling (i.e. by moving from finished product testing to environmental sampling).

Effects on analytical results and processes

Most of the reference laboratories experienced considerable positive effects of using WGS with respect to the quality of the results produced in terms of detail, accuracy, specificity, and sensitivity. For example, in the context of avian influenza identification and surveillance, the use of WGS provides many sequence reads, resulting in higher accuracy and greater statistical confidence in the outputs, and allowing viral genome-spanning information to be rapidly obtained regarding genotype, pathotype, and mutations. For foodborne pathogens, WGS analysis provides insights into how bacterial strains diversify over time, allowing strains to be identified as linked when under previous methods they would have been considered unrelated. It also allows for the investigation of resistance gene profiles.

Positive effects on laboratory processes and resources were reported to be mostly negligible by the reference laboratories dealing with avian and human influenza. In contrast, the reference laboratories that use WGS in the context of routine surveillance of foodborne pathogens emphasised the simplification of laboratory workflows, especially with respect to the reduction of the number of hands-on steps

for analysis. In a report published in August 2018[23], PHE outlined the following specific effects on the streamlining of laboratory processes experienced since adopting WGS:

- At least 10 different validated processes for different bacteria had been replaced with WGS;
- Pathogens were being processed in fewer rooms (e.g. *Salmonella* samples were now being processed in one room rather than travelling through nine different laboratories); and
- Samples containing live organisms now required fewer hands-on interactions (from being handled 7-9 times before WGS to 2 times after WGS), reducing accident risks for laboratory staff.

PHE also indicated that WGS had improved laboratory management, reporting that replacing conventional methods with WGS made it easier to monitor its own laboratory processes, predict costs, and identify ways to reduce costs in the future.

For all institutions, the use of WGS also affected the *turnaround time*, defined as the usual number of days of work from receipt and opening of an incoming sample to the reporting of the results:

- For the reference laboratories dealing with avian and human influenza, the turnaround time ranged between 2 and 5 days of work for WGS analysis (and as low as 10 hours using Nanopore sequencing), compared to 1-2 days for HA/NA analysis or 8 days for analysis of a whole genome using Sanger sequencing;
- For the foodborne pathogen case studies, the usual turnaround time was 5-10 days for WGS analysis. The turnaround time for the full analysis of a foodborne pathogen using conventional methods was typically 4-15 days, depending on the pathogen and analysis required.

The differential effect of WGS on turnaround time depends on the level of information needed about the pathogen and thus the complexity of the conventional analysis that would be required. The turnaround time for conventional methods increases based on the amount of information required and the corresponding number of different tests (especially consecutive tests) that are needed, while the turnaround time for WGS analysis remains relatively constant. Consequently, the turnaround time for WGS tends to be higher than the turnaround time for conventional methods when only basic information about the pathogen is needed, and lower when more a detailed characterisation is required.

Effects on research and epidemiological methods

Most reference laboratories experienced positive effects of using WGS in terms of understanding of disease transmission, and several reported that it had led to improvements in epidemiological methods. With respect to the analysis of viruses, the benefits of using WGS included obtaining more detailed genetic information regarding virus strains and how these evolve. As viruses mutate particularly quickly, WGS can be used to identify novel viruses, reassortants, and mixed infections that would be missed by other methods. In the foodborne disease context, WGS has improved the microbiological understanding of pathogens as well as understanding of their transmission pathways, e.g. with respect to enteric pathogens[24]. Another example of

[23] Grant, K., Jenkins, C., Arnold, C., Green, J., & Zambon, M. (2018). *Implementing pathogen genomics. A case study.* Public Health England. p. 22.

[24] Grant, K., Jenkins, C., Arnold, C., Green, J., & Zambon, M. (2018). *Implementing pathogen genomics. A case study.* Public Health England. p. 23-4.

WGS research applications in a non-outbreak context was a study by one of the case study institutions that focused on environmental sampling for Listeria along the production chain for ham using WGS[25]. The analysis indicated at which stages in the production chain and on which types of environmental surfaces contamination was most likely to occur. Clonal contamination patterns were also examined to draw insights on transmission within and between plants, as well as assess the efficacy of hygiene measures through repeated sampling more than six months later.

A minority of the reference laboratories also observed positive effects of WGS on the development of better diagnostic tests, e.g. by evaluating the robustness of real-time PCR assays[26], or using WGS in the development of new PCR assays (as reported by PHE). Other reported benefits for research mostly related to the large amount of sequence data available through WGS, which can be explored for further research. WGS makes it easier for reference laboratories to collaborate internationally, as genome sequences can be sent more quickly and easily than physical samples. Genomic data can also be stored indefinitely, and can be mined again as new genes or other genetic elements become relevant.

Effects on outbreak detection and response, including wider effects

All eight reference laboratories experienced clear positive effects of using WGS in terms of improved detection that outbreaks are related and improved information on outbreak epidemiology. WGS 'makes a striking difference in pathogen typing and source attribution', as one noted. Several case study institutions indicated a clear effect of using WGS on the number and size of clusters detected, with a larger number of smaller outbreaks being identified. In a 2018 publication aiming to quantify the operational burden associated with the use of WGS for cluster analysis of two *Salmonella* serovars, PHE determined that during a one year period between 2014 and 2015, WGS had identified a notably larger number of both *Salmonella* Enteritidis and *Salmonella* Typhimurium clusters than conventional methods[27]. While PHE reported that it currently did not have the resources to investigate all the clusters uncovered with WGS, it expected that resolving more outbreaks through the use of WGS would eventually lead to an overall reduction in the disease burden. PHAC reported that the number of *Salmonella* Enteritidis outbreaks detected increased substantially from less than 20 each year between 2012 and 2016 to more than 100 in 2017, the first year with routine use of WGS. PHAC also reported, however, that the number of *Listeria* outbreaks detected had actually decreased in the first year of WGS implementation, as PFGE had previously been detecting outbreaks that did not exist, leading to an inefficient use of resources investigating non-existent outbreaks. Other case study institutions confirmed that WGS is helping them in the identification of real outbreaks, thereby preventing false alerts.

The practical benefits of using WGS in an outbreak context were documented by several of the reference laboratories with respect to specific outbreaks, including in terms of the earlier detection of outbreaks of foodborne pathogens and linkage to the

[25] Morganti, Marina, Erika Scaltriti, Paolo Cozzolino, Luca Bolzoni, Gabriele Casadei, Marco Pierantoni, and others, 'Processing-Dependent and Clonal Contamination Patterns of Listeria Monocytogenes in the Cured Ham Food Chain Revealed by Genetic Analysis', *Applied and Environmental Microbiology*, 82 (2015), 822–31.

[26] Jansen van Rensburg MJ, Swift C, Cody AJ, Jenkins C, Maiden MC. Exploiting Bacterial Whole-Genome Sequencing Data for Evaluation of Diagnostic Assays: Campylobacter Species Identification as a Case Study. *J Clin Microbiol.* 2016 Dec;54(12):2882-2890.

[27] Mook, P., et al. (2018). Operational burden of implementing *Salmonella* Enteritidis and Typhimurium cluster detection using whole genome sequencing surveillance data in England: a retrospective assessment. *Epidemiology and Infection*, 1-9.

sources of the outbreak. For example, the retrospective analysis of a 2013 outbreak of *Salmonella* in Italy by IZLER provides evidence that the use of WGS would have allowed for human cases to be linked to the source of the outbreak much earlier than had been possible at the time using conventional methods. With WGS, the first isolates unambiguously linking human cases to the salami facility which had been the source of the outbreak were available more than a month in advance of the outbreak onset (as identified based on incidence) and more than 2 months before the source had been identified using PFGE and MLVA[28]. A specific benefit of WGS was reported with respect to so-called 'slow-burn' outbreaks with low case numbers but continuous transmission over a long period of time which are often not identified with traditional statistical methods. In a case reported by PHAC, the use of WGS allowed for the identification of 17 separate outbreaks of *Salmonella* Enteritidis associated with the same food (raw frozen breaded chicken products), which had not been picked up with conventional methods. Data provided by WGS allowed for stricter, Canada-wide regulations to be adopted for this product category, which was estimated by PHAC to be responsible for up to 40% of the disease burden attributable to *Salmonella* Enteritidis[29]. Similarly, an outbreak of *Salmonella* Enteritidis in reptile feeder mice in the UK might not have been detected at all without WGS due to the low case numbers[30]. The outbreak was detected in 2015 following the implementation of SNP typing at PHE, and had been occurring undetected by traditional surveillance procedures since at least January 2012. The results of the epidemiological investigation initiated on basis of the WGS data allowed for the identification of the outbreak source (handling of the feeder mice or snakes infected by the mice) and to subsequently issue a series of recommendations to control infections at the farm level and point of sale. Both cases provide clear evidence that the use of WGS has led in practice to a reduction in the disease burden in humans, because measures were taken to end the (previously undetected) outbreaks. Whether or not WGS leads to earlier detection of outbreaks depends, however, on the point in time that WGS is used in the analytical process. In a 2016-17 HPAI outbreak in Germany (reported by FLI) and a 2016 *Shigella sonnei* outbreak in Buenos Aires (reported by INEI-ANLIS), the use of WGS did not lead to an earlier detection, as sequencing was only conducted after the outbreak had been detected through conventional methods. But even in these and similar cases, the use of WGS allowed for a better linkage to the sources of the outbreak, as confirmed by several case study institutions.

Finally, the outbreak cases analysed (in the context of the avian influenza and foodborne pathogen case studies) confirm that WGS provides better information for imposing control measures and for assessing the effectiveness of the measures taken. For example, a reference laboratory dealing with avian influenza reported that the data provided by WGS enabled them to better assess the public health risk of an outbreak by revealing whether particular avian influenza strains included mutations that could pose a risk of transmission to humans (compared to the previous situation when HA/NA analysis with Sanger sequencing was used). The use of WGS also allowed for confirmation of whether cases of avian influenza in domestic poultry occurred through introduction by wild birds, or also through secondary infections between

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[28] Morganti, M., et al. (2018). Rise and fall of outbreak-specific clone inside endemic pulsotype of *Salmonella* 4,[5],12:i:-; insights from high resolution molecular surveillance in Emilia-Romagna, Italy, 2012 to 2015. Eurosurveillance, 23(13), 1–11

[29] Public Health Agency of Canada (2019), Public Health Notice - Outbreaks of *Salmonella* infections linked to raw chicken, including frozen raw breaded chicken products. https://www.canada.ca/en/public-health/services/public-health-notices/2018/outbreaks-*Salmonella*-infections-linked-raw-chicken-including-frozen-raw-breaded-chicken-products.html.

[30] Kanagarajah, S., et al. (2018). Whole genome sequencing reveals an outbreak of *Salmonella* Enteritidis associated with reptile feeder mice in the United Kingdom, 2012-2015. Food Microbiology, 71, 32-38.

farms, indicating the presence of gaps in farm biosecurity measures[31,32]. WGS data provided additional information (e.g. on clusters and possible sources) that helped to determine possible transmission routes, concerning e.g. whether a subsequent infection on the same farm was the result of inadequate cleaning measures or a separate introduction. One of the case study institutions (APHA) concluded that the use of WGS had reduced negative effects on livestock industry and trade as well as improved the overall biosecurity of the country. Similar experiences were reported by case study institutions dealing with foodborne pathogens. For example, in the case of a large EU-wide *Salmonella* outbreak in eggs, measures had been taken to address the problem, but WGS was able to identify the re-emergence of human cases, indicating that the issue had not yet been resolved. With previous typing methods it would not have been possible to show that it was the same strain with the level of certainty provided by WGS.

[31] Conraths, F. J. (2017). Making worst case scenarios real: The introduction of highly pathogenic avian influenza of subtype H5N8 led to the largest fowl plague outbreak ever recorded in Germany. *Lohmann Information*, 51(1), 36–41; Conraths, F. J., et al. (2017).

[32] Epidemiologie des aktuellen Geflügelpestgeschehens in Deutschland [Epidemiology of the current incidence of avian influenza in Germany], presentation given at the meeting of the Gesellschaft der Förderer und Freunde für Geflügel- und Kleintierforschung e.V. at the Institut für Tierschutz und Tierhaltung in Celle on 3 May 2017.

5. Break-even analysis for the case of Salmonella

This section presents the results of the breakeven analysis, which applies a cost of illness approach to determine the number of cases of illness that would need to be avoided through the use of WGS in order for the introduction of WGS to be cost-neutral from a public health perspective. It first provides contextual information on the burden of illness for the chosen pathogen (Salmonella) in the case study countries. The cost of illness is calculated. The results of the breakeven analysis are then presented and discussed in relation to the burden of illness.

As discussed in the previous section, the use of WGS for pathogen identification and surveillance is considered by the case study institutions to have positive effects on analytical results and processes (e.g. through providing higher-definition results) and on outbreak investigation and response (e.g. through improved epidemiological analysis). In the long run, the use of WGS is expected to lead to a reduction in the number of cases of illness, and thus in the disease burden, due to a better-targeted response. The breakeven analysis presented in this section aims to estimate the number of cases of illness that would need to be avoided each year through the use of WGS in order to 'break even' on costs, i.e. in order to make the use of WGS cost-neutral.

The breakeven analysis calculates the cost of illness in terms of health care utilisation costs, productivity loss, and premature death, and compares this to the additional cost of using WGS. As the analysis focuses only on offsetting the cost of illness and does not take into account additional benefits of using WGS for pathogen identification and surveillance in terms of e.g. effects on research, trade, or industry, its results should be understood to be a conservative estimate.

The costs of illness are pathogen-specific, and therefore the breakeven analysis is carried out at the pathogen level. The assessment focuses on *Salmonella*, as all case study institutions in this study dealing with foodborne pathogens use WGS to sequence *Salmonella* samples. There is also an existing European and international body of work dealing with the costs of salmonellosis infection in depth,[33] making this pathogen the most suitable candidate for the breakeven analysis.

Data on confirmed cases of salmonellosis is essential for the breakeven analysis by indicating the scale of the burden of illness. Data on confirmed salmonellosis cases is presented in the following table for the geographical jurisdictions covered by each case study institution, including data on the approximate number of annual hospitalisations and deaths where this information is available.

[33] Burden of illness and cost of illness estimations for *Salmonella* have been made by public health authorities such as DG SANCO in the EU, the Centers for Disease Control and Prevention (CDC) and US Department of Agriculture (USDA) in the United States, PHAC in Canada, and the Food Standards Agency in the UK. These estimates are cited in the following subsections.

Table 4: Burden of illness (salmonellosis), by case study jurisdiction

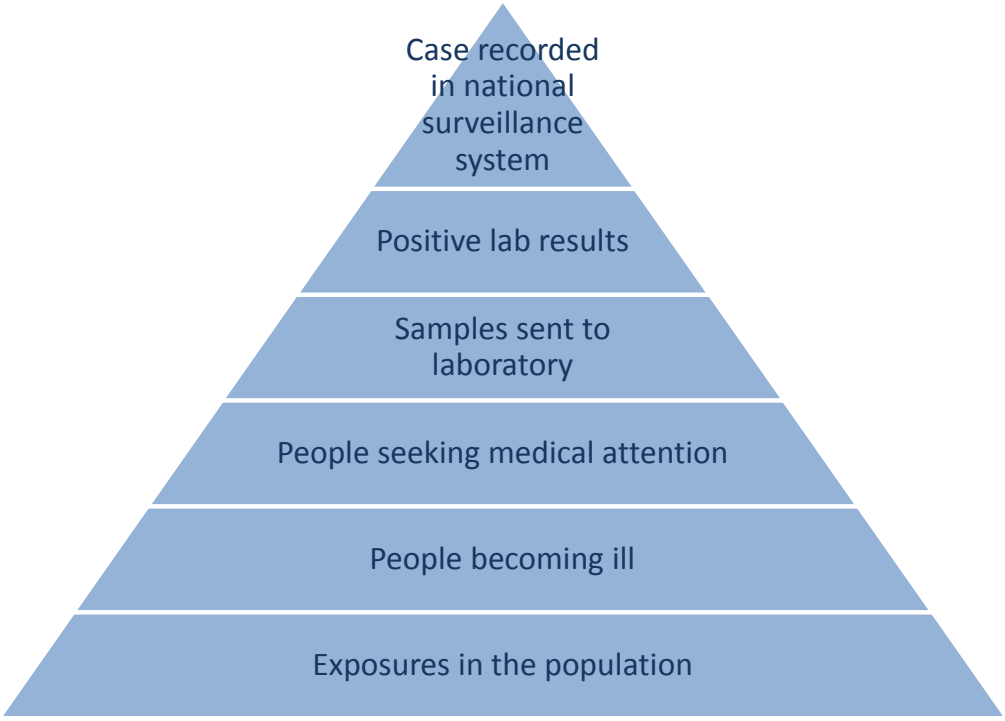
Case study jurisdiction	Number of cases reported annually (3-yr average)	Approx number of hospitalisat-ions reported annually	Approx number of deaths reported annually
Italy – Emilia-Romagna (IZSLER)	276 *	n.a.	n.a.
Argentina (INEI-ANLIS)	758	n.a.	n.a.
UK – England, Wales and Northern Ireland (PHE)	8 770	968 *	52 *
Canada (PHAC)	7 665	925	17
US - Maryland (MDH)	906	273	3

Sources: IT - ECDC (2018), *The European Surveillance System (TESSy)*; UK - PHE (2018), *Salmonella data 2007 to 2016* and ECDC (2018), *The European Surveillance System (TESSy)*; CAN - PHAC (2018), *Reported cases from 1924 to 2016 in Canada - Notifiable diseases on-line* and PHAC (2016), *Yearly food-borne illness estimates for Canada*; US - CDC (2018), *FoodNet Fast*; Argentina - *Laboratory Surveillance System (SIVILA) of the National Health Surveillance System*. Notes: Data provided on cases of salmonellosis refer to the geographical jurisdictions of the institution as indicated in the case study report. Where a case study institution processes samples originating from the whole country (Canada, Argentina), data on salmonellosis refer to the country as a whole. Where a case study institution only processes samples from a specific geographical region within a country, data on salmonellosis refer to this particular region (England, Wales and Northern Ireland in the UK, Emilia-Romagna in Italy, and Maryland in the US). * Regional data approximated as a population-based proportion of national data, as no regional data was available.

The table above shows how the burden of illness varies across case study jurisdictions. In the largest jurisdiction by population, England, Wales and Northern Ireland (PHE), an average of 8 770 confirmed salmonellosis cases were reported annually between 2015 and 2017, of which approximately 968 were serious enough to require hospitalisation and 52 resulted in the death of the patient. In contrast, in the smallest jurisdiction by population, the Italian region of Emilia-Romagna (IZSLER), an average of 276 cases were reported annually between 2015 and 2017, and no data is available on the number of associated hospitalisations or deaths.

However, it is important to note that confirmed cases of salmonellosis as presented in the table above are not equivalent to the total number of cases in the community, and understate the actual prevalence of salmonellosis (and thus the actual burden of disease) in any given jurisdiction. Although salmonellosis is a notifiable disease, meaning that confirmed cases of infection are required by law to be reported to public health authorities, a number of steps must be achieved in order for the case to be recorded in national surveillance statistics. The relationship between the (observed) number of reported cases and the (unobserved) total number of infections or exposures in the community can be illustrated through the use of surveillance pyramid, such as the one depicted below.

Figure 7: Surveillance pyramid for nofitiable diseases (foodborne pathogens)



Source: Adapted from EFSA, *Scientific Opinion of the Panel on Biological Hazards on a request from the European Commission on a quantitative microbiological risk assessment on Salmonella in meat* (2008), and the CDC's *Foodborne Diseases Active Surveillance Network (FoodNet)* (2015).

As shown in the surveillance pyramid above, cases are only recorded in national statistics where the patient has chosen to seek medical attention, and where a sample has been taken by the health care provider and produced a positive result. This means that 'mild' cases of salmonellosis, in which patients simply recover at home and do not seek out medical care, are excluded from national statistics by definition. Even where patients do seek out medical care, cases will only be included in national statistics for salmonella when the health care provider takes a clinical sample, and where the laboratory results are positive for salmonella (instead of e.g. inconclusive). As a result, the number of confirmed cases of salmonellosis reported in national statistics are only a subset of total cases in the community.

Previous studies have generated multipliers at key levels of the surveillance pyramid in order to estimate the unobserved number of cases in the community. In the EU, for example, these community multipliers have been estimated to range between 3.2 and 16.5, with an average value of 7.3.[34] This estimate suggests that for every 1 case recorded in national statistics, there are approximately 7.3 cases occurring in the community, most of which remain unreported. Given the assumptions and uncertainties involved in calculating the total burden of illness based on community multipliers, we have chosen to focus only on *confirmed* cases of salmonellosis in the breakeven analysis. The fact that a larger number of cases are estimated to go unreported, however, means that the results derived in the following subsection reflect highly conservative estimates of the burden of illness.

[34] DG SANCO, *Analysis of the costs and benefits of setting a target for the reduction of Salmonella in breeding pigs* (2011), p. 23-6.

5.1. Cost of illness calculation

Calculating the average cost of a foodborne illness is a highly complex task which requires non-trivial choices to be made regarding which cost elements to include and which elements to leave out. Our approach closely follows (with some adaptations) the methodology used in the cost-benefit analyses of reducing *Salmonella* in breeding pigs and slaughter pigs, which were conducted for DG SANCO in 2010 and 2011 in close coordination with the European Food Safety Authority (EFSA).[35] It also draws on the latest cost of illness model developed by the US Department of Agriculture (USDA).[36]

Salmonellosis infections can result in a number of different outcomes for patients, ranging from mild cases (in which the patient does not seek medical care and recovers at home) to severe cases (in which the patient is hospitalised). In rare cases, salmonellosis infections can also result in death. In order to calculate the cost of illness for an 'average' salmonellosis infection, our approach divides these potential outcomes into different 'severity levels'. Each severity level is associated with different costs, which result from different levels of health care utilisation, time missed from work, and the cost of premature death. After calculating the costs for each severity level, the costs per severity level are then weighted by the relative likelihood of each outcome in order to come up with one 'average' cost of a salmonellosis infection.

Following the approach used in the EC study and the USDA's cost estimates, the cost of illness model for *Salmonella* distinguishes between four different severity levels for the outcome of a salmonellosis infection:[37]

- Level 1: The patient does not visit a physician and recovers from the infection.
- Level 2: The patient visits a physician and subsequently recovers from the infection.
- Level 3: The patient is hospitalised and subsequently recovers from the infection.
- Level 4: The patient is hospitalised and dies.

The four possible outcomes can be illustrated in the form of an infection tree, along with estimates of the relative outcome distribution (i.e. what proportion of cases will result in each outcome). We use the same outcome distributions as the 2011 DG SANCO study,[38] which was adapted for the European context from the USDA model[39] based on consultations with the public health authorities of EU Member States. The *Salmonella* infection tree with the outcome distribution among the severity levels is presented in the figure below.

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[35] DG SANCO/FCC Consortium (2010), *Analysis of the costs and benefits of setting a target for the reduction of Salmonella in slaughter pigs – Final report*; DG SANCO/FCC Consortium (2011), *Analysis of the costs and benefits of setting a target for the reduction of Salmonella in breeding pigs – Final report*.

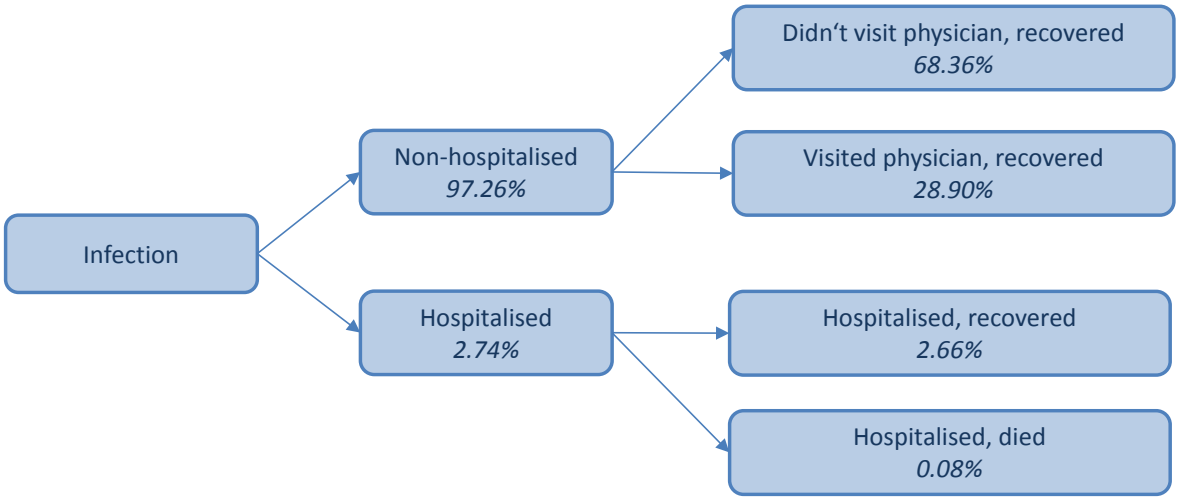
[36] USDA Economic Research Service (2014), *Cost estimates of foodborne illnesses*. https://www.ers.usda.gov/data-products/cost-estimates-of-foodborne-illnesses.aspx

[37] In order to simplify the analysis, it is assumed that the patients with outcomes of severity levels 1-3 make a full recovery and do not suffer from longer-term effects (chronic sequelae) such as reactive arthritis.

[38] DG SANCO/FCC Consortium (2011), *Analysis of the costs and benefits of setting a target for the reduction of Salmonella in breeding pigs – Final report*, p. 23-8.

[39] The USDA cost of illness model assumes different outcome distributions than the ones used in the 2011 DG SANCO study, which would have a - notable effect on the results if applied. See the discussion regarding sensitivity analysis.

Figure 8: Infection tree for Salmonella with outcome distribution



Source: Adapted from DG SANCO/FCC Consortium (2011), *Analysis of the costs and benefits of setting a target for the reduction of Salmonella in breeding pigs – Final report*.

As shown in the figure above, the most common outcome for a salmonellosis infection is that the patient does not visit a physician and makes a full recovery (68.4% of cases), followed by the outcome in which the patient visits a physician and then recovers (28.9% of cases). In total, therefore, the vast majority of salmonellosis cases (97.3%) do not result in hospitalisation. An estimated 0.08% of total infections result in the death of the patient.

As indicated previously, each of the four severity levels are associated with different levels of costs. The following three types of costs are considered in the cost of illness model:

- Health care utilisation;
- Productivity loss; and
- Premature death.

The following subsections address each of these cost types in turn.

5.2. Health care utilisation

Health care utilisation costs include the costs of physicians' visits, emergency room visits, outpatient clinic visits, and hospitalisation. In order to calculate the health care utilisation costs per severity level, we first estimate the type and amount of health care services accessed by patients at each severity level, and then multiply this by the unit cost for each type of health care service. As health care costs vary across jurisdictions, the unit cost of various health care services is estimated separately for each case study country.

For estimating the amount of health care services used at each severity level, we use the service utilisation assumptions by Frenzen et al (1999),[40] which have been used without adaptation in both the DG SANCO studies and the USDA estimates. These assumptions are presented for each severity level in the following table.

[40] Frenzen et al (1999), '*Salmonella* Cost Estimate Updated Using FoodNet Data.' *FoodReview* (22)2: 10-15.

Table 5: Health care service utilisation assumptions, by severity level

Severity level	Physicians' visits	Emergency room visits	Outpatient clinic visits	Hospitalisation
Didn't visit physician, recovered	0	0	0	0
Visited physician, recovered	1.4	0.1	0.3	0
Hospitalised, recovered	0.7	0.3	0.2	1.0
Hospitalised, died	1.0	0.3	0.2	0.9

Source: Frenzen et al (1999), '*Salmonella* Cost Estimate Updated Using FoodNet Data.' *FoodReview* (22)2: 10-15.

As shown in the table above, the lowest severity level (didn't visit physician, recovered) is assumed to make no use of health care services, while the three higher severity levels are assumed to make at least some use of various health care services depending on the severity of the case.

The unit costs for each form of health care service accessed have been adapted from the 2010 DG SANCO study and inflated to 2017 (Euro) values using Eurostat's labour cost index.[41] Average costs at the EU28 level are considered to form the 'base costs'. In order to adjust these base costs for each of the case study countries, the base costs are multiplied by a country index for each of the foodborne surveillance case studies, which is based on the ratio of average gross earnings in each country to the EU28 average.[42] An exception to this approach is the USA, as the USDA has provided its own cost estimates for the exact same service types in the context of a nearly-identical model; in this case, the USDA estimates are converted into EUR and taken as given. The table below shows the unit cost assumptions for health care services used for each case study country, with the EU28 base costs presented for reference.

[41] Eurostat, *Labour cost index by NACE Rev. 2 activity - nominal value, annual data* [lc_lci_r2_a]. Extracted 14 January 2019. The Eurostat labour cost index was used in the 2010 and 2011 DG SANCO studies to inflate service utilisation costs and is used here for the same purpose, as the consumer price index (HICP) focuses on consumer goods and is not considered appropriate for health care costs.

[42] Source of data for average gross earnings is Eurostat, *Annual net earnings* [earn_nt_net] (using 'Gross earnings' variable) extracted 14 January 2019, for the UK, Italy, and the USA; and ILOSTAT (Average monthly earnings of employees) for Canada and Argentina. The index is constructed around a base value of EU28 = 1.00.

Table 6: Unit cost assumptions for health care services, by case study country (in EUR 2017)

Case study country	Country index	Physicians visit	Emergency room visit	Outpatient clinic visit	Hospitalisation
EU28 (Base)	1.00	€ 28.41	€ 113.65	€ 170.47	€ 2 841.15
UK	1.42	€ 40.45	€ 161.81	€ 242.71	€ 4 045.13
Italy	0.88	€ 24.99	€ 99.96	€ 149.94	€ 2 498.95
Canada	0.93	€ 26.53	€ 106.11	€ 159.16	€ 2 652.68
US	N/A	€ 110.47	€ 465.53	€ 535.32	€ 11 325.15
Argentina	0.21	€ 6.01	€ 24.03	€ 36.04	€ 600.64

Source: Base values adapted from DG SANCO/FCC Consortium (2010), *Analysis of the costs and benefits of setting a target for the reduction of Salmonella in slaughter pigs – Final report,* p. 90. Country index for Canada and Argentina compiled based on wage costs from ILOSTAT, Annual monthly earnings of employees. USA cost figures are taken from USDA Economic Research Service (2014), *Cost estimates of foodborne illnesses*, converted to EUR and inflated to 2017 using Eurostat's labour cost index [lc_lci_r2_a].

As the table above shows, hospitalisation has the highest unit cost among the various health care services, with a base cost of EUR 2 841 for the EU28. Physicians' visits are the least costly, with a base cost of EUR 28.41. Based on the data provided by the USDA, unit costs for health services in the USA are markedly higher than in the other case study countries, with unit costs ranging from EUR 110 for a physicians' visit to EUR 11 325 for hospital admittance.

The country-adjusted service utilisation costs in the table above are multiplied by the service utilisation rates in the previous table to generate the total health care utilisation costs at each severity level per case study. These costs are indicated in the table below. The right-most column shows the weighted average health care utilisation costs per case study, taking into account the relative outcome distribution.

Table 7: Total health care utilisation costs per severity level, by case study country (in EUR 2017)

Case study country	Severity level				Weighted average health care utilisation cost
	Didn't visit physician, recovered *(68.36% of cases)*	Visited physician, recovered *(28.90% of cases)*	Hospitalised, recovered *(2.66% of cases)*	Hospitalised, died *(0.08% of cases)*	
UK	€ 0.00	€ 145.62	€ 4 170.53	€ 3 778.15	**€ 156.04**
Italy	€ 0.00	€ 89.96	€ 2 576.42	€ 2 334.02	**€ 96.40**
Canada	€ 0.00	€ 95.50	€ 2 734.91	€ 2 477.60	**€ 102.33**
US	€ 0.00	€ 361.81	€ 11 649.20	€ 10 549.83	**€ 422.87**
Argentina	€ 0.00	€ 21.62	€ 619.26	€ 561.00	**€ 23.17**

Source: Own calculation.

As indicated in the table above, the four severity levels show considerable differences in health care utilisation costs, with the two hospitalisation outcomes incurring markedly higher costs than either of the non-hospitalisation outcomes. As the hospitalisation outcomes collectively represent fewer than 3% of total cases, however, and more than half of all cases incur no health care expenses at all, the weighted average health care utilisation costs are bought down to a range between EUR 96.40 and EUR 422.87, with an average base cost of EUR 109.60 for the EU28. As noted

previously, the highest costs at all severity levels are reported in the US, due to the higher unit costs for health care services.

5.3. Productivity loss

The costs of productivity loss are equal to the value of missed time from work. This is calculated first by estimating the number of days missed from work due to a salmonellosis infection, which is assumed to vary by severity level, and then multiplying the number of missed days by the average gross daily earnings in each case study country. Finally, in order to account for the fact that not all patients are employed, we multiply these costs by the proportion of the population in each country that is economically active to get country-specific estimates of the cost of lost productivity.

Assumptions regarding the number of days missed from work due to a salmonellosis infection for each severity level are based on the estimates used in the DG SANCO studies. These are presented in the table below.

Table 8: Days missed from work per severity level

	Didn't visit physician, recovered	Visited physician, recovered	Hospitalised, recovered	Hospitalised, died
Days missed from work	0.5	1.6	4.5	4.5

Source: DG SANCO/FCC Consortium (2010), *Analysis of the costs and benefits of setting a target for the reduction of Salmonella in slaughter pigs – Final report*.

As the table above shows, the number of days missed from work starts with 0.5 for the lowest severity level and increases to 4.5 for both of the hospitalisation levels.

The monetary value of time missed from work depends on the average gross wage, which varies across the case study countries. The table below shows the average gross daily earnings per case study country.

Table 9: Average gross daily earnings, by case study country (in EUR 2017)

Case study countries	Average gross daily earnings
UK	€ 199.40
Italy	€ 123.18
Canada	€ 130.76
US	€ 184.58
Argentina	€ 29.61

Source: Eurostat, *Annual net earnings* [earn_nt_net] (variable: 'Gross earnings'), extracted 14 January 2019, for the UK, Italy and the USA; ILOSTAT for Canada and Argentina. All figures inflated to 2017 using Eurostat's labour cost index [lc_lci_r2_a] and converted to EUR where necessary.

Finally, the costs of productivity loss accrue only to economically active persons. The proportion of economically active persons can be calculated by multiplying the labour market participation rate by the proportion of the total population that is of working age (15-64). As these factors vary across countries, this calculation has been performed separately for each case study country. The table below shows the proportion of the population which is economically active by case study country.

Table 10: Economically active population per case study country

Case study countries	Working age as proportion of total population	Labour market participation rate	Proportion of cases economically active
UK	0.641	0.776	0.497
Italy	0.641	0.654	0.419
Canada	0.670	0.785	0.526
US	0.657	0.733	0.481
Argentina	0.639	0.674	0.431

Source: Eurostat, *Population structure and aging* [demo_pjanind] and *Employment and activity by sex and age - annual data* [lfsi_emp_a], both extracted 14 January 2019, for the UK and Italy; ILOSTAT, *Population by sex and age* and *Labour force participation rate by sex and age* for the US, Canada and Argentina.

In order to calculate the total costs of productivity loss for each case study country, the number of days missed from work at each severity level is multiplied by the gross daily earnings and by the proportion of cases that are assumed to be economically active. The weighted average costs of productivity loss are then calculated by weighting the costs at each severity level by the outcome distribution value. These costs are shown in the table below per severity level and in total.

Table 11: Total costs of productivity loss per severity level, by case study country (in EUR 2017)

Case study countries	Severity level				Weighted average cost of product-ivity loss
	Didn't visit physician, recovered	Visited physician, recovered	Hospitalised, recovered	Hospitalised, died	
	(68.36% of cases)	*(28.90% of cases)*	*(2.66% of cases)*	*(0.08% of cases)*	
UK	€ 49.59	€ 158.69	€ 446.32	€ 446.32	**€ 91.99**
Italy	€ 25.82	€ 82.62	€ 232.38	€ 232.38	**€ 47.90**
Canada	€ 34.38	€ 110.02	€ 309.44	€ 309.44	**€ 63.78**
US	€ 44.43	€ 142.17	€ 399.85	€ 399.85	**€ 82.41**
Argentina	€ 6.38	€ 20.41	€ 57.40	€ 57.40	**€ 11.83**

Source: Own calculation.

As indicated in the table above, productivity loss is higher for the two hospitalisation outcomes than for the two non-hospitalisation outcomes. As with the health care utilisation costs, the weighted average cost is brought down considerably by the fact that the hospitalisation cases are a small proportion of total cases (less than 3%). The total weighted average cost of productivity loss ranges from a low of EUR 47.90 to a high of EUR 91.99.

5.4. Premature death

The costs of premature death accrue only to the 0.08% of cases that fall into the highest severity level. The question of how to calculate a monetary value for a statistical human life is highly controversial. Common methods employed to quantify this figure include the 'value of a statistical life' (VOSL) method, which is derived from individuals' willingness-to-pay (WTP) for a lower risk of death, the 'value of a statistical life year' (VOLY) method, which measures the WTP for an additional year of

life expectancy, and the human capital method (HC), which measures the loss of projected future earnings.

Estimates of the value of a human life based on the methods listed above have been calculated for use in cost-effectiveness analyses by numerous European, national, and international authorities. Selected estimates are presented in the table below.

Table 12: Various cost-effectiveness estimates for the value of a human life

Source	Estimate	Method
DG SANCO study (2011)	€ 60 000 to 1 million (in EUR 2011)	HC
USDA	$ 1.6 million to 15.7 million, mean value $ 8.7 million (in USD 2013)	VOLY
UK Green Book/Dept of Transport	£ 1.9 million (in GBP 2018)	VOLY/HC
OECD	$ 1.8 million to 5.4 million (in USD 2005)	VOSL
European Chemicals Agency (ECHA)	€ 3.5 million (lower estimate; EUR 2012) € 5.0 million (higher estimate)	VOSL

Source: DG SANCO/FCC Consortium (2011), *Analysis of the costs and benefits of setting a target for the reduction of Salmonella in breeding pigs – Final report*; USDA Economic Research Service (2014), *Cost estimates of foodborne illnesses;* UK Department of Transport (2018), *WebTAG Databook* [data supplement to the Green Book]; OECD (2012), *Mortality risk valuation in environment, health and transport policies*; ECHA (2016), *Willingness-to-pay values for various health endpoints associated with chemicals exposure*.

As illustrated in the table above, the estimated value of a human life for the purpose of cost-effectiveness analysis varies between sources and across methods, ranging from a low of EUR 60 000 in the 2011 DG SANCO study to a high of 15.7 million USD (approximately EUR 13.8 million) used as a higher-bound estimate by the USDA. While some sources, such as the UK government, prefer to use a standard value for all valuations of human life, other sources allow values to vary based on different levels of WTP (which is largely driven by income or wealth) or based on the value of lost productivity (which is determined by local wage rates).

In the 2011 DG SANCO study, the cost of a premature death was based on a HC approach examining the value of lost productivity, which generated values of a human life ranging from EUR 60 000 to 1 million, depending on the local wage rate in each country. In contrast, for the current study we apply a standard value of a human life across all case studies. The reasons for this are as follows: firstly, WTP-based approaches are more common than human capital approaches for this type of assessment, as illustrated in the table above; secondly, applying very different values of life in different countries based on income levels raises issues regarding equity with respect to human life; thirdly, because premature death is so costly compared to other factors that it is the single most influential cost component in the cost of illness analysis (see the next section), the results of the analysis are very sensitive to any country differences in the value of human life, which would reduce comparability between the case study results. We have therefore chosen to use the reference values calculated by the European Chemicals Agency (ECHA), which are presented in the table above.[43] We use the average value of EUR 4.6 million as a standard assumption for the cost of a premature death across all case studies, while retaining the low and high estimates for later sensitivity analysis.

[43] The ECHA values are also provided as reference in the European Commission's Better Regulation Toolbox, the standard guidance for assessing interventions at EU level. See *European Commission (2017), Better Regulation Toolbox – Tool #31: Health Impacts*.

5.5. Average cost per case of salmonellosis

The table below shows the estimated cost per case of salmonellosis at each level of severity for each case study.

Table 13: Cost of a salmonellosis infection per severity level, by case study country (in EUR 2017)

Case study countries	Severity levels			
	Didn't visit physician, recovered	Visited physician, recovered	Hospitalised, recovered	Hospitalised, died
	(68.36% of cases)	*(28.90% of cases)*	*(2.66% of cases)*	*(0.08% of cases)*
UK	€ 49.59	€ 304.32	€ 4 616.85	€ 4 640 974.47
Italy	€ 25.82	€ 172.58	€ 2 808.79	€ 4 639 316.39
Canada	€ 34.38	€ 205.52	€ 3 044.35	€ 4 639 537.04
US	€ 44.43	€ 503.98	€ 12 049.05	€ 4 647 699.68
Argentina	€ 6.38	€ 42.03	€ 676.66	€ 4 637 368.40

Source: Own calculation.

As can be seen in the table above, the estimated cost per case of salmonellosis varies considerably by severity level. Costs at the lowest severity level comprise only the costs of productivity loss, and range between approximately EUR 26 and EUR 50. The costs of an infection then rise with the severity level and peak with the outcome of patient death at the highest severity level, with a total cost of approximately EUR 4.6 million per case for all case studies.

The average cost per generic case of salmonellosis, weighted by the outcome distribution values for each severity level, ranges from EUR 3 854 to EUR 3 957, depending on the country. However, the more relevant value for the breakeven analysis is in fact the average cost of a *reported* case of salmonellosis, since this is the base against which the number of cases to be avoided will be compared. By definition, reported cases of salmonellosis exclude all patients in the lowest severity category, since these patients do not enter the health care system and are therefore not registered in surveillance statistics (see the discussion above in section 7.1). The table below shows the average cost of a reported case of salmonellosis, which is calculated by dropping severity level 1 and rebasing the outcome distribution.[44]

[44] Some patients in severity levels 2-4, but especially at severity level 2, will also not be recorded in national statistics; see the surveillance pyramid and related discussion in section 7.1. However, in order to make the calculation more straightforward and avoid unnecessary guesswork, we have decided simply to drop severity level 1 and rebase the outcome distribution on that basis.

Table 14: Cost of a reported salmonellosis infection per severity level, by case study country (in EUR 2017)

Case study countries	Severity levels			Average cost of a reported case (weighted)
	Visited physician, recovered	Hospitalised, recovered	Hospitalised, died	
	(91.34% of reported caes)	*(8.41% of reported cases)*	*(0.25% of reported cases)*	
UK	€ 304.32	€ 4 616.85	€ 4 640 974.47	**€ 12 400.55**
Italy	€ 172.58	€ 2 808.79	€ 4 639 316.39	**€ 12 124.03**
Canada	€ 205.52	€ 3 044.35	€ 4 639 537.04	**€ 12 174.48**
US	€ 503.98	€ 12 049.05	€ 4 647 699.68	**€ 13 224.76**
Argentina	€ 42.03	€ 676.66	€ 4 637 368.40	**€ 11 820.61**

Source: Own calculation.

As the table above shows, the average cost of a reported case of salmonellosis is considerably higher than the average cost of a generic case, ranging from EUR 11 821 to EUR 13 225. The table below further deconstructs this cost according to the individual cost components for each case study country.

Table 15: Average cost per reported case of salmonellosis, by case study country, deconstructed by cost component (in EUR 2017)

Case study countries	Health care utilisation	Productivity loss	Premature death	Average cost (weighted)
UK	€ 493.19	€ 183.60	€ 11 723.77	**€ 12 400.55**
Italy	€ 304.67	€ 95.59	€ 11 723.77	**€ 12 124.03**
Canada	€ 323.42	€ 127.29	€ 11 723.77	**€ 12 174.48**
US	€ 1 336.51	€ 164.48	€ 11 723.77	**€ 13 224.76**
Argentina	€ 73.23	€ 23.61	€ 11 723.77	**€ 11 820.61**

Source: Own calculation.

As indicated in the table above, the largest single cost component in the average cost per reported case of salmonellosis is premature death. Despite a rate of occurrence of just 0.25% among reported cases, death comprises at least 95% of the total average cost in every case study country except the US, where it only comprises 89% of the average cost of a reported case due to the higher costs of health care utilisation. The dominant role played by death is due to the large value placed on a human life (EUR 4.6 million), which, even at a low rate of occurrence, overshadows most country-specific differences in the costs of health care or productivity loss.

5.6. Results of the breakeven analysis

As discussed in the previous section, the aim of the breakeven analysis is to estimate the number of cases of salmonellosis that would need to be avoided each year through the use of WGS to make its use cost-neutral compared to the costs of using conventional methods. In the previous sections, we have calculated the cost per case of salmonellosis in terms of health care utilisation costs, productivity loss, and premature death, and on this basis, we have estimated the average cost per case of salmonellosis for each of the case study countries. In this section, we compare these estimates to the total cost difference due to the use of WGS versus the use of conventional methods.

The process and results of the breakeven analysis are presented in the following table. For each case study institution, the following aspects are presented:

- The differential cost per sample of using WGS for pathogen identification and surveillance, calculated as difference of the cost per sample using WGS and the costs per sample using conventional methods (presented in detail above);
- The number of *Salmonella* samples analysed per year;
- The total cost difference per year due to the use of WGS, calculated by multiplying the differential costs per sample by the number of samples per year;
- The average cost per *reported* case of salmonellosis in the respective country, as calculated in the previous sub-section;
- The results of the breakeven analysis both in terms of the absolute number of reported cases of salmonellosis and in terms of the percentage of reported cases of *Salmonella* in the geographical jurisdiction of the case study institution that would need to be avoided to make the use of WGS cost-neutral.

Table 16: Breakeven analysis – Number and percentage of reported cases of salmonellosis that need to be avoided to make the use of WGS cost-neutral

Case study institution (country)	Cost per sample (WGS)	Cost per sample (conven-tional methods)	Differential cost of WGS compared to conventional methods	Number of samples analysed per year	Total cost difference per year due to the use of WGS	Average cost per reported case of salmonellosis in case study country	Number of reported cases of salmonellosis that need to be avoided to break even	Number of cases of salmo-nellosis reported annually*	Percentage of total number of reported cases of salmonellosis that need to be avoided to break even
PHE (UK)	€ 124.59	€ 65.46	€ 59.13	10 147	€ 599 992.11	€ 12 400.55	48	8 770	0.6 %
IZSLER (Italy)	€ 395.14	€ 91.87	€ 303.27	110	€ 33 360.21	€ 12 124.03	3	** 276	1.0 %
PHAC (Canada)	€ 215.37	€ 94.29	€ 121.07	8 273	€ 1 001 622.97	€ 12 174.48	82	7 665	1.1 %
MDH (US)	€ 154.51	€ 81.16	€ 73.35	1 010	€ 74 083.50	€ 13 224.76	6	906	0.6 %
INEI-ANLIS (Argentina)	€ 154.49	€ 46.61	€ 107.88	128	€ 13 808.64	€ 11 820.61	1	758	0.2 %
Average	**€ 208.82**	**€ 75.88**	**€ 132.94**	**3 934**	**€ 344 573.48**	**€ 12 348.89**	**28**	**4 404**	**0.7 %**

Own compilation based on case study results. Sources for the number of infections reported annually in each jurisdiction: ECDC (2018), *The European Surveillance System (TESSy)* (IT); PHE (2018), *Salmonella data 2007 to 2016* (UK); PHAC (2018), *Reported cases from 1924 to 2016 in Canada - Notifiable diseases on-line*; CDC (2015-17), *National Notifiable Infectious Diseases and Conditions in the United States 2015, 2016, 2017* (US); *Laboratory Surveillance System (SIVILA) of the National Health Surveillance System* (Argentina). Note that the averaging rows present averages of the case study figures in each respective column. Notes: * Data provided on cases of salmonellosis refer to the geographical jurisdictions of the institution as indicated in the case study report. Where a case study institution processes samples originating from the whole country (Canada, Argentina), data on salmonellosis refer to the country as a whole. Where a case study institution only processes samples from a specific geographical region within a country, data on salmonellosis refer to this particular region (England, Wales and Northern Ireland in the UK, Emilia-Romagna in Italy, and Maryland in the US). ** Regional data approximated as a population-based proportion of national data, as no regional data was available.

The average cost per reported case of salmonellosis is generally comparable between case studies, as indicated in the table above and discussed in the previous subsection; the key factor determining the absolute number of cases that need to be avoided to break even on costs is therefore the total cost difference per year due to the use of WGS. This figure in turn depends on both the differential cost per sample of using WGS as well as the total number of samples processed, with higher differential costs per sample and higher numbers of samples processed resulting in higher estimates of the number of avoided cases of salmonellosis needed to break even on costs.

The number of cases of salmonellosis that need to be avoided annually to break even on costs ranges from 1 case within INEI-ANLIS' area of jurisdiction (Argentina) to a maximum of 82 cases within PHAC's area of jurisdiction (Canada). While the absolute numbers differ considerably, the number of cases that need to be avoided to break even as a *proportion* of reported cases of infection within each jurisdiction is comparable, lying at 1.1% or less of reported cases for all case studies.

It is important to note that the estimates of 0.2% to 1.1% of cases to be avoided refer to the proportion of *reported* cases and not to the proportion of *total* cases in the community. As discussed above in the introduction to section 5.5, the majority of salmonellosis cases in each country are not recorded in national surveillance statistics. The estimates of 0.2% to 1.1% of cases that would need to be avoided in order to break even on the costs of WGS are therefore conservative figures, with the real proportions of cases that need to be avoided being considerably lower. The reason for this is that reported cases of salmonellosis by definition do not include the estimated 68% of cases at the lowest severity level, as these patients do not present to the health care system. However, it is also relevant to note in this respect that unreported cases are likely to be mostly comprised of 'low cost' cases.

It is also notable that due to the high costs associated with premature death (see the discussion above), the number of deaths that would need to be avoided to break even on WGS lies well below 1 for all case studies, indicating that if even a single death from salmonellosis were avoided each year through the case of WGS in any case study jurisdiction, it would more than break even on costs. For comparison, approximately 52 deaths from salmonellosis are reported each year in PHE's jurisdiction of England, Wales and Northern Ireland, meaning that one death avoided annually would comprise less than 2% of all salmonellosis deaths. In fact, given the high cost attached to premature death, avoiding one death every 7.7 years in PHE's jurisdiction would be sufficient to break even on costs; the corresponding values for the other case studies are one avoided death every 5 years in Canada; every 63 years in Maryland (US); every 139 years in Emilia-Romagna (Italy); and every 336 years in Argentina.[45]

5.7. Sensitivity analysis

As previously noted in section 5.5.1.4, the largest single cost component in the average cost per case of salmonellosis is premature death, which comprises approximately 95% of the total average cost. This is due to the large value placed on a human life (EUR 4.6 million), which, even at a low rate of occurrence, overshadows costs of health care or productivity loss. Because the cost of premature death is so dominant in the valuation, it is important to test the robustness of the results against different assumptions regarding the cost or likelihood of premature death.

[45] The number of years here is calculated by dividing the cost of a case at severity level 4 (hospitalised, died) over the total cost difference per year due to the use of WGS.

The first assumption to be tested is the estimated *value of a premature death*. In order to test this assumption, we recalculate the breakeven analysis using the lower estimate for premature death according to ECHA (EUR 3.9 million in EUR 2017) and alternatively using the higher estimate for premature death according to ECHA (EUR 5.5 million in EUR 2017).

The second assumption relates to the *likelihood* of a case of salmonellosis resulting in an outcome of premature death. To test this assumption, we recalculate the breakeven analysis using the outcome distribution used in the USDA's cost of illness model, which assign a lower likelihood to the outcome of premature death. The following table compares the USDA outcome distribution to be used in the sensitivity analysis to the outcome distributions used in the 2011 DG SANCO study (and therefore in our original model).

Table 17: Outcome distributions – USDA compared to DG SANCO (2011)

	Didn't visit physician, recovered	Visited physician, recovered	Hospitalised, recovered	Hospitalised, died
DG SANCO (Base)	68.36 %	28.90 %	2.66 %	0.08 %
USDA	90.92 %	7.20 %	1.84 %	0.04 %

Source: DG SANCO/FCC Consortium (2011), *Analysis of the costs and benefits of setting a target for the reduction of Salmonella in breeding pigs – Final report*; USDA Economic Research Service (2014), *Cost estimates of foodborne illnesses*.

As can be seen in the table above, the USDA outcome distribution roughly halves the proportion of cases resulting in premature death relative to the 2011 DG SANCO study, with 0.04% of cases assumed to result in death instead of 0.08%. The USDA also assumes that lower proportions of cases result in hospitalisation or visits to a physician, while a much higher proportion (90.92%) of cases are assumed to recover at home without accessing health care services.

The table below shows the results of the breakeven analysis when recalculated under the three sensitivity scenarios of a lower value of premature death, higher value of premature death, and lower likelihood of premature death.

Table 18: Sensitivity analysis – base estimate and three sensitivity scenarios

Case study institution (country)	Base estimate using average cost of premature death and likelihood of death according to 2011 SANCO study Cost of premature death: €4.6m Likelihood of death: 0.25%		Revised using lower estimate for value of premature death Cost of premature death: €3.8m Likelihood of death: 0.25%		Revised using higher estimate for value of premature death Cost of premature death: €5.5m Likelihood of death: 0.25%		Revised using a likelihood of death in line with USDA outcome distribution Cost of premature death: €4.6m Likelihood of death: 0.12%	
	Weighted average cost of reported illness	Number of reported cases avoided to break even	Weighted average cost of reported illness	Number of reported cases avoided to break even	Weighted average cost of reported illness	Number of reported cases avoided to break even	Weighted average cost of reported illness	Number of reported cases avoided to break even
PHE (UK)	€ 12 400.55	48	€ 10 320.97	58	€ 14 458.77	41	€ 5 906.29	102
IZSLER (Italy)	€ 12 124.03	3	€ 10 048.64	3	€ 14 186.44	2	€ 5 694.49	5
PHAC (Canada)	€ 12 174.48	82	€ 10 098.53	99	€ 14 236.33	70	€ 5 734.59	175
MDH (US)	€ 13 224.76	6	€ 11 128.17	7	€ 15 265.97	5	€ 6 505.77	11
INEI-ANLIS (Argentina)	€ 11 820.61	1	€ 9 750.15	1	€ 13 887.95	1	€ 5 464.40	3

Own compilation based on case study results. Sources: ECHA (2016), *Willingness-to-pay values for various health endpoints associated with chemicals exposure*; USDA Economic Research Service (2014), *Cost estimates of foodborne illnesses*.

As shown in the table above, the sensitivity scenario with the largest impact on the cost of illness and therefore on the number of reported cases of salmonellosis that need to be avoided to break even is the third scenario using the USDA outcome distribution, which reduces the estimated cost of a reported case of salmonellosis by about half, in line with the reduction in the likelihood of death. In contrast, the use of lower and higher estimates for the value of a premature death have a relatively smaller impact on the results.

In terms of the range of results produced by the sensitivity analysis, varying the assumptions related to death has the following results for each case study:

- For PHE, the cost of reported illness ranges from EUR 5 906 to EUR 14 459. The number of reported cases needed to be avoided in order to break even now ranges from 41 (or 0.5% of reported cases) to 102 (equivalent to 1.2% of reported cases);
- For IZSLER, the cost of a reported illness under the sensitivity scenarios ranges from EUR 5 694 to EUR 14 186. The number of reported cases that need to be avoided to break even ranges from 2 (representing 0.9% of reported cases) to 6 (2.1% of reported cases);
- For PHAC, the cost of a reported illness ranges from EUR 5 735 to EUR 14 236. The number of reported cases that would need to be avoided to break even ranges from 70 (representing 0.9% of reported cases) to 175 (representing 2.3% of reported cases);
- For MDH, the cost of a reported illness ranges from EUR 6 506 to EUR 15 266. The number of reported cases to be avoided ranges between 5 (0.5% of reported cases) and 11 (1.3% of reported cases); and
- For INEI-ANLIS, the cost of reported illness ranges from EUR 5 464 to EUR 13 888. This corresponds to a range of between 1 and 3 reported cases that would need to be avoided each year (0.1% to 0.3% of reported cases).

The effect on the overall results, while non-trivial, is relatively modest. Even under the highest impact scenario, i.e. the use of the USDA outcome distribution, the proportion of reported cases that would need to be avoided in each case study jurisdiction in order to break even on the costs of WGS still lies lower than 2.5%.

More importantly, however, the sensitivity analysis does not change the core conclusions of the breakeven analysis relating to the high value of avoiding premature deaths in particular. The estimated value of a premature death, even under the lower estimate, is still very high relative to the additional annual cost of using WGS, so that avoiding just one premature death due to salmonellosis over a period of several years would suffice in all case studies to break even on costs from a public health perspective.

6. Factors affecting cost-effectiveness and options for improving overall cost-effectiveness of the system

This section discusses the results of the analysis of costs and benefits presented in the previous sections, and identifies factors affecting cost-effectiveness of using WGS for pathogen identification and surveillance. We then discuss conclusions from case study results for improving overall cost-effectiveness of the system and provide recommendations on this basis.

This analysis of the practical experiences of eight reference laboratories in Europe and the Americas confirms that WGS has higher per-sample costs on average than conventional laboratory methods: WGS is between 1.2 and 4.3 times more expensive than routine conventional methods. When interpreting these results, it is crucial to note that the per sample costs calculated in this study are the actual costs incurred by the reference laboratories, reflecting the specific situation of each laboratory. While this implies that the cost estimates cannot be used to extrapolate costs to other institutions, this approach has the advantage that the results reflect the concrete experiences of leading institutions in the field in varying circumstances. The approach chosen for the assessment (focusing on the analysis of differential costs) simplified the complex analysis, as costs that are clearly unaffected (e.g. for depreciation of laboratory buildings) did not need to be assessed, allowing the analysis to focus in detail on those costs and benefits where changes due to the use of WGS occurred.

The analysis also shows that there are several factors that affect the costs of WGS. These include:

- Increasing returns to scale with WGS analysis;
- Costs of the sequencing platform used;
- Costs of the bioinformatics infrastructure used;
- Lack of competition among suppliers of sequencing equipment and consumables, and resulting pricing policies of producers or local distributors;
- In addition, and depending on the country, import duties, and variations in exchange rates may also affect the feasibility of using WGS for reference laboratories.

In the following paragraphs, we discuss each of the factors, and consider how considering this factor could improve overall cost-effectiveness of using WGS for pathogen identification and surveillance:

6.1. Increasing returns to scale

The results from the case studies indicate an inverse relationship between sample volume/batch size and total per-sample costs. Excluding the EMC case study (in which a lower-cost Nanopore sequencer was used), the total per-sample costs decrease almost uniformly as the total sample volume increases. The increasing returns to scale are visible to at least some extent in all major cost types (equipment, consumables and staff time).

As time pressure in an outbreak context often does not allow for batching of samples, cost of using WGS for avian influenza outbreak surveillance is high, the average cost of the two reference laboratories analysed in this context being EUR 793 per sample. In contrast, the average cost for the five reference laboratories that used WGS for routine surveillance of foodborne pathogens is much lower at EUR 209 per sample.

The increasing returns to scale with WGS analysis imply that centralised reference laboratories which deal with a high volume of samples are likely to achieve a lower per-sample cost than smaller institutions processing fewer samples. This would indicate that a centralisation strategy for reference laboratories could help reducing per-sample costs, as the case of Public Health England illustrates. However, there may be trade-offs in terms of turnaround time to the extent that this increases time for shipping of samples, and the diverse organisation of public health systems across different countries also means that in decentralised countries regional laboratories often have an important role in the overall surveillance sytem of the country (e.g. in Italy), which limits the volume of samples per laboratory. In conclusion this would suggest that it is recommended to target for each specific situation an adequate level of centralisation for WGS analysis, which balances the costs reductions through economies of scale with the required level of decentralisation.

6.2. Costs of sequencing platform and bioinformatics infrastructure

The costs of the sequencing platform used (in terms of producer, model and related consumables) may differ considerably, varying in our case studies between EUR 45 000 for a GridION, EUR 75 000 to 100 000 for an Illumina MiSeq or IonTorrent PGM, and around EUR 600 000 for an Illumina HiSeq.[46] The results of the case study at EMC (human influenza) which uses the GridIon as sequencing platform suggest that lower cost per sample can also potentially be achieved at a medium batch size/sample volume through third generation (Nanopore) sequencing, as the total per-sample costs in this case study (EUR 98) lie below even the costs calculated for the reference laboratory that had the highest throughput of samples and batch sizes during the reference period (PHE).

Per-sample costs are further influenced by the extent to which sequencers and other equipment are used at full capacity or not. Several reference laboratories in our sample did not use or could not use equipment at full capacity for a variety of reasons, including time constraints (outbreak context), overall sample volume and the degree to which the equipment purchased considered future (potentially higher) sample volumes. If sequencers and other equipment are used at full capacity this reduces the equipment costs per sample considerably. A large batch size for sequencing reduces both per-sample equipment and consumables costs. A lower capacity sequencer can therefore be more cost-effective, if this capacity is fully used at maximum batch size, compared to a higher capacity sequencer that is used only to half of the maximum capacity.

In this context it is notable that the costs of the bioinformatics infrastructure differed greatly between reference laboratories, and may considerable affect per sample costs. This was the case at PHAC, where the more extensive bioinformatics infrastructure contributed to a substantially higher equipment and staff time cost.

From the case study results the conclusion could be drawn that especially for smaller or regional laboratories, cloud-based applications for the bioinformatics analysis may lead to considerable cost-savings. This was the case for MDH, which used online tools for sequencing analysis, which were partly developed through the COMPARE project (www.genomicepidemiology.org). MDH reported an average professional staff time for the bioinformatics analysis of only 15 minutes per sample – markedly lower than the other case study institutions except EMC (which also reported a similarly low figure of 12 minutes).

[46] Note that the purchase year differed, so that prices are not necessarily comparable.

Taking the rapid innovation in sequencing technologies into account, it may therefore be advisable to purchase sequencing equipment that can be used at full capacity with current sample throughput, rather than to invest into reserve capacities, e.g. for expected future increases in sample numbers. While other considerations (such as data protection and sovereignty) may affect decisions regarding bioinformatics infrastructure, case study results indicate that large-scale bioinformatics infrastructures may be less cost-effective than small scale solutions, and/or the use of online tools for sequencing analysis.

6.3. Competition and pricing policies of suppliers

The lack of competition among suppliers of sequencing equipment and consumables was reported by the reference laboratories to be a key factor driving costs. Some case study institutions reported having success in lowering costs through forming partnerships with other institutions that were able to access supplies at a lower cost, or through joining with other institutions to negotiate bulk prices. This seems to indicate that profit margins of equipment and consumables suppliers are currently considerable. It is thefore recommended that public health institutions including reference laboratories leverage their purchasing power through forming of partnerships for joint purchasing of sequencing equipment and consumables.

In some countries, it seems hardly possible to conduct meaningful WGS analysis at current market prices for supplies. As the Argentinan case study illustrates, costs could only be kept in a comparable range to the other reference laboratories analysed because sequencing equipment and consumables were purchased in the USA in the framework of an international pilot project. Argentinian market prices were reportedly much higher. In expert interviews conducted in Kenya, South Africa and Vietnam, it was confirmed that costs for sequencing kits are often considerably higher (even prohibitively high) compared to highly industrialised countries, with possible reasons being the pricing policies of the producers or the local distributors of consumables, import duties, and variations in exchange rates. In light of the global importance of effective surveillance and early identification of pathogens it is recommended that national governments, the European Commission and the relevant international organisations (such as WHO and OIE) address this issue, with the aim of negotiating international agreements that safeguard that WGS equipment and consumables are available in all countries (including mid- and low-income countries) at price levels that are lower, or at least not higher than in highly industrialised countries.

6.4. Outlook and overall conclusions

Case study institutions noted that future economies of scale could drive down costs as individual institutions begin scaling up their use of WGS and transitioning from pilot projects to routine use. Unlike conventional methods, it is also possible to develop standardised and pathogen-neutral workflows for WGS, making the process more amenable to automation and more efficient. Future cost reduction in sequencing is expected to drive down the costs of pathogen surveillance using WGS substantially, as are future cost reductions in computing and storage capacities.

Even at current cost levels, WGS provides a level of additional information that more than balances out the additional costs if used effectively. All case study institutions experienced major benefits of using WGS for pathogen identification and surveillance, streamlining their work flows, analytical processes and the ways in which outbreaks are detected and controlled. One of the reference laboratories conducting surveillance of foodborne pathogens reported that 'outbreak detection has dramatically changed due to WGS', explaining that more outbreaks are being detected than previously, that there are 'larger outbreaks than before (e.g. large multinational outbreaks) that previously would not have been confirmed with such certainty', and that they are 'now

detecting more smaller outbreaks that would previously have been under the radar due to the previous typing method or where cases have occurred over a long time frame'. As the example of foodborne illnesses shows most clearly, the higher number of outbreak clusters identified with WGS will likely lead to a reduction of overall cases of illness, if public health systems are equipped and funded adequately to allow effective measures to be taken. Our breakeven analysis indicates that in the case of *Salmonella* surveillance, for example, only a modest percentage (0.2% to 1.1%) of reported salmonellosis cases would need to be avoided each year through the use of WGS in order to make the adoption of the technology cost-neutral from a public health perspective. While this result cannot be directly applied to other pathogens, it is clear from our analysis that there are potentially large public health benefits of using WGS. The case studies also show that the benefits of using WGS for pathogen identification and surveillance depend largely on the set up and functioning of the surveillance system in a region or country: the later in the chain WGS is used, the more limited the potential benefits are in terms of the earlier detection of outbreaks. Case study results therefore highlight the benefits of using WGS as part of an One Health approach, especially in the surveillance of foodborne pathogens. Identifying linkages between human cases and sources in the food system through WGS in real-time critically depends on the routine laboratory surveillance of samples from human, animal and food sources being conducted through the same institution; or, if several institutions are involved, on a continuous exchange of sequencing data.

Appendix. Cost data collected from case study institutions

ANNEX : Data collected for cost calculation - APHA

I. WGS

Equipment

In the following, the equipment used for sample preparation, sequencing, bioinformatics and other analyses considered for the cost calculation is listed. For each piece of equipment, the table provides the total unit price at the time of purchase (including VAT), annual maintenance costs, and predicted lifespan. Only equipment was considered that costed EUR 400 or more that qualify as capital expenditure relevant for WGS, such as sequencing machines and durable lab equipment as well as specific software purchasing or licensing fees. Not included were basic laboratory equipment (e.g. refrigerators, centrifuges or pipettes), standard office computers and standard office software.

This approach was similarly applied for all methods listed below.

	Total purchase price (Euro)	*Annual maintenance costs (Euro)*	*Predicted lifespan (years)*
Illumina MiSeq	€ 104 826	€ 12 000	10
Computer	€ 2 355	€ 0	5

Consumables

In the following, the consumables used for sample preparation and sequencing considered for the cost calculation are listed. Consumables include items that are used up in laboratory processes, such as chemicals, petri dishes, etc. For each item, the table provides the cost per sample, the step of analysis it is used for and the failure rate. The failure rate refers to the percentage of consumables that are wasted, e.g. due to failed runs, and is taken into account in the cost calculation.

This approach was similarly applied for all methods listed below.

	Cost per sample (Euro)	*Step of analysis*	*% failure*
Qiagen viral RNA extraction kit	€ 4.59	Sample processing	1
Roche cDNA synthesis kit	€ 69.58	Library preparation	1
Nextera XT kit	€ 748.57	Sequencing	1

Staff time per sample in minutes

The following provides the estimated staff time per sample spent on each step, separately for professionals and for technicians. The amount of 'hands-on staff time' is indicated, i.e. the amount of staff time actually used to perform an activity, and not the duration of the activity, including for maintenance of equipment and staff time used for failed runs. Where several samples are treated at the same time, total staff time is divided to obtain the per-sample staff time. For example, if sample processing for 40 samples takes 2 hours and 40 minutes for a laboratory technician, this figure is converted to minutes (160 minutes), and divided by 40, resulting in a technician staff time of 4 minutes per sample.

This approach was similarly applied for all methods listed below.

Staff category / *Step*	*Professionals* (staff time in minutes)*	*Technicians** (staff time in minutes)*
Sample processing	0	60
Library preparation	0	60
Sequencing	0	90
Bioinformatics & other	60	0

analyses		
Reference dataset	0	0

The definition of these catgories is based on the International Standard Classification of Occupations of the International Labour Office (ILO).

**For "Professionals", occupations typically involve the performance of tasks that require complex problem-solving, decision-making and creativity based on an extensive body of theoretical and factual knowledge in a specialised field. The knowledge and skills required are typically obtained as the result of study at a higher educational institution for a period of 3-6 years following completion of secondary education leading to the award of a first degree or higher qualification. This category includes PhD candidates and Post-docs.*

***For "Technicians", occupations typically involve the performance of complex technical and practical tasks that require an extensive body of factual, technical and procedural knowledge in a specialised field. The knowledge and skills required are usually obtained as the result of study at a higher educational institution for a period of 1-3 years following completion of secondary education. This category includes laboratory assistants.*

II. Conventional method A: Sanger Sequencing

Equipment

	Total purchase price (Euro)	*Annual maintenance costs (Euro)*	*Predicted lifespan (years)*
ABI Capillary sequencer 37/30	€ 198 667	€ 8 000	10
G storm thermocycler	€ 2 355	€ 388	5
LazerGene software licence	€ 16 474	0	1

Consumables

	Cost per sample (Euro)	*% failure*
Viral RNA extraction kit	€ 4.59	1
PCR kit	€ 4.75	1
Gel extraction kit	€ 1.68	0
Labelling kit	€ 10.28	5

Staff time per sample in minutes

	Professionals	*Technicians*
Staff time in minutes	60	360

III. Key variables

Labour costs

The following table provides the hourly labour cost data (in Euro) used for monetisation of staff time. Figures below refer to Eurostat data on labour costs for 2017 (by staff category), plus a 25% surcharge for overheads.

	Professionals	*Technicians*
UK	€ 39.63	€ 25.00
EU	€ 45.13	€ 24.50

Source: Eurostat, Labour cost levels by NACE Rev. 2 activity [lc_lci_lev]. Construct: Labour cost for LCI (compensation of employees plus taxes minus subsidies). NACE categories: Professional, scientific and technical activities; Administrative and support service activities. Extracted in June 2018.
Other

…	

ANNEX : Data collected for cost calculation - FLI

I. WGS

Equipment

In the following, the equipment used for sample preparation, sequencing, bioinformatics and other analyses considered for the cost calculation is listed. For each piece of equipment, the table provides the total unit price at the time of purchase (including VAT), annual maintenance costs, and predicted lifespan. Only equipment was considered that costed EUR 400 or more that qualify as capital expenditure relevant for WGS, such as sequencing machines and durable lab equipment as well as specific software purchasing or licensing fees. Not included were basic laboratory equipment (e.g. refrigerators, centrifuges or pipettes), standard office computers and standard office software. Note that the predicted lifespan of equipment is based on standard values and applied uniformly across case studies. Lifespans used for accounting purposes by each case institution may differ.

This approach was similarly applied for all methods listed below.

	Total purchase price (Euro)	*Annual maintenance costs (Euro)*	*Predicted lifespan (years)*
Covaris sonicator	€ 27 300	€ 0	10
Agilent bioanalyzer	€ 22 000	€ 0	10
Ion Torrent PGM bundle	€ 93 000	€ 11 500	10
Server for assembly computation	€ 34 700	€ 0	5

Consumables

In the following, the consumables used for sample preparation and sequencing considered for the cost calculation are listed. Consumables include items that are used up in laboratory processes, such as chemicals, petri dishes, etc. For each item, the table provides the cost per sample, the step of analysis it is used for and the failure rate. The failure rate refers to the percentage of consumables that are wasted, e.g. due to failed runs, and is taken into account in the cost calculation.

This approach was similarly applied for all methods listed below.

	Cost per sample (Euro)	*Step of analysis*	*% failure*
96-Well PCR-plates qPCR	€ 0.86	Sample processing	10
96-Well PCR-plates PCR	€ 0.69		
Reaction tubes 1.5 ml	€ 0.40		
Reaction tubes 2 ml	€ 0.54		
Pipette tips 1000 µl	€ 1.12		
Pipette tips 200 µl	€ 1.05		
Pipette tips 100 µl	€ 1.05		
Pipette tips 10 µl	€ 1.05		
Pipette tips 2 µl	€ 1.05		
RNA-Purification	€ 5.59		
Gelextraction/DNA-Purification	€ 2.04		
DNA/RNA-Extraction	€ 3.71		
RT-PCR	€ 5.15		
PCR	€ 1.33		
Lab gloves	€ 3.76		

Covaris-Vials	€ 6.91		
Agilent Bioanalyzer RNA Pico Kit	€ 5.00		
GeneRead Library Prep Kit	€ 29.35	Library preparation	10
Adapter	€ 12.01		
Agilent Bioanalyzer DNA HS Kit	€ 5.86		
KAPA Library Quant IonTorrent	€ 23.64		
Onetouch Reagents	€ 21.31	Sequencing	10
Enrichment Beads	€ 0.86		
Chips (316v2)	€ 50.52		
Sequencing Reagents	€ 45.16		
Nitrogen	€ 0.48		
W2-Bottles	€ 1.21		

Staff time per sample in minutes

The following provides the estimated staff time per sample spent on each step, separately for professionals and for technicians. The amount of 'hands-on staff time' is indicated, i.e. the amount of staff time actually used to perform an activity, including maintenance of equipment and staff time used for failed runs, but excluding unsupervised processes (e.g. time that the sequencer is running unsupervised). Where several samples are treated at the same time, total staff time is divided to obtain the per-sample staff time. For example, if sample processing for 40 samples takes 2 hours and 40 minutes for a laboratory technician, this figure is converted to minutes (160 minutes), and divided by 40, resulting in a technician staff time of 4 minutes per sample.

This approach was similarly applied for all methods listed below.

Staff category *Step*	*Professionals** *(staff time in minutes)*	*Technicians*** *(staff time in minutes)*
Sample processing	8	40
Library preparation	3	60
Sequencing	7	35
Bioinformatics & other analyses	20	0
Reference dataset	10	0

The definition of these categories is based on the International Standard Classification of Occupations of the International Labour Office (ILO).

**For "Professionals", occupations typically involve the performance of tasks that require complex problem-solving, decision-making and creativity based on an extensive body of theoretical and factual knowledge in a specialised field. The knowledge and skills required are typically obtained as the result of study at a higher educational institution for a period of 3-6 years following completion of secondary education leading to the award of a first degree or higher qualification. This category includes PhD candidates and Post-docs.*

***For "Technicians", occupations typically involve the performance of complex technical and practical tasks that require an extensive body of factual, technical and procedural knowledge in a specialised field. The knowledge and skills required are usually obtained as the result of study at a higher educational institution for a period of 1-3 years following completion of secondary education. This category includes laboratory assistants.*

II. Conventional method A: Sanger Sequencing			
Equipment			
	Total purchase price (Euro)	*Annual maintenance costs (Euro)*	*Predicted lifespan (years)*
ABI Sequencer	€ 120 000	€ 8 000	10

Consumables		
	Cost per sample (Euro)	*% failure**
96-Well PCR-plates qPCR	€ 0.86	10
96-Well PCR-plates PCR	€ 0.69	
Reaction tubes 1.5 ml	€ 0.40	
Reaction tubes 2 ml	€ 0.54	
Pipette tips 1000 µl	€ 1.12	
Pipette tips 200 µl	€ 1.05	
Pipette tips 100 µl	€ 1.05	
Pipette tips 10 µl	€ 1.05	
Pipette tips 2 µl	€ 1.05	
RNA-Purification	€ 10.00	
Gelextraction/DNA-Purification	€ 24.25	
RT-PCR	€ 34.87	
Lab gloves	€ 3.76	
EtOH	€ 0.05	0
2-Mercaptoethanol	€ 0.02	
Agarose	€ 1.95	
TBE-Buffer (0.5X)	€ 0.52	
Ethidiumbromid-Lsg.	€ 0.26	
52/4000 Seq.-Kit	€ 120.00	
Nucleoseq Columns	€ 72.28	
Formamide	€ 0.50	
Capillary array	€ 39.80	
Sequencing buffer	€ 0.13	
Polymer POP7	€ 36.60	

Staff time per sample in minutes		
	Professionals	*Technicians*
Staff time in minutes	260	240

III. Key variables

Labour costs		
The following table provides the hourly labour cost data (in Euro) used for monetisation of staff time. Figures below refer to Eurostat data on labour costs for 2017 (by staff category), plus a 25% surcharge for overheads.		
	Professionals	*Technicians*
Germany	€ 53.3	€ 26.8
EU	€ 45.1	€ 24.5
Source: Eurostat, Labour cost levels by NACE Rev. 2 activity [lc_lci_lev]. Construct: Labour cost for LCI (compensation of employees plus taxes minus subsidies). NACE categories: Professional, scientific and technical activities; Administrative and support service activities. Extracted in June 2018.		

ANNEX : Data collected for cost calculation - EMC

I. WGS

Equipment

In the following, the equipment used for sample preparation, sequencing, bioinformatics and other analyses considered for the cost calculation is listed. For each piece of equipment, the table provides the total unit price at the time of purchase (including VAT), annual maintenance costs, and predicted lifespan. Only equipment was considered that costed EUR 400 or more that qualify as capital expenditure relevant for WGS, such as sequencing machines and durable lab equipment as well as specific software purchasing or licensing fees. Not included were basic laboratory equipment (e.g. refrigerators, centrifuges or pipettes), standard office computers and standard office software. Note that the predicted lifespan of equipment is based on standard values and applied uniformly across case studies. Lifespans used for accounting purposes by each case institution may differ.

This approach was similarly applied for all methods listed below.

	Total purchase price (Euro)	*Annual maintenance costs (Euro)*	*Predicted lifespan (years)*
Gel electrophoreses system	€ 4 000	€ 0	10
PCR machine	€ 5 000	€ 0	10
Qubit	€ 3 000	€ 0	10
Magnate 96 wells	€ 800	€ 0	10
GridION	€ 45 000	€ 4 500	10
Computer (server)	€ 15 060	€ 0	5
Computer (back-up)	€ 0	€ 700	1
Computer (CLC)	€ 1 000	€ 0	5
CLC Software	€ 500	€ 0	1

Consumables

In the following, the consumables used for sample preparation and sequencing considered for the cost calculation are listed. Consumables include items that are used up in laboratory processes, such as chemicals, petri dishes, etc. For each item, the table provides the cost per sample, the step of analysis it is used for and the failure rate. The failure rate refers to the percentage of consumables that are wasted, e.g. due to failed runs, and is taken into account in the cost calculation.

This approach was similarly applied for all methods listed below.

	Cost per sample (Euro)	*Step of analysis*	*% failure*
RNA isolation kit	€ 6.00	Sample processing	20
RT-PCR kit	€ 5.00		
Consumables	€ 3.00		
Ligase	€ 0.50	Library Preparation	0
Sequencing kit	€ 2.50		
Consumables	€ 2.50		
Flowcell	€ 11.00	Sequencing	2

Staff time per sample in minutes

The following provides the estimated staff time per sample spent on each step, separately for professionals and for technicians. The amount of 'hands-on staff time' is indicated, i.e. the amount of staff

time actually used to perform an activity, including maintenance of equipment and staff time used for failed runs, but excluding unsupervised processes (e.g. time that the sequencer is running unsupervised). Where several samples are treated at the same time, total staff time is divided to obtain the per-sample staff time. For example, if sample processing for 40 samples takes 2 hours and 40 minutes for a laboratory technician, this figure is converted to minutes (160 minutes), and divided by 40, resulting in a technician staff time of 4 minutes per sample.

This approach was similarly applied for all methods listed below.

Staff category *Step*	*Professionals** *(staff time in minutes)*	*Technicians*** *(staff time in minutes)*
Sample processing	0	48
Library preparation	0	13
Sequencing	6	6
Bioinformatics & other analyses	12	24
Reference dataset	0	0

The definition of these catgories is based on the International Standard Classification of Occupations of the International Labour Office (ILO).

**For "Professionals", occupations typically involve the performance of tasks that require complex problem-solving, decision-making and creativity based on an extensive body of theoretical and factual knowledge in a specialised field. The knowledge and skills required are typically obtained as the result of study at a higher educational institution for a period of 3-6 years following completion of secondary education leading to the award of a first degree or higher qualification. This category includes PhD candidates and Post-docs.*

***For "Technicians", occupations typically involve the performance of complex technical and practical tasks that require an extensive body of factual, technical and procedural knowledge in a specialised field. The knowledge and skills required are usually obtained as the result of study at a higher educational institution for a period of 1-3 years following completion of secondary education. This category includes laboratory assistants.*

II. Conventional method A: Real Time PCR

Equipment

	Total purchase price (Euro)	*Annual maintenance costs (Euro)*	*Predicted lifespan (years)*
Lightcycler	€ 40 200	€ 3 931	10
Magnapure 96	€ 125 619	€ 9 309	10

Consumables

	Cost per sample (Euro)	*% failure**
RNA isolation kit	€ 6.00	0
Real Time PCR kit (5x per sample)	€ 25.00	

Staff time per sample in minutes

	Professionals	*Technicians*
Staff time in minutes	0	84

III. Conventional method B: Sanger Sequencing

Equipment			
	Total purchase price (Euro)	*Annual maintenance costs (Euro)*	*Predicted lifespan (years)*
3130XL sequencer	€ 44 118	€ 13 759	10
Computer + DNAstar	€ 500	€ 0	5

Consumables		
	Cost per sample (Euro)	*% failure**
RT-PCR Kit (2x per sample HA NA)	€ 20.00	0
Big Dye Terminator	€ 0.75	
Consumables	€ 3.00	

Staff time per sample in minutes		
	Professionals	*Technicians*
Staff time in minutes	0	60

III. Conventional method C: Virus isolation

Equipment			
	Total purchase price (Euro)	*Annual maintenance costs (Euro)*	*Predicted lifespan (years)*
CO2 incubators	€ 14 528	€ 0	10

Consumables		
	Cost per sample (Euro)	*% failure**
Culture media and plasticware	€ 10.00	0

Staff time per sample in minutes		
	Professionals	*Technicians*
Staff time in minutes	0	30

IV. Conventional method D: Hemagglutination inhibition

Equipment			
	Total purchase price (Euro)	*Annual maintenance costs (Euro)*	*Predicted lifespan (years)*
Tecan EVO	€ 59 000	€ 6 000	15

Consumables		
	Cost per sample (Euro)	*% failure**
Plasticware, red blood cells, ferret sera	€ 3.00	0

Staff time per sample in minutes			
	Professionals		*Technicians*
Staff time in minutes	5		18
V. Conventional method E: Virus neutralisation			
Equipment			
	Total purchase price (Euro)	*Annual maintenance costs (Euro)*	*Predicted lifespan (years)*
CTL-immunospot	€ 100 000	€ 0	10
Consumables			
	Cost per sample (Euro)		*% failure**
Plasticware, red blood cells, ferret sera	€ 13.00		0
Staff time per sample in minutes			
	Professionals		*Technicians*
Staff time in minutes	5		102
VI. Conventional method F: NA star			
Equipment			
	Total purchase price (Euro)	*Annual maintenance costs (Euro)*	*Predicted lifespan (years)*
Tecan Infinite	€ 25 000	€ 2 500	15
Consumables			
	Cost per sample (Euro)		*% failure**
Chemicals	€ 2.00		0
Staff time per sample in minutes			
	Professionals		*Technicians*
Staff time in minutes	0		42
XIII. Key variables			
Labour costs			
The following table provides the hourly labour cost data (in Euro) used for monetisation of staff time. Figures below refer to Eurostat data on labour costs for 2017 (by staff category), plus a 25% surcharge for overheads.			
	Professionals		*Technicians*
Netherlands	€ 53.20		€ 28.20

EU	€ 45.10	€ 24.50
Source: Eurostat, Labour cost levels by NACE Rev. 2 activity [lc_lci_lev]. Construct: Labour cost for LCI (compensation of employees plus taxes minus subsidies). NACE categories: Professional, scientific and technical activities; Administrative and support service activities. Extracted in June 2018.		
Other		
…		

ANNEX: Data collected for cost calculation - IZLER

I. WGS

Equipment

In the following, the equipment used for sample preparation, sequencing, bioinformatics and other analyses considered for the cost calculation is listed. For each piece of equipment, the table provides the total unit price at the time of purchase (including VAT), annual maintenance costs, and predicted lifespan. Only equipment was considered that costed EUR 400 or more that qualify as capital expenditure relevant for WGS, such as sequencing machines and durable lab equipment as well as specific software purchasing or licensing fees. Not included were basic laboratory equipment (e.g. refrigerators, centrifuges or pipettes), standard office computers and standard office software. Note that the predicted lifespan of equipment is based on standard values and applied uniformly across case studies. Lifespans used for accounting purposes by each case institution may differ.

This approach was similarly applied for all methods listed below.

	Total purchase price (Euro)	*Annual maintenance costs (Euro)*	*Predicted lifespan (years)*
Biorad-T100 thermal cycler	€ 4 000	€ 0	10
Biorad-CFX96 RT-System	€ 24 400	€ 0	10
Microplate-Genie-Shaker	€ 700	€ 0	10
MiSeq (Illumina, USA)	€ 100 000	€ 12 000	10
Workstations (3 pieces)	€ 5 000	€ 0	5
Storage unit	€ 18 500	€ 0	5
Bionumerics License	€ 10 720	€ 0	10

Consumables

In the following, the consumables used for sample preparation and sequencing considered for the cost calculation are listed. Consumables include items that are used up in laboratory processes, such as chemicals, petri dishes, etc. For each item, the table provides the cost per sample, the step of analysis it is used for and the failure rate. The failure rate refers to the percentage of consumables that are wasted, e.g. due to failed runs, and is taken into account in the cost calculation.

This approach was similarly applied for all methods listed below.

	Cost per sample (Euro)	*Step of analysis*	*% failure*
Qiagen DNAeasy Kit	€ 4.00	Sample processing	1
Tips	€ 0.25		
Eppendeorfs vials	€ 0.01		
Gloves	€ 0.01		
General Reagents	€ 0.01		
Tips 200ul	€ 0.37	Library preparation	5
Tips 100 ul	€ 0.36		
Tips 1000 ul	€ 0.01		
Nextera Xt index	€ 2.49		
Agencourt Ampure XP	€ 1.77		
Tips 20 ul	€ 0.37		
PCR-tube	€ 0.02		

Micro-Plate	€ 0.29		
Gloves	€ 0.01		
Deepwell plate	€ 0.25		
Microseal A	€ 0.48		
Microseal B	€ 0.08		
Nextera XT DNA SAMP Prep	€ 38.12		
MiSeq Reagent Kit V2 (2x250)	€ 113.07	Sequencing	1

Staff time per sample in minutes

The following provides the estimated staff time per sample spent on each step, separately for professionals and for technicians. The amount of 'hands-on staff time' is indicated, i.e. the amount of staff time actually used to perform an activity, including maintenance of equipment and staff time used for failed runs, but excluding unsupervised processes (e.g. time that the sequencer is running unsupervised). Where several samples are treated at the same time, total staff time is divided to obtain the per-sample staff time. For example, if sample processing for 40 samples takes 2 hours and 40 minutes for a laboratory technician, this figure is converted to minutes (160 minutes), and divided by 40, resulting in a technician staff time of 4 minutes per sample.

This approach was similarly applied for all methods listed below.

Staff category *Step*	*Professionals** *(staff time in minutes)*	*Technicians*** *(staff time in minutes)*
Sample processing	0	20
Library preparation	0	10
Sequencing	0	5
Bioinformatics & other analyses	60	0
Reference dataset	10	0

The definition of these categories is based on the International Standard Classification of Occupations of the International Labour Office (ILO).

**For "Professionals", occupations typically involve the performance of tasks that require complex problem-solving, decision-making and creativity based on an extensive body of theoretical and factual knowledge in a specialised field. The knowledge and skills required are typically obtained as the result of study at a higher educational institution for a period of 3-6 years following completion of secondary education leading to the award of a first degree or higher qualification. This category includes PhD candidates and Post-docs.*

***For "Technicians", occupations typically involve the performance of complex technical and practical tasks that require an extensive body of factual, technical and procedural knowledge in a specialised field. The knowledge and skills required are usually obtained as the result of study at a higher educational institution for a period of 1-3 years following completion of secondary education. This category includes laboratory assistants.*

II. Conventional method A: Serotyping

Equipment

No equipment other than basic laboratory equipment is used for serotyping, therefore there are no associated costs.

Consumables

	Cost per sample (Euro)	*% failure**
Media	€ 2.29	0.1
Antisera	€ 4.84	
Plasticware and gloves	€ 0.62	

Staff time per sample in minutes

	Professionals	*Technicians*
Staff time in minutes	3	38

III. Conventional method B: PFGE

Equipment

	Total purchase price (Euro)	*Annual maintenance costs (Euro)*	*Predicted lifespan (years)*
Shacking waterbath	€ 3 000	€ 0	10
Biorad Mapper Apparatus	€ 21 000	€ 0	10
Image Acquisition apparatus	€ 12 000	€ 0	10
Bionumerics License	€ 11 170	€ 0	10

Consumables

	Cost per sample (Euro)	*% failure**
Media	€ 0.17	3
Buffers	€ 12.31	
Restriction Enzymes	€ 1.06	
Plasticware and gloves	€ 0.46	

Staff time per sample in minutes

	Professionals	*Technicians*
Staff time in minutes	2.5	38

IV. Conventional method C: PCR Verification

Equipment

	Total purchase price (Euro)	*Annual maintenance costs (Euro)*	*Predicted lifespan (years)*
Biorad-T100 thermal cycler	€ 4 000	0	10
Image Acquisistioin apparatus	€ 12 000	0	10

Consumables

	Cost per sample (Euro)	*% failure**

Media	€ 0.02	5
Baffers and reagents	€ 2.03	
Oligos and Taq	€ 0.36	
Plasticware and gloves	€ 0.24	
Staff time per sample in minutes		
	Professionals	*Technicians*
Staff time in minutes	1	10
V. Conventional method D: MLVA		
MLVA is outsourced to another lab in the institute's network, for a cost of € 43.13 per sample.		
VI. Key variables		
Labour costs		
The following table provides the hourly labour cost data (in Euro) used for monetisation of staff time. Figures below refer to Eurostat data on labour costs for 2017 (by staff category), plus a 25% surcharge for overheads.		
	Professionals	*Technicians*
Italy	€ 44.9	€ 23.9
EU	€ 45.1	€ 24.5
Source: Eurostat, Labour cost levels by NACE Rev. 2 activity [lc_lci_lev]. Construct: Labour cost for LCI (compensation of employees plus taxes minus subsidies). NACE categories: Professional, scientific and technical activities; Administrative and support service activities. Extracted in June 2018.		
Exchange rate (if relevant)		
…		
…		
Other		
…		
…		

ANNEX: Data collected for cost calculation - ANLIS

I. WGS

Equipment

In the following, the equipment used for sample preparation, sequencing, bioinformatics and other analyses considered for the cost calculation is listed. For each piece of equipment, the table provides the total unit price at the time of purchase (including VAT), annual maintenance costs, and predicted lifespan. Only equipment was considered that costed EUR 400 or more that qualify as capital expenditure relevant for WGS, such as sequencing machines and durable lab equipment as well as specific software purchasing or licensing fees. Not included were basic laboratory equipment (e.g. refrigerators, centrifuges or pipettes), standard office computers and standard office software. Note that the predicted lifespan of equipment is based on standard values and applied uniformly across case studies. Lifespans used for accounting purposes by each case institution may differ.

This approach was similarly applied for all methods listed below.

	Total purchase price (Euro)	*Annual maintenance costs (Euro)*	*Predicted lifespan (years)*
Qiacube DNA	€ 13 724	€ 974	10
Qubit 3.0	€ 1 743	€ 0	10
Bioshake iQ Thermomixer	€ 1 201	€ 0	10
MiSeq Illumina	€ 75 273	€ 6 072	10
Server	€ 19 474	€ 0	5
Computer	€ 3 614	€ 452	5
Computer	€ 3 614	€ 452	5

Consumables

In the following, the consumables used for sample preparation and sequencing considered for the cost calculation are listed. Consumables include items that are used up in laboratory processes, such as chemicals, petri dishes, etc. For each item, the table provides the cost per sample, the step of analysis it is used for and the failure rate. The failure rate refers to the percentage of consumables that are wasted, e.g. due to failed runs, and is taken into account in the cost calculation.

This approach was similarly applied for all methods listed below.

	Cost per sample (Euro)	*Step of analysis*	*% failure*
Qiacube box	€ 1.70	Sample processing	0
2mL Eppendorf DNA LoBindMicrocentifuge Tubes	€ 0.00		
Filter tips 200ul (1024) for Qiacube	€ 1.04		
Filter tips 1000ul (1024) for Qiacube	€ 0.70		
96 samples (Illumina, Cat # FC-131-1096)	€ 27.66	Library preparation	5
96 indices, 384 samples (Illumina, Cat # FC-131-1002)	€ 2.24		
Agencourt AMPure XP Beads, 60 ml (Beckman	€ 0.69		

Coulter, Cat # A63881)			
Qubit reagent BR	€ 0.46		
Qubit reagent HS	€ 0.46		
100 ul Filter tips	€ 0.11		
10 ul Filter tips	€ 0.11		
1000 ul filter tips	€ 0.07		
General consumables	€ 1.77		
MiSeq Reagent Kit v2 500 cycles	€ 62.79	Sequencing	5

Staff time per sample in minutes

The following provides the estimated staff time per sample spent on each step, separately for professionals and for technicians. The amount of 'hands-on staff time' is indicated, i.e. the amount of staff time actually used to perform an activity, including maintenance of equipment and staff time used for failed runs, but excluding unsupervised processes (e.g. time that the sequencer is running unsupervised). Where several samples are treated at the same time, total staff time is divided to obtain the per-sample staff time. For example, if sample processing for 40 samples takes 2 hours and 40 minutes for a laboratory technician, this figure is converted to minutes (160 minutes), and divided by 40, resulting in a technician staff time of 4 minutes per sample.

This approach was similarly applied for all methods listed below.

Staff category *Step*	*Professionals** *(staff time in minutes)*	*Technicians*** *(staff time in minutes)*
Sample processing	11	0
Library preparation	18	0
Sequencing	2	0
Bioinformatics & other analyses	60	0
Reference dataset	0	0

The definition of these categories is based on the International Standard Classification of Occupations of the International Labour Office (ILO).

**For "Professionals", occupations typically involve the performance of tasks that require complex problem-solving, decision-making and creativity based on an extensive body of theoretical and factual knowledge in a specialised field. The knowledge and skills required are typically obtained as the result of study at a higher educational institution for a period of 3-6 years following completion of secondary education leading to the award of a first degree or higher qualification. This category includes PhD candidates and Post-docs.*

***For "Technicians", occupations typically involve the performance of complex technical and practical tasks that require an extensive body of factual, technical and procedural knowledge in a specialised field. The knowledge and skills required are usually obtained as the result of study at a higher educational institution for a period of 1-3 years following completion of secondary education. This category includes laboratory assistants.*

II. Conventional method A: Biochemical testing

Equipment

No equipment other than basic laboratory equipment is used for biochemical testing, therefore there are no associated costs.

Consumables		
	Cost per sample (Euro)	*% failure**
General consumables	*Not available*	*Not available*

Staff time per sample in minutes		
	Professionals	*Technicians*
Staff time in minutes	2	13.8

III. Conventional method B: Serotyping

Equipment

No equipment other than basic laboratory equipment is used for biochemical testing, therefore there are no associated costs.

Consumables		
	Cost per sample (Euro)	*% failure**
General consumables	*Not available*	*Not available*

Staff time per sample in minutes		
	Professionals	*Technicians*
Staff time in minutes	10	35

IV. Conventional method C: PCR typing

Equipment

	Total purchase price (Euro)	*Annual maintenance costs (Euro)*	*Predicted lifespan (years)*
Biorad Mycycler thermal cycler	€ 2 466	0	10

Consumables		
	Cost per sample (Euro)	*% failure**
General consumables	*Not available*	*Not available*

Staff time per sample in minutes		
	Professionals	*Technicians*
Staff time in minutes	20	0

V. Conventional method D: MaldiTOF

Equipment

	Total purchase price (Euro)	*Annual maintenance costs (Euro)*	*Predicted lifespan (years)*

MaldiTOF	€ 188 239	0	10

Consumables		
	Cost per sample (Euro)	*% failure**
General consumables	*Not available*	*Not available*

Staff time per sample in minutes		
	Professionals	*Technicians*
Staff time in minutes	10	0

VI. Conventional method E: PFGE

Equipment			
	Total purchase price (Euro)	*Annual maintenance costs (Euro)*	*Predicted lifespan (years)*
PFGE Biorad	€ 32 157	0	10

Consumables		
	Cost per sample (Euro)	*% failure**
General consumables	*Not available*	*Not available*

Staff time per sample in minutes		
	Professionals	*Technicians*
Staff time in minutes	25	0

VII. Key variables

Labour costs

The following table provides the hourly labour cost data (in Euro) used for monetisation of staff time. Figures below refer to data provided by ANLIS on labour costs for professional staff for 2017, plus a 25% surcharge for overheads. Labour costs for technician staff were imputed from professional staff costs.

	Professionals	*Technicians*
Argentina	€ 4.52	€ 2.67

ANNEX : Data collected for cost calculation - MDH

I. WGS

Equipment

In the following, the equipment used for sample preparation, sequencing, bioinformatics and other analyses considered for the cost calculation is listed. For each piece of equipment, the table provides the total unit price at the time of purchase (including VAT), annual maintenance costs, and predicted lifespan. Only equipment was considered that costed EUR 400 or more that qualify as capital expenditure relevant for WGS, such as sequencing machines and durable lab equipment as well as specific software purchasing or licensing fees. Not included were basic laboratory equipment (e.g. refrigerators, centrifuges or pipettes), standard office computers and standard office software. Note that the predicted lifespan of equipment is based on standard values and applied uniformly across case studies. Lifespans used for accounting purposes by each case institution may differ.

This approach was similarly applied for all methods listed below.

	Total purchase price (Euro)	*Annual maintenance costs (Euro)*	*Predicted lifespan (years)*
MagNA Pure 24	€ 44 260	€ 8 062	10
Multichannel & Single Channel Pipettes	€ 3 203	€ 0	5
Illumina MiSeq	€ 84 093	€ 13 694	10
Illumina MiSeq	€ 71 531	€ 13 694	10
CLC Genomics WorkBench	€ 3 895	€ 974	10
BaseSpace annual iCredit subscription	€ 0	€ 1 328	1
PC	€ 1 770	€ 0	5

Consumables

In the following, the consumables used for sample preparation and sequencing considered for the cost calculation are listed. Consumables include items that are used up in laboratory processes, such as chemicals, petri dishes, etc. For each item, the table provides the cost per sample, the step of analysis it is used for and the failure rate. The failure rate refers to the percentage of consumables that are wasted, e.g. due to failed runs, and is taken into account in the cost calculation.

This approach was similarly applied for all methods listed below.

	Cost per sample (Euro)	*Step of analysis*	*% failure*
MagNA Pure 24 Processing Cartridge	€ 3.58	Sample processing	1
Magnapure 24 Total NA isolation kit	€ 5.60		
MagNA Pure Filter Tips 1000uL	€ 0.86		
MagNA Pure Tube (2mL)	€ 0.94		
Sealing Foil	€ 0.14		
MagNA Pure 24 Tip Park & Piercing tools	€ 0.24		
*Nextera XT Library Prep (v2 kit)**	€ 26.28	Library preparation	5.25

Nextera XT Library Prep (v3 kit)†	€ 26.28		
*Index Set A**	€ 2.12		
Index Set A†	€ 2.12		
*Index Set C**	€ 2.12		
Index Set C†	€ 2.12		
Ampure XP	€ 1.33		
Disposables (racks, pipette tips, gown, gloves, etc)	€ 10.62		*Factored into per-sample cost*
*500 Cycle v2 Kit**	€ 56.43	Sequencing	7.4
600 Cycle v3 Kit†	€ 40.19		6.6

*Note: MDH used both v2 (batch size of 16) and v3 (batch size of 32) library preparation and sequencing kits during the case study period, and indicated that these kits were used about equally. The per-sample costs for these consumables have been adjusted for their relative use and batch sizes. Items in the list above indicated with * belong to the v2 kit and † to the v3 kit.*

Staff time per sample in minutes

The following provides the estimated staff time per sample spent on each step, separately for professionals and for technicians. The amount of 'hands-on staff time' is indicated, i.e. the amount of staff time actually used to perform an activity, including maintenance of equipment and staff time used for failed runs, but excluding unsupervised processes (e.g. time that the sequencer is running unsupervised). Where several samples are treated at the same time, total staff time is divided to obtain the per-sample staff time. For example, if sample processing for 40 samples takes 2 hours and 40 minutes for a laboratory technician, this figure is converted to minutes (160 minutes), and divided by 40, resulting in a technician staff time of 4 minutes per sample.

This approach was similarly applied for all methods listed below.

Staff category / *Step*	*Professionals** *(staff time in minutes)*	*Technicians*** *(staff time in minutes)*
Sample processing	1.87	0
Library preparation	12.19	0
Sequencing	0	0
Bioinformatics & other analyses	15.31	0
Reference dataset	0	0

The definition of these catgories is based on the International Standard Classification of Occupations of the International Labour Office (ILO).

**For "Professionals", occupations typically involve the performance of tasks that require complex problem-solving, decision-making and creativity based on an extensive body of theoretical and factual knowledge in a specialised field. The knowledge and skills required are typically obtained as the result of study at a higher educational institution for a period of 3-6 years following completion of secondary education leading to the award of a first degree or higher qualification. This category includes PhD candidates and Post-docs.*

***For "Technicians", occupations typically involve the performance of complex technical and practical tasks that require an extensive body of factual, technical and procedural knowledge in a specialised field.*

The knowledge and skills required are usually obtained as the result of study at a higher educational institution for a period of 1-3 years following completion of secondary education. This category includes laboratory assistants.

II. Conventional method A: PFGE			
Equipment			
	Total purchase price (Euro)	*Annual maintenance costs (Euro)*	*Predicted lifespan (years)*
GelDoc	€ 16 880	€ 531	10
GelDoc	€ 20 140	€ 531	10
GelDoc	€ 23 109	€ 531	10

Consumables		
	Cost per sample (Euro)	*% failure*
Reagents	€ 13.72	*2*
Lab Supplies	€ 16.82	

Staff time per sample in minutes		
	Professionals	*Technicians*
Staff time in minutes	58	0

III. Conventional method B: Real-Time PCR			
Equipment			
	Total purchase price (Euro)	*Annual maintenance costs (Euro)*	*Predicted lifespan (years)*
ABI 7500	€ 46 669	€ 7 967	10

Consumables		
	Cost per sample (Euro)	*% failure**
Reagents	€ 7.78	*1*
Lab Supplies	€ 4.65	

Staff time per sample in minutes		
	Professionals	*Technicians*
Staff time in minutes	30	0

IV. Conventional method C: MALDI-TOF			
Equipment			
	Total purchase price	*Annual maintenance*	*Predicted lifespan*

	(Euro)	*costs (Euro)*	*(years)*
MALDI-TOF	€ 195 140	€ 17 704	10

Consumables		
	Cost per sample (Euro)	*% failure**
Reagents	€ 1.33	5
Lab Supplies	€ 1.77	

Staff time per sample in minutes		
	Professionals	*Technicians*
Staff time in minutes	2	0

XIII. Key variables

Labour costs

The following table provides the hourly labour cost data (in Euro) used for monetisation of staff time. Figures below refer to labour costs provided by the case study institution for country-specific costs and Eurostat data on labour costs for 2017 (by staff category) for EU costs. In both cases, a 25% surcharge has been added for overheads.

	Professionals	*Technicians*
US	€ 42.05	*N/A*
EU	€ 45.10	€ 24.50

Source: US – data provided by MDH. EU - Eurostat, Labour cost levels by NACE Rev. 2 activity [lc_lci_lev]. Construct: Labour cost for LCI (compensation of employees plus taxes minus subsidies). NACE categories: Professional, scientific and technical activities; Administrative and support service activities. Extracted in June 2018.

Other	
…	
…	

ANNEX : Data collected for cost calculation - PHAC

I. WGS

Equipment

In the following, the equipment used for sample preparation, sequencing, bioinformatics and other analyses considered for the cost calculation is listed. For each piece of equipment, the table provides the total unit price at the time of purchase (including VAT), annual maintenance costs, and predicted lifespan. Only equipment was considered that costed EUR 400 or more that qualify as capital expenditure relevant for WGS, such as sequencing machines and durable lab equipment as well as specific software purchasing or licensing fees. Not included were basic laboratory equipment (e.g. refrigerators, centrifuges or pipettes), standard office computers and standard office software. Note that the predicted lifespan of equipment is based on standard values and applied uniformly across case studies. Lifespans used for accounting purposes by each case institution may differ.

This approach was similarly applied for all methods listed below.

	Total purchase price (Euro)	*Annual maintenance costs (Euro)*	*Predicted lifespan (years)*
Tapestation	€ 38 883.96	€ 0.00	5
Blue Pippin	€ 10 232.62	€ 0.00	10
QUBIT	€ 2 524.05	€ 0.00	10
Illumina Miseq	€ 88 115.04	€ 9 216.90	10
Illumina Miseq	€ 88 115.04	€ 9 216.90	10
Illumina Miseq	€ 88 115.04	€ 9 216.90	10
Storage, NAS, 26 Nodes	€ 1 381 852.94	€ 0.00	5
Internal Networking	€ 142 691.34	€ 0.00	5
Compute Servers, 30 Nodes	€ 1 269 884.62	€ 0.00	5
BioNumerics Calculation Engine	€ 0.00	€ 10 923.74	10
BioNumerics Server	€ 17 054.37	€ 0.00	10
BioNumerics Client (7.x) x 10	€ 0.00	€ 12 289.21	1
BioNumerics Client (7.x) x 10	€ 75 039.23	€ 0.00	10
BioNumerics master scripts	€ 6 139.57	€ 0.00	10

Consumables

In the following, the consumables used for sample preparation and sequencing considered for the cost calculation are listed. Consumables include items that are used up in laboratory processes, such as chemicals, petri dishes, etc. For each item, the table provides the cost per sample, the step of analysis it is used for and the failure rate. The failure rate refers to the percentage of consumables that are wasted, e.g. due to failed runs, and is taken into account in the cost calculation.

This approach was similarly applied for all methods listed below.

	Cost per sample (Euro)	*Step of analysis*	*% failure*
EZ1 kit	€ 6.25	Sample processing	5
BioRad plates	€ 5.24		

Plates	€ 0.28	Library preparation	5
PCR CleanDX	€ 0.55		
TapeStation Tape + Reagent	€ 0.42		
TapeStation Tips	€ 0.04		
TapeStation 8-strip tubes	€ 0.02		
TapeStation plate	€ 0.00		
Reservoirs	€ 0.08		
Nextera XT Library Kit	€ 16.20		
2X KAPA HiFi HotStart ReadyMix	€ 3.73		
Pippin casette	€ 1.09		
Qubit (2x for each pool, reagent & tubes)	€ 0.21		
PCR CleanDX	€ 0.01		
Micrcon column	€ 0.29		
Cartridge + flow cell (600 v3)	€ 32.00	Sequencing	5

Staff time per sample in minutes

The following provides the estimated staff time per sample spent on each step, separately for professionals and for technicians. The amount of 'hands-on staff time' is indicated, i.e. the amount of staff time actually used to perform an activity, including maintenance of equipment and staff time used for failed runs, but excluding unsupervised processes (e.g. time that the sequencer is running unsupervised). Where several samples are treated at the same time, total staff time is divided to obtain the per-sample staff time. For example, if sample processing for 40 samples takes 2 hours and 40 minutes for a laboratory technician, this figure is converted to minutes (160 minutes), and divided by 40, resulting in a technician staff time of 4 minutes per sample.

This approach was similarly applied for all methods listed below.

Staff category *Step*	*Professionals** *(staff time in minutes)*	*Technicians*** *(staff time in minutes)*
Sample processing	0	19.2†
Library preparation	0	
Sequencing	0	
Bioinformatics & other analyses	71.4	0
Reference dataset	19.0	0

† Figure provided for all wet-lab steps, including sample processing, library preparation and sequencing. Based on an average batch size of 32.

The definition of these categories is based on the International Standard Classification of Occupations of the International Labour Office (ILO).

**For "Professionals", occupations typically involve the performance of tasks that require complex*

problem-solving, decision-making and creativity based on an extensive body of theoretical and factual knowledge in a specialised field. The knowledge and skills required are typically obtained as the result of study at a higher educational institution for a period of 3-6 years following completion of secondary education leading to the award of a first degree or higher qualification. This category includes PhD candidates and Post-docs.
***For "Technicians", occupations typically involve the performance of complex technical and practical tasks that require an extensive body of factual, technical and procedural knowledge in a specialised field. The knowledge and skills required are usually obtained as the result of study at a higher educational institution for a period of 1-3 years following completion of secondary education. This category includes laboratory assistants.*

II. Conventional method A: Biochemical testing		
Equipment		
Basic laboratory equipment only (conventional test tubes)		
Consumables		
	Cost per sample (Euro)	*% failure*
General consumables	€ 2.30	5
Staff time per sample in minutes		
	Professionals	*Technicians*
Staff time in minutes	0	40

III. Conventional method B: Serotyping		
Equipment		
Basic laboratory equipment only (conventional slide aggutination methods)		
Consumables		
	Cost per sample (Euro)	*% failure**
General consumables	€ 4.87	5
Staff time per sample in minutes		
	Professionals	*Technicians*
Staff time in minutes	0	40

IV. Conventional method C: PFGE			
Equipment			
	Total purchase price (Euro)	*Annual maintenance costs (Euro)*	*Predicted lifespan (years)*
PFGE – CHEF DRIII	€ 37 855	€ 6 827	10
PFGE – CHEF DRIII	€ 37 855	€ 6 827	10
PFGE – CHEF DRIII	€ 37 855	€ 6 827	10

PFGE – CHEF DRIII	€ 37 855	€ 6 827	10
PFGE – CHEF DRIII	€ 37 855	€ 6 827	10
PFGE – CHEF DRIII	€ 37 855	€ 6 827	10
PFGE – CHEF DRIII	€ 37 855	€ 6 827	10
PFGE – CHEF DRIII	€ 37 855	€ 6 827	10
PFGE – CHEF DRIII	€ 37 855	€ 6 827	10
PFGE – CHEF DRIII	€ 37 855	€ 6 827	10

Consumables		
	Cost per sample (Euro)	*% failure**
General consumables	€ 39.60	5

Staff time per sample in minutes		
	Professionals	*Technicians*
Staff time in minutes	14.8	30.0

XIII. Key variables

Labour costs

The following table provides the hourly labour cost data (in Euro) used for monetisation of staff time. Figures below refer to labour costs provided by the case study institution for country-specific costs and Eurostat data on labour costs for 2017 (by staff category) for EU costs. In both cases, a 25% surcharge has been added for overheads.

	Professionals	*Technicians*
Canada	€ 41.03	€ 24.62
EU	€ 45.10	€ 24.50

Source: Canada – data provided by PHAC. EU - Eurostat, Labour cost levels by NACE Rev. 2 activity [lc_lci_lev]. Construct: Labour cost for LCI (compensation of employees plus taxes minus subsidies). NACE categories: Professional, scientific and technical activities; Administrative and support service activities. Extracted in June 2018.

Other	
…	
…	

ANNEX : Data collected for cost calculation - PHE

I. WGS

Equipment

In the following, the equipment used for sample preparation, sequencing, bioinformatics and other analyses considered for the cost calculation is listed. For each piece of equipment, the table provides the total unit price at the time of purchase (including VAT), annual maintenance costs, and predicted lifespan. Only equipment was considered that costed EUR 400 or more that qualify as capital expenditure relevant for WGS, such as sequencing machines and durable lab equipment as well as specific software purchasing or licensing fees. Not included were basic laboratory equipment (e.g. refrigerators, centrifuges or pipettes), standard office computers and standard office software. Note that the predicted lifespan of equipment is based on standard values and applied uniformly across case studies. Lifespans used for accounting purposes by each case institution may differ.

This approach was similarly applied for all methods listed below.

	Total purchase price (Euro)	*Annual maintenance costs (Euro)*	*Predicted lifespan (years)*
QIASYMPHONY	€ 59 693	€ 17 681	10
QIASYMPHONY	€ 59 693	€ 17 681	10
ROCHE MAGNA PURE 96	€ 99 195	€ 6 844	10
cBot Cluster Generation System	€ 49 174	€ 4 563	10
cBot Cluster Generation System	€ 49 174	€ 4 563	10
LABCHIP GX	€ 52 950	€ 6 844	10
LABCHIP GX	€ 52 950	€ 6 844	10
ASSY-SCICLONE, G3 WGS, HV HEAD, L GRIP	€ 91 635	€ 10 266	10
ASSY-SCICLONE, G3 WGS, HV HEAD, L GRIP	€ 91 635	€ 10 266	10
ASSY-SCICLONE, G3 WGS, HV HEAD, L GRIP	€ 91 635	€ 10 266	10
LABCHIP-DS SPECTROPHOTOMETER 96	€ 48 584	€ 5 703	10
Glomax: 96 well plate Fluorometer	€ 14 749	€ 2 281	10
Glomax: 96 well plate Fluorometer	€ 14 749	€ 2 281	10
Biomek NXp Span-8 with integrated sealer and chilled storage	€ 160 770	€ 9 125	10
Biomex NXP Multichannel	€ 78 896	€ 8 745	10
Biomex NXP Multichannel	€ 78 896	€ 8 745	10
Biomex NXP Multichannel	€ 78 896	€ 8 745	10

Biomek NXP Span-8	€ 63 600	€ 9 125	10
Illumina HI-SEQ	€ 606 410	€ 57 034	10
Illumina HI-SEQ	€ 606 410	€ 57 034	10
Bioinformatics	Per-sample cost provided by PHE: € 4.89		

Consumables

In the following, the consumables used for sample preparation and sequencing considered for the cost calculation are listed. Consumables include items that are used up in laboratory processes, such as chemicals, petri dishes, etc. For each item, the table provides the cost per sample, the step of analysis it is used for and the failure rate. The failure rate refers to the percentage of consumables that are wasted, e.g. due to failed runs, and is taken into account in the cost calculation.

This approach was similarly applied for all methods listed below.

	Cost per sample (Euro)	*Step of analysis*	*% failure*
Various reagents and consumables	€ 6.84	Sample processing	0
96 indices, 384 samples	€ 1.94	Library preparation	0.1
nextera 96	€ 23.71		
PE Rapid cluster kit 2x96	€ 5.64		
cBot loading kit (rapid only) 2x 96	€ 1.84		
200 cycle rapid v2 2x96	€ 7.77	Sequencing	0.1
Other various costs	€ 1.88		

Staff time per sample in minutes

The following provides the estimated staff time per sample spent on each step, separately for professionals and for technicians. The amount of 'hands-on staff time' is indicated, i.e. the amount of staff time actually used to perform an activity, including maintenance of equipment and staff time used for failed runs, but excluding unsupervised processes (e.g. time that the sequencer is running unsupervised). Where several samples are treated at the same time, total staff time is divided to obtain the per-sample staff time. For example, if sample processing for 40 samples takes 2 hours and 40 minutes for a laboratory technician, this figure is converted to minutes (160 minutes), and divided by 40, resulting in a technician staff time of 4 minutes per sample.

This approach was similarly applied for all methods listed below.

Staff category *Step*	*Professionals** *(staff time in minutes)*	*Technicians*** *(staff time in minutes)*
Sample processing	2.65	16.85
Library preparation	1.60	0
Sequencing	2.60	0.30
Bioinformatics & other analyses	36.00	0
Reference dataset	0	0

The definition of these catgories is based on the International Standard Classification of Occupations of the International Labour Office (ILO).

**For "Professionals", occupations typically involve the performance of tasks that require complex problem-solving, decision-making and creativity based on an extensive body of theoretical and factual*

knowledge in a specialised field. The knowledge and skills required are typically obtained as the result of study at a higher educational institution for a period of 3-6 years following completion of secondary education leading to the award of a first degree or higher qualification. This category includes PhD candidates and Post-docs.
***For "Technicians", occupations typically involve the performance of complex technical and practical tasks that require an extensive body of factual, technical and procedural knowledge in a specialised field. The knowledge and skills required are usually obtained as the result of study at a higher educational institution for a period of 1-3 years following completion of secondary education. This category includes laboratory assistants.*

II. Conventional method A: PCR (Taqman)

Equipment

	Total purchase price (Euro)	*Annual maintenance costs (Euro)*	*Predicted lifespan (years)*
TaqMan 7500	€ 43 000	€ 1 141	10
TaqMan 7500	€ 43 000	€ 1 141	10
TaqMan 7500	€ 43 000	€ 1 141	10
TaqMan 7500	€ 43 000	€ 1 141	10
TaqMan 7500	€ 43 000	€ 1 141	10

Consumables

	Cost per sample (Euro)	*% failure**
Cupule	€ 0.08	*Costed into per-sample price*
Molecular water	€ 0.05	
Pipette tips	€ 0.07	
Plastic loops	€ 0.02	
Pre-aliquoted PCR strip HilA	€ 1.78	
Pre-aliquoted PCR strip lacZ+ttR	€ 0.14	

Staff time per sample in minutes

	Professionals	*Technicians*
Staff time in minutes	0	5.63

III. Conventional method B: PCR (Monophasic)

Equipment

	Total purchase price (Euro)	*Annual maintenance costs (Euro)*	*Predicted lifespan (years)*
TaqMan 7500	€ 43 000	€ 1 141	10
TaqMan 7500	€ 43 000	€ 1 141	10
TaqMan 7500	€ 43 000	€ 1 141	10
TaqMan 7500	€ 43 000	€ 1 141	10
TaqMan 7500	€ 43 000	€ 1 141	10

Consumables		
	Cost per sample (Euro)	*% failure**
Cupule	€ 0.08	*Costed into per-sample price*
Molecular water	€ 0.05	
Takyon PCR mastermix	€ 1.07	
fliC probe	€ 0.18	
fljB probe	€ 0.15	
fljB/IS200 probe	€ 0.14	
fliC_fw primer	€ 0.04	
fliC_rev primer	€ 0.05	
fljB_fw primer	€ 0.07	
fljB_rev primer	€ 0.05	
fliB/IS200_fw primer	€ 0.22	
fliB/IS200_rev primer	€ 0.05	
Fast 96 well PCR plate	€ 0.22	
Pipette tips	€ 0.05	
Plastic loops	€ 0.02	
Eppendorf tubes	€ 0.00	

Staff time per sample in minutes		
	Professionals	*Technicians*
Staff time in minutes	0	3.96

IV. Conventional method C: PCR (Real-Time)

Equipment			
	Total purchase price (Euro)	*Annual maintenance costs (Euro)*	*Predicted lifespan (years)*
Thermal cyclers	€ 2 446	€ 570	10
Thermal cyclers	€ 2 446	€ 570	10
Thermal cyclers	€ 2 446	€ 570	10
Thermal cyclers	€ 2 446	€ 570	10
Rotor gene	€ 30 831	€ 1 528	10
Rotor gene	€ 30 831	€ 1 528	10
Robot (Beckman etc.)	€ 61 662	€ 8 003	10

Consumables		
	Cost per sample (Euro)	*% failure**
Pipette tips filter	€ 0.77	*Costed into per-sample price*
Pastette fine tip	€ 0.06	

Pastette graduated	€ 0.03	
Universal Plastic 25ml	€ 0.56	
1.5ml skirted Microtube	€ 0.05	
gloves nitrile	€ 0.06	
Dispojar	€ 4.12	
Rotagene PCR strips	€ 0.09	
Probes	€ 1.39	
Primers	€ 1.39	
Water	€ 0.24	
Takyon	€ 0.74	
Staff time per sample in minutes		
	Professionals	*Technicians*
Staff time in minutes	2.50	3.00
V. Conventional method D: MLVA/MLST/fAFLP		
Equipment		
No equipment other than basic laboratory equipment is used for serotyping, therefore there are no associated costs.		
Consumables		
	Cost per sample (Euro)	*% failure**
Cupule	€ 0.08	*Costed into per-sample price*
Molecular water	€ 0.05	
Difco NA plates	€ 0.71	
MOLIS labels	€ 0.06	
Primers	€ 0.41	
Qiagen taq mix	€ 0.27	
2 ml tube	€ 0.04	
Nuclease free water (Severn)	€ 0.01	
filtered tips	€ 0.14	
microamp PCR plate	€ 0.36	
microamp PCR caps	€ 0.03	
Hi-Di	€ 0.04	
PCR plate Foil	€ 0.00	
Liz 1200	€ 0.62	
DBHT Frag. Analysis	€ 1.01	
Tips	€ 0.04	
Staff time per sample in minutes		

	Professionals	*Technicians*
Staff time in minutes	0	7.71

VI. Conventional method E: Serotyping			
Equipment			
	Total purchase price (Euro)	*Annual maintenance costs (Euro)*	*Predicted lifespan (years)*
Thermal cyclers	€ 2 466	€ 570	10
Thermal cyclers	€ 2 466	€ 570	10
Thermal cyclers	€ 2 466	€ 570	10
Thermal cyclers	€ 2 466	€ 570	10
Robot (Beckman etc.)	€ 61 662	€ 8,003	10

Consumables		
	Cost per sample (Euro)	*% failure**
MaConkey plates	€ 0.25	*Costed into per-sample price*
GIA	€ 0.75	
BHI (5ml,UV)	€ 1.86	
BHI (5ml,Tube)	€ 1.42	
Craigies	€ 1.19	
NA slopes (Tubes)	€ 0.71	
DE slopes	€ 0.68	
MOLIS labels	€ 0.02	
Microtitre plates	€ 0.43	
Serum (for'O' microtitre plates, 1:8)-2.7ml/plate	€ 2.89	
Serum (for'H' microtitre plates, 1:32)-2.7ml/plate	€ 0.88	
Serum (for craigies, 1:4)	€ 1.14	
Serum(for slide agglutination)	€ 0.19	
Serum (for titrations)	€ 0.06	
Formal saline	€ 0.41	
Phenol saline	€ 0.02	
Plastic loops	€ 0.11	
Plastic needles	€ 0.02	
Pastettes (short)	€ 0.17	
Gilson tips	€ 0.16	

Staff time per sample in minutes		
	Professionals	*Technicians*
Staff time in minutes	0	27.25

VII. Conventional method F: Phage Typing			
Equipment			
	Total purchase price (Euro)	*Annual maintenance costs (Euro)*	*Predicted lifespan (years)*
Thermal cyclers	€ 2 466	€ 570	10
Thermal cyclers	€ 2 466	€ 570	10
Thermal cyclers	€ 2 466	€ 570	10
Thermal cyclers	€ 2 466	€ 570	10
Consumables			
	Cost per sample (Euro)	*% failure**	
Difco NA plates	€ 1.42	*Costed into per-sample price*	
Dorsets egg slopes	€ 0.68		
Difco nutrient broth (double strength-4ml in tubes)	€ 0.59		
Pastettes	€ 0.07		
Plastic tips (for Pipetmax)	€ 0.14		
Phage suspension (0.16ml/NA plate)	€ 0.08		
Pipette tips	€ 0.05		
MOLIS labels (small)	€ 0.26		
MOLIS labels (V.small)	€ 0.19		
Staff time per sample in minutes			
	Professionals	*Technicians*	
Staff time in minutes	2.25	12.5	
VIII. Conventional method G: PFGE			
No detailed cost data was available for PFGE. PHE's internal calculation of € 97.82 per sample was used instead as a unit cost.			
IX. Conventional method H: D-Tartrate			
Equipment			
No equipment other than basic laboratory equipment is used for serotyping, therefore there are no associated costs.			
Consumables			
	Cost per sample (Euro)	*% failure**	
D-Tartrate tubes	€ 3.84	*Costed into per-sample price*	

Plastic loops	€ 0.05	
Pastettes (short)	€ 0.03	
Lead acetate - saturated solution	€ 3.20	
MOLIS labels	€ 0.13	
Staff time per sample in minutes		
	Professionals	*Technicians*
Staff time in minutes	0	25.00
X. Conventional method I: Glucose gas		
Equipment		
No equipment other than basic laboratory equipment is used for serotyping, therefore there are no associated costs.		
Consumables		
	Cost per sample (Euro)	*% failure**
Glucose tube	€ 0.71	*Costed into per-sample price*
Plastic loop	€ 0.02	
MOLIS label	€ 0.06	
Staff time per sample in minutes		
	Professionals	*Technicians*
Staff time in minutes	0	10.00
XI. Conventional method J: AMR		
Equipment		
No equipment other than basic laboratory equipment is used for serotyping, therefore there are no associated costs.		
Consumables		
	Cost per sample (Euro)	*% failure**
Mackoney plates	€ 0.07	*Costed into per-sample price*
Saline in tubes	€ 0.07	
Microtitre plate	€ 0.01	
Plates	€ 0.58	
ISO agar + antibiotic	€ 0.33	
Muller hinton agar + antibiotic	€ 0.08	
Chromagenic agar	€ 0.01	
Loops	€ 0.04	

Tips	€ 0.04	
Labels	€ 0.14	
Eppendorf tubes	€ 0.04	

Staff time per sample in minutes		
	Professionals	*Technicians*
Staff time in minutes	0	2.00

XII. Conventional method K: Biochemistry

Equipment

	Total purchase price (Euro)	*Annual maintenance costs (Euro)*	*Predicted lifespan (years)*
Thermal cyclers	€ 2 466	€ 570	10
Thermal cyclers	€ 2 466	€ 570	10
Thermal cyclers	€ 2 466	€ 570	10
Thermal cyclers	€ 2 466	€ 570	10
Biolog	€ 110 930	€ 11 115	10
Biolog	€ 110 930	€ 11 115	10

Consumables

	Cost per sample (Euro)	*% failure**
Pipette tips filter	€ 1.54	*Costed into per-sample price*
Pastette fine tip	€ 0.13	
Pastette graduated	€ 0.07	
Universal Plastic 25ml	€ 0.56	
Gloves nitrile	€ 0.11	
Dispojar	€ 0.41	
Microgen plate	€ 9.73	
Inoculators	€ 1.16	
Reservoirs	€ 0.53	
Inoculating fluid	€ 0.44	
Other biochemistry media	€ 11.30	

Staff time per sample in minutes		
	Professionals	*Technicians*
Staff time in minutes	6.00	36.00

XIII. Key variables

Labour costs

The following table provides the hourly labour cost data (in Euro) used for monetisation of staff time.

Figures below refer to Eurostat data on labour costs for 2017 (by staff category), plus a 25% surcharge for overheads.		
	Professionals	*Technicians*
UK	€ 39.6	€ 25.0
EU	€ 45.1	€ 24.5
Source: Eurostat, Labour cost levels by NACE Rev. 2 activity [lc_lci_lev]. Construct: Labour cost for LCI (compensation of employees plus taxes minus subsidies). NACE categories: Professional, scientific and technical activities; Administrative and support service activities. Extracted in June 2018.		
Other		
…		
…		

Deliverable

14.5 Assessment of options for refining selected elements of COMPARE in view of improving the overall cost-effectiveness of the system, with recommendations

Part 2: the economics of disease surveillance from a societal perspective

Version: 1

Due: Month 60

Completed: Month 60

Contributing Partners for this deliverable: EUR

Contents

1. Introduction

This is the fifth deliverable of Work Package 14, which aims to develop a standardised framework for estimating the cost-effectiveness of the COMPARE system and related methods and tools, including the value of safety. The activities of the work package are carried out jointly by WP partners Civic Consulting and Erasmus University Rotterdam (EUR). Deliverable 14.5 consists of two parts.

Part 2 (this document) presents work on the economics of disease surveillance and in particular disease surveillance using Next Generation Sequencing (NGS). Hereby, we take a societal perspective which aims to look at all possible consequences and tries to value these consequences. Chapter 2 starts with a literature review of economic evaluations of interventions related to pandemics and focuses on the costs and benefits that are included in those evaluations. Chapter 3 presents a case study where we estimate societal costs and benefits of early detection in an Ebola outbreak. Chapter 4 presents wider economic issues related the economics of upgrading disease surveillance using NGS. Chapter 5 presents conclusions and recommendations.

2. Costs and benefits of interventions aimed at major infectious disease threats: a review of the literature

2.1 Background

Historically, infectious disease outbreaks have proven to be potentially devastating. A prominent example is the Spanish influenza which may have claimed as many as 50 million lives (1). It is unlikely that no pandemic with the same catastrophic potential will ever emerge again. The number of outbreaks of infectious diseases has been increasing since 1980, as has the number of unique pathogens (2). In order to prevent and effectively combat outbreaks, reporting agreements such as those arranged in the International Health Regulations (IHR) between national governments and international organizations, were established (3). The current IHR require the countries which ratified them to develop a minimum capacity of core functions related to surveillance and response (3). However, with new threats emerging and given the fragile health systems in many parts of the world, outbreaks still have the potential to occur with potentially severe consequences in multiple countries. Therefore, there is a continuous pressure to improve available detection and response systems, and to increase the possibilities of preventing new threats from doing too much harm.

A recent example that illustrates the relevance of outbreak containment, is the Ebola outbreak of 2014. The response to this outbreak received important criticisms, and, as a consequence, the World Health Organization reformed, improving its response to infectious threats (4). Aside from international organizations and non-governmental organizations, under the IHR nations are obliged to have at least a minimum threat handling capacity. However, countries are usually faced with limited healthcare budgets, which require prioritization of what to fund and in which disease areas to invest. Funding of detection and response facilities in case of an outbreak also needs to compete for available resources. Preferably, decisions on how to optimally allocate scarce health care resources are informed by sound estimates of potential costs and benefits of various policy scenarios. Assessing the cost-effectiveness of different prevention and treatment strategies is of utmost importance in order to ensure value for money and optimal health and welfare from the available budgets (5). However, obtaining sound estimates of both costs and effects of intervention strategies, compared to a relevant comparator (such as the current situation or doing nothing) is not a straightforward task, and one that is full of methodological challenges.

To comprehensively capture the costs and benefits related to an intervention, numerous issues need to be considered, including the costs of the intervention itself, the incurred and avoided health losses, and the incurred and avoided treatment costs. A full analysis may also include elements such as production losses due to illness and premature death from the disease, or even broader economic impacts such as those due to reduced trade and tourism. Clearly, some of these elements may be more difficult to estimate and quantify. Importantly, in applied cost-effectiveness analyses, the decision regarding which costs to include, depends on the perspective chosen. The societal perspective aims to capture all relevant costs and effects, regardless of where, when or on whom in society they fall (6). Narrower perspectives, such as the patient's perspective or a healthcare perspective are sometimes used, which limits the scope of the evaluation. Especially for interventions targeted at preventing outbreaks, which can have rather broad impacts, adopting a societal perspective seems warranted (7). Indeed, the impact of outbreaks is not confined to the healthcare sector and interventions to prevent or mitigate these outbreaks are often not confined to healthcare interventions (or funding).

Simulation models are often used to estimate the consequences of preventing or mitigating disease outbreaks (8). Modeling of infectious diseases is typically done using either so-called static or dynamic transmission mod-

els (9). Static models, such as decision trees and Markov models, assume that the probability of infection between individuals is constant over time. Dynamic models allow for the force of infection to be varied, and can include possible herd immunity effects (10). Dynamic models are often considered to be more complex, but may be preferred to static models because they are able to take into account a varying transmission rate, which is highly relevant in this context (9). Both types of models offer the ability to model different scenarios and interventions, and costs and benefits can be estimated using these models by linking them to events and/or states distinguished in the model (9).

An important challenge in infectious disease modeling is to account for behavioral responses that occur when under the threat of an infection (11,12). Whether or not individuals themselves take action in the face of an outbreak (threat), may introduce bias in the evaluation of a policy to mitigate an outbreak (13). For instance, when the actual severity and the perceived severity of an illness diverge, this may complicate forecasts of the impact of interventions. Apart from the challenges in modeling the disease itself, there is also room for improvement in other parts of infectious outbreak policy evaluation. Previous research indicated that outbreak evaluations are often biased towards high-income settings and that little research is done in low-income regions (12). High-income and low-income countries may face a different set of challenges, including different resource and capacity constraints, different threats and different living environments. Such differences need to be accounted for in evaluations and when attempting to translate results of interventions across settings. Furthermore, it should be acknowledged that an intervention, like setting up a surveillance system or response protocol, targeted at one specific disease may strengthen the health care system more generally. This means that the effects of such a measure could go beyond preventing and mitigating one particular type of outbreak. Such "policy spill-over effects" are rarely included (14).

The aim of this study is to systematically review cost-effectiveness studies of major outbreak threats, based on WHO publications (15). The focus of this review will be on investigating the methodological approaches used to estimate costs and (health) benefits, with the aim of improving our understanding of how evaluations of interventions related to outbreaks are currently conducted. This is key, because if decisions are to be based on available evidence, the evidence itself should preferably be comparable, valid and broad enough for policy-makers to consider all relevant elements in the decision-making process.

2.2 Methods

To determine how costs and benefits in economic evaluations of interventions aimed at (potential) outbreaks are estimated, we first compiled a list of major outbreak threats of the 21st century. We based this on publications of the WHO which were produced for the meeting ''Anticipating Emerging Infectious Disease Epidemics' (15). The aim of selecting diseases based on this list was not to capture the most severe diseases or those that, in retrospect, turned out to be found the most costly outbreaks, rather we aimed to collect a broad sample of diseases that have the potential of causing large-scale health and economic damage. Future major outbreaks may have similar characteristics to their predecessors, implying that policy decisions regarding preventing or countering them will (need to) be based on similar information as found in the economic evaluations included here. In this review, we extracted information on study outcomes and methods, using a pre-determined protocol.

Data

We searched PubMed and SCOPUS in April 2018 for the following major outbreaks in the 21st century; SARS in 2003, H5N1 in 2003, H1N1 in 2009, Cholera in Haiti in 2010, MERS-CoV in 2013, H7N9 in 2013 and the West

African Ebola outbreak in 2014. For this search, we constructed three blocks, which we used in combination and all terms were searched for in title and/or abstract. The full syntax for both Pubmed and SCOPUS is available in Appendix 1. The first block was the list of the relevant diseases in various combinations: Middle East respiratory syndrome coronavirus OR SARS OR H5N1OR H1N1 OR Cholera OR MERS-CoV OR H7N9 OR Ebola. The second block defined the study type: economic OR cost* OR costing. The third block complemented the second: benefits OR effectiveness OR cost-effectiveness OR cost-benefit OR cost-utility. Lastly, filters were applied to include studies from 2003 and onwards and exclude studies with only animal subjects. We only considered articles published from 2003, given that we focused on the outbreaks of 2003 and later. We assumed that no articles had been published on the relevant outbreaks before their occurrence.

Study selection

We performed two screening rounds. In the first round, we screened articles based on title and abstract. In the second round, we screened full-text articles. Studies reviewed in full-text, but subsequently excluded, are shown with a justification for their exclusion in Appendix 2. We included peer-reviewed studies that conducted a quantitative economic evaluation of any form (cost-minimization, cost-effectiveness, cost-utility, or cost-benefit evaluations) with one or more comparators, and evaluated one or more interventions within the context of the outbreaks previously mentioned. We included studies based on actual reported case data but also included studies using measures of how infectious a disease is based on observations to model the outbreak, for example force of infection. We excluded review papers and only included studies written in English.

Data extraction and analysis

The in-depth reviewing of the selected studies focused on characteristics of the study setting (target disease, country, interventions evaluated), issues related to modeling, and, finally, the included costs and health gains. We will elaborate on the latter two.

We extracted information about what type of model (dynamic or static) was used in the included studies, and how the studies dealt with uncertainty around estimates. Some models, such as microsimulations, are stochastic by definition while other models may employ various types of sensitivity analyses. Sensitivity analyses may be used to test uncertainties, but also to test different assumptions of the transmission model and the economic model. Such analyses may involve varying assumptions and parameters related to the specific setting of a study, which can inform the generalizability of the results to other settings, for instance other drug prices or intervention efficacies (16). Thus, we also extracted information about the setting of the included studies and grouped these settings according to the World Bank Country and Lending Groups (17).

Economic evaluations can be categorized depending on how the benefits are expressed: cost-minimization, cost-effectiveness, cost-utility, or cost-benefit analyses (18). Cost-minimization studies assume that the effectiveness of the evaluated interventions is equal and therefore focus only on cost differences between interventions. Cost-effectiveness studies express health benefits in natural units, such as cases or deaths averted, a decrease in infection rates, or live years gained. While potentially easy to quantify, comparing interventions across diseases is hampered when different outcome measures are used. For instance, when comparing which intervention to choose from two interventions targeting different diseases of which one disease has a high mortality rate and the other disease much lower mortality rate but leaves the infected with chronic conditions, choosing to measure the outcome in averted deaths or averted cases can have a large impact on which intervention is estimated to be the most cost-effective. Cost-utility analysis captures health benefits in terms of DALYs or QALYs. Both of these measurements comprise the mortality and morbidity from an illness, which

separates them from many other often used outcomes (5). The use of DALYs is recommended in the WHO guide to cost-effectiveness analysis (19). Cost-benefit analyses express health benefits in monetary terms. While this allows direct comparison to costs, is grounded in welfare economics and the results of an analysis can be summarized in a unidimensional outcome measure, expressing health benefits in monetary terms is not straightforward and not uncontroversial (20).

We divided costs into two categories: (i) costs that occur within the healthcare sector and (ii) costs that occur outside of the healthcare sector. For both categories, we further divided the costs into short-term costs and future costs. We defined short-term cost as the costs that occur during the outbreak, and the future costs as those that occur when life is extended. Short term costs within the healthcare sector are for example staff, equipment, and current treatment costs. Future costs within the healthcare sector include both future consumption of healthcare related to the specific disease being targeted but also future utilization of healthcare due to other diseases in life years gained (21).

Short term costs outside the healthcare sector are costs that arise for example for the patient or the caregiver of a patient. These costs can be for transportation, time off from work to undergo treatment in a healthcare facility, or out-of-pocket expenses. Future costs outside the healthcare sector include productivity losses due to disability and premature mortality. Productivity losses are often estimated by methods such as the Human capital approach or the Friction cost method. The human capital approach quantifies the remaining productivity that would have occurred during all life-years lost (22). The friction cost method quantifies the time required to replace a worker by someone else, like a formerly unemployed person (23).

There is currently an ongoing debate on which future costs to include in health economic evaluations (24). This particularly relates to costs in gained life years (i.e., those years that patients would not have lived without the intervention, but do with). If the aim is to comprehensively capture all impacts of an intervention, future costs and benefits, related to consumption and production, cannot be excluded from an analysis (21,25).

For all cost categories distinguished we extracted information regarding the measurement and valuation of these costs and categorized them according to a micro-costing or a gross-costing approach. Micro-costing refers to the approach of costs estimation where the unit cost is multiplied by the used quantity of the referred unit, gross-costing, on the other hand, is when a budget is divided into sectors of usage (26). Micro-costing is considered a more precise estimation of cost but may be more demanding in term of data availability, and the sum may even exceed the total budget (26). Gross costing is less data demanding but may misclassify costs between sectors.

To fully account for all the relevant effects the time horizon should be long enough to capture all costs and benefits of the intervention. Therefore, we extracted this information from the included articles. Additionally, we extracted information about discounting of cost and health effects. Discounting is common in economic evaluations as the effects that occur in the present are valued higher than similar effects occurring in the future. The WHO-CHOICE uses an annual discount rate of 3% for both health effects and costs, but national guidelines may recommend different rate(s) (19).

2.3 Results

The literature search resulted in 298 records, of which 76 met the inclusion criteria and were assessed in full-text. Of the 76 records, 34 were considered eligible for inclusion in our study. The 42 excluded records were excluded due to: not conducting any form of economic evaluation (10 records), methodology paper (6 records),

not based on relevant outbreaks (4 records), effectiveness study (3 records), not in English (3 records), studying animal subjects (3 records), not quantifying the impact of an intervention against outbreak (3 records), reviews (2 records), not comparing intervention against baseline (1 record), being a preliminary study to an already included study (1 record), budget impact analysis (1 record), not able to access (5 records).

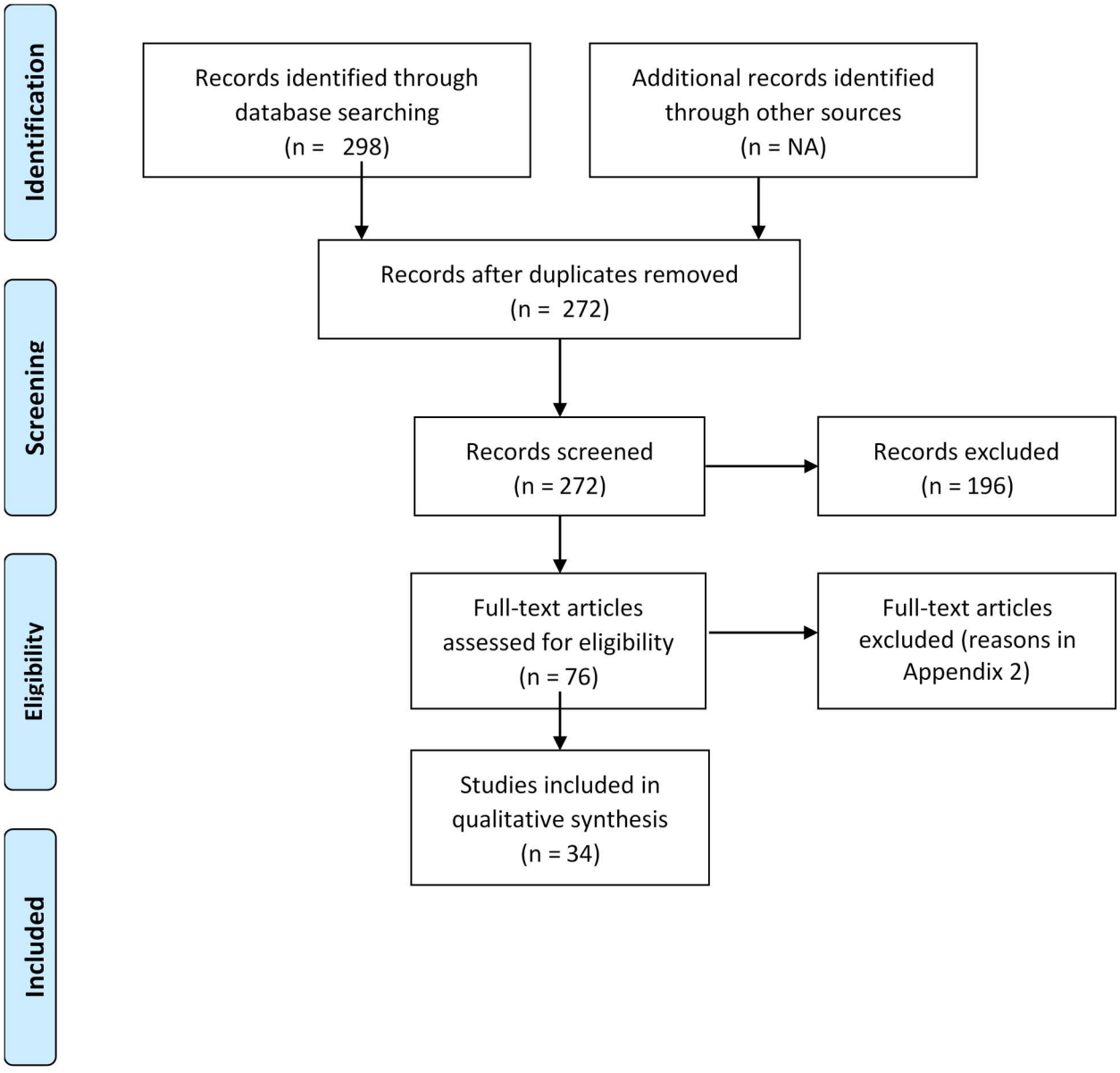


FIGURE 2.1 SCHEMATIC FLOWCHART OF STUDY SELECTION PROCESS

As shown in Table 2.1, H1N1 was the most frequently studied outbreak, with 29 of the included studies. Few studies compared more than two interventions. Pharmaceutical interventions (vaccinations and antivirals) were studied in 23 included studies. Vaccinations were most commonly studied, followed by school closure. Evaluated non-pharmaceutical interventions mostly consisted of strategies aimed at decreasing contact between infected and susceptible individuals. Only four studies compared pharmaceutical interventions with non-pharmaceutical interventions.

Of the included studies, 15 were cost-effectiveness analyses (27,28,37–42,29–36) and two cost-minimization analyses (41,43). Cost-utility analyses were performed in 13 studies (44,45,54–56,46–53), and four studies performed cost-benefit analyses (57–60). 29 studies were conducted in a high-income setting, 4 were conducted in an 'upper-middle' income setting and only one was conducted in a low-income setting. Of the high-income studies, a majority (i.e. 16 out of 29) were situated in the US.

Table 2.1 Sample descriptive

Outbreak	**Frequency***	**%***
H1N1	29	85%
H5N1	3	9%
SARS	3	9%
Ebola	1	3%
H7N9	1	3%
Intervention	**Frequency***	**%***
Vaccination	16	47%
School closure	8	24%
Antivirals	6	18%
Quarantine	2	6%
Personal Protective Equipment	2	6%
Social distancing	2	6%
Screening	1	3%
Whole response program	1	3%
Sick leave policies	1	3%
Non-specified non-pharmaceutical	1	3%
Other pharmaceutical	1	3%
Setting	**Frequency**	**%**
High income	29	85%
Upper middle income	4	12%
Low income	1	3%

* Sum of frequencies and/or percentages larger than number of studies included as some studies evaluated more than one outbreak/intervention.

A dynamic model was used in 19 studies, while 11 studies used a static model. Four studies, all evaluating interventions against H1N1, did not use a transmission model and instead used trial data. One study evaluated the impact of individuals taking own initiative to have less contact with others, thereby aiming to reduce the risk of contracting the disease, in a sensitivity analysis (49).

Of all included studies 30 conducted at least some sort of sensitivity analysis by varying parameter values. A univariate analysis was conducted in 19 studies, a probabilistic in 10 studies and a multivariate sensitivity analysis in one study (31). For dynamic models, in which probabilistic sensitivity analysis is inherently difficult due

to the parameters in the model being highly inter-dependent, univariate sensitivity analyses on key or all parameters were performed. Only 11 out of the 34 included studies discounted both costs and health benefits. The applied discount rates ranged from two to five percent, with nine studies employing a uniform rate of three percent for both costs and effects.

Nine studies did not mention the perspective used, however, several of those studies did include costs outside the healthcare perspective suggesting the use of a societal perspective. Fourteen studies used a societal perspective and six studies a healthcare perspective. Four studies assessed the costs and benefits from both a healthcare perspective and the societal perspective. One study used a patient perspective (27). Nine studies stated a time horizon, of which six studies employed a lifetime horizon and three studies used a 1-year horizon. Of the studies stating a lifetime horizon, two included some types of future costs (49,52).

All of the thirteen cost-utility analyses used QALYs as the outcome measure. Among the 15 cost-effectiveness studies the outcome measure varied greatly. Two studies did not include benefits and were labeled as cost-minimization studies. Of the 15 full cost-effectiveness studies five used cases averted as outcome measure, four estimated the reduced attack rates, two assessed life years lost (36,38). Of these one study assessed both reduced attack rates and cases averted (32), while the remaining studies all used different outcome measures, including: deaths averted (31), averted admissions (30), care quality indicators (such as turn-around time and emergency department recidivism) (37), proportion vaccinated (40), or days of sick leave per 100 healthcare workers (42).

All but two studies included treatment costs within the healthcare sector. Both of the studies that did not include these costs assessed the cost-effectiveness of school closures (36,44). Other included health care costs were administration costs (19 studies), equipment (two studies) (30,57), co-payments (one study) (28), and costs due to days of sick leave of health care workers (one study) (42). One study mentioned healthcare costs but subsequently did not define the costs explicitly (31). Only one study included future non-related healthcare costs (49). With respect to costs outside the healthcare sector, 24 studies included productivity losses due to short-term absenteeism, transportation (two studies) (33,54), administration (one study) (35), treatment (one study) (33), presenteeism (one study) (47),and energy savings (one study) (54).

Ten studies included some form of future costs. Eight of these included future productivity losses, one included non-related medical costs (49) and one included related medical costs (52). No study included more than one type of future costs. The studies that included productivity losses all used the human capital approach, basing calculations on wages and remaining life expectancy. One study included future related medical costs in the form of lifetime disability caused by the illness (52). Another study included future non-related medical consumption by age based on insurance data in the US (49). Four of the ten studies including future costs did not discount these costs.

When possible, we assessed the most likely costing method used, based on the (sometimes limited) information provided in the manuscripts. We refrained from labeling the costing method in two studies as the data used for costing was not described. The most common method found was micro-costing, which was used in 27 of the studies. Mixed costing methods using both micro and gross costing were the second most frequently used, while gross-costing was third.

Table 2.2 Overview of included articles.

Author	Type	Setting	Outbreak	Intervention	model type	Uncertainty	Perspective stated	Time horizon stated	Costs					Health outcome	Discount rate (%)
									Within HC		Outside HC		Costing method		
									Short term	Future	Short term	Future			
Basurto-Davila (57)	CBA	US	H1N1	Vaccination	Dynamic	Probabilistic	Societal		T,ADM,EQ		AB	FNM	Micro-costing	Benefit in monetary terms	3
Brown (58)	CBA	US	H1N1	School closure	Dynamic	Univariate	Societal		T		AB	FNM	Mixed	Benefit in monetary terms	3
Mamma (59)	CBA	Greece	H1N1	Vaccination	Static	Univariate			T		AB		Micro-costing	Benefit in monetary terms	
Tracht (60)	CBA	US	H1N1	PPE	Dynamic	Univariate			T,ADM		AB	FNM	Micro-costing	Benefit in monetary terms	
Lee2 (27)	CEA	US	H1N1	Vaccination	Static	Probabilistic	Patient		T		AB		Micro-costing	Cases averted	3
Andradóttir (28)	CEA	US	H1N1	vaccination, antiviral, school closure, social distancing	Dynamic	Univariate			T, CP		AB	FNM	Micro-costing	Attack rates	

Brouwers (29)	CEA	Sweden	H1N1	Vaccination	Dynamic	Univariate	Societal		T,ADM	AB		Mixed	Cases averted	
Carias (30)	CEA	west Africa	Ebola	Other pharmaceutical	Dynamic	Probabilistic	Health care	1-year	T,ADM,EQ			Micro-costing	averted admissions	
Dan (31)	CEA	Singapore	SARS, H1N1, 1918 Spanish influenza	PPE	Dynamic	Multivariate	Health care		T, UNDEF			not described	Deaths averted	
Halder (32)	CEA	Australia	H1N1	school closure, antiviral	Dynamic	Univariate	Societal		T,ADM	AB	FNM	Micro-costing	Attack rate reduction, cases averted	3
Jamotte (33)	CEA	Australia	H1N1	Vaccination	Static	univariate	Societal & health care		T,ADM	AB, TR,T		Micro-costing	Cases averted	
Kelso (34)	CEA	Australia	H5N1	school closure, antiviral, workforce reduction, social distancing	Dynamic	Univariate	Societal	Lifetime	T	AB		Micro-costing	Attack rates	3
Li (35)	CEA	China	H1N1	Quarantine	Dynamic	-			T	ADM		Not described	Cases averted	
Nishiura (36)	CEA	Japan	H1N1	School closure	Dynamic	Univariate	Societal			AB		Micro-costing	Years of life saved	
Pershad (37)	CEA	US	H1N1	Screening	Trial data	Univariate	Health care		T,ADM			Micro-costing	care quality indicators	

Tsuzuki (38)	CEA	Japan	H1N1	Vaccination	Dynamic	Prob abil-istic	Socie-tal & health care		T,AD M		AB	FNM	Micro-costing	Years of life saved	2
Wong (61)	CEA	Hong Kong	H1N1	School closure	Dynamic	Prob abil-istic			T		AB		Micro-costing	Attack rates	
Yoo (40)	CEA	US	H1N1	Vaccination	Trial data	Prob abil-istic	Socie-tal		T,AD M		AB		Micro-costing	Proportion vac-cinated	
Mota (42)	CEA	Brazil	H1N1	Sick leave policies	Trial data	-			T,AB				Mixed	Days of sick leave averted per 100 HCWs	
Gupta (41)	CMA	Canada	SARS	Quarantine	Static	-			T,AD M		AB	FNM	Mixed		
Araz (44)	CUA	US	H1N1	School closure	Dynamic	Uni-vari-ate	Socie-tal				AB		Micro-costing	QALY	3
Beigi (45)	CUA	US	H1N1	Vaccination	Static	Prob abil-istic	Socie-tal & health care		T		AB		Micro-costing	QALY	3
Giglio (46)	CUA	Argentina	H1N1	Vaccination	Static	Uni-vari-ate			T,AD M				Micro-costing	QALY	3
Hibbert (47)	CUA	US	H1N1	Vaccination	Trial data	Uni-vari-ate	Socie-tal	1-ye ar	T,AD M		AB, PR		Micro-costing	QALY	
Khazeni (49)	CUA	US	H7N9, H5N1	Vaccination	Dynamic	Uni-vari-ate	Socie-tal	Lif eti me	T	FNRM	AB		Micro-costing	QALY	3

Khazeni2 (50)	CUA	US	H5N1	Non defined non-pharmaceutical interventions, Vaccination, Antiviral,	Dynamic	Univariate	Societal	Lifetime	T,ADM		AB		Micro-costing	QALY	3
Khazeni3 (48)	CUA	US	H1N1	Vaccination	Dynamic	Univariate	Societal	Lifetime	T,ADM		AB		Micro-costing	QALY	3
Lee (51)	CUA	US	H1N1	Antivirals	Static	Probabilistic	Societal & health care		T,ADM		AB		Micro-costing	QALY	3
McGarry (52)	CUA	US	H1N1	Vaccination	Static/mathematical	Univariate	Health care	Lifetime	T	FRM			Mixed	QALY	3
Sander (53)	CUA	Canada	H1N1	Vaccination	Dynamic	Probabilistic	Health care	Lifetime	T,ADM				Micro-costing	QALY	5
Xue (54)	CUA	Norway	H1N1	School closure	Dynamic	Univariate	Societal		T		AB, ES,TR		Micro-costing	QALY	4
You (55)	CUA	Hong Kong	H1N1	Antivirals	Static	Probabilistic	Health care		T,ADM				Micro-costing	QALY	3
Prosser (56)	CUA	US	H1N1	Vaccination	Static	Univariate	Societal	1-year	T,ADM				Micro-costing	QALY	3
Wang (43)	CMA	China	H1N1	Whole response program	Static/mathematical	-			T,ADM		AB	FNM	Micro-costing		

Cost abbreviations: T= treatment, A= administrative, EQ= equipment, AB= absenteeism, PR= presenteeism, TR= travel expenses, CP= co-payments, ES= energy savings,, FRM= future related medical costs, FUM= future unrelated medical costs, FNM= future nonmedical costs. Treatment costs may include the cost of vaccination if applicable, Absenteeism may include the estimated opportunity loss for students not attending school during school closures and the opportunity cost lost from educational professionals during school closure.

2.4 Discussion

This study identified a substantial number of studies evaluating intervention strategies for important recent major outbreaks in terms of costs and benefits. We found a strong focus on the H1N1 outbreak and a clear bias towards high-income settings. We also found a discrepancy between pharmaceutical and non-pharmaceutical interventions being evaluated. The majority of the studies adopted a societal perspective but its operationalization varied substantially between studies, also in terms of which costs were included in the evaluation. Furthermore, although many studies modeled future health gains, the inclusion of future costs was limited.

In this study, we presented an overview of economic evaluations in multiple settings without restrictions to certain interventions. This allowed us to create an overview of the methods used in these economic evaluations of strategies to prevent or mitigate the consequences of major outbreaks. Our focus was on the economic aspects, rendering a comprehensive appraisal of the disease and transmission models used beyond the scope of this study. Still, we emphasize the need for high-quality transmission models in producing reliable economic estimations.

Some limitations of our study need mentioning. First, our search strategy was broad, but may have missed specific studies. It seems unlikely this would have changed our results. Indeed, we believe that the included studies are relevant and form a sample large enough to base our conclusions on. Second, we searched for economic evaluations in relation to specific outbreaks. in particular, the sample of studies included in this review represents outbreaks that were identified as being potentially large threats. Other criteria could have been used for selecting outbreaks and interventions, which would have resulted in a different sample of studies. We cannot generalize to economic evaluations of interventions targeted at other outbreaks. For, example, outbreaks that may have or have had an even larger impact on health and society than the ones included here, may have been evaluated more extensively, potentially leading to different conclusions. Third, included articles were primarily screened by one researcher (KK). Having a second reviewer for all studies would have been more appropriate. Fourth, , we encountered some difficulties in extracting the methods used and assumptions made in some studies. Given the level of information provided in those studies, we cannot rule out that some studies or methods were misclassified in this review. A more detailed presentation of the included elements, methods used and the data sources would facilitate the interpretation of the results and add to the transparency as well as the ability to replicate and compare studies.

To the best of our knowledge, there are no previous studies with a similar scope as ours. Previous reviews often applied a narrower scope by either restricting the search for a specific disease or to a specific setting. Pérez Velasco *et al* (62), reviewed the strategies against influenza pandemics. Consistent with our results they found an overrepresentation of pharmaceutical interventions in high-income countries. Pérez Velasco *et al* also assessed the quality of the included articles in their study, but focused less on variation in methods. A systematic review by Drake *et al* (63), focusing on dynamic transmission economic evaluations of infectious disease interventions in low- and middle-income countries, highlighted the lack of reporting parameter values. This was also the case in our review. Drake *et al*. emphasized the lack in highlighting the uncertainty surrounding cost estimates in modelling studies. In our sample we found a vast majority of studies using secondary cost data, with a large number of the studies performing a sensitivity analysis of the cost data. Specifically, many studies addressed uncertainty regarding parameters influencing prices or volumes either using uncertainty applied as a proportion of the mean price estimate or uncertainty regarding the mean cost estimates directly obtained. The number of parameters varied in the sensitivity analyses ranged substantially, from all too just a few. A possible explanation for this difference with the findings from the study by Drake *et al*, is that in our sample the studies mostly originated from high-income settings where the availability of data might be better. Drake *et al* (63) proposed a value of information (VOI) framework to address the indicated shortcomings. This was also suggested by Pérez Velasco *et al* (62). VOI analysis may provide insights about potential beneficial areas to conduct further investigation. In addition, other topics could be addressed such as capacity constraints

of the healthcare providers, especially in extra resource constrained or vulnerable settings (64). A major outbreak with a large number of cases will require large efforts in any setting, which may affect the provision of other healthcare service when resources are diverted.

Our results show that there are large differences in the methods used to estimate the costs and benefits of different interventions. These differences can only very partially be explained by differences in the perspective adopted in the studies, as we found large differences within perspectives as well. Therefore, we conclude that there is a need to standardize which costs to include in economic evaluations in this context. Differences in the inclusion of costs will lead to difficulties comparing studies and their results. Moreover, excluding certain cost categories might create biases in results of economic evaluations and can be done strategically. By ignoring real costs, one also risks unwanted or unexpected effects when the intervention is actually implemented.

Another recommendation is to adopt a lifetime time horizon and to include all relevant benefits and costs during that period. This also implies that future costs need to be included in the evaluation. If life is prolonged due to an intervention, the life years gained can result in additional contributions to society (e.g. productivity) but may also result in additional costs, such as healthcare consumption and other consumption. Using long time horizons also increases the importance of discounting, which was not performed in all studies including costs beyond the outbreak duration. Not discounting future costs and effects may lead to biases in the results of an economic evaluation and its influence may be profound (65). As no global standards exist on which costs to include and which rates to use for discounting costs and effects and whether these should be identical presentation of results with and without discounting (at varying rates) and with and without future costs would be a practical approach (66,67).

The lack of evaluations from non-high-income countries and regions creates difficulties in generalizing the results to other countries and regions. The importance of this issue is emphasized by the fact that most of the burden of communicable diseases still occurs in low- and middle-income settings. The current bias may therefore leave exactly those policy makers who stand to gain most from better evidence on these matters without it.

Previous studies have addressed the challenge of incorporating behavioral aspects into infectious disease models (11,68). In the studies we selected, only one performed a sensitivity analysis in which the effect of individuals limiting their contact with others on their own initiative was explored (49). This is a topic on which further research is needed, including aimed at standardization of how to include such behavioral changes in economic evaluations. Another topic which needs further research is the impact of outbreaks on the broader economy: the so-called disruptive effects. None of the included studies attempted to incorporate these effects, while they may have a substantial effect on the estimated cost-effectiveness of interventions. For instance, Prager *et al* (69) estimated the economic costs of a pandemic influenza to amount to a possible $25 billion in the US. When incorporating avoidance and resilience behavior the potential loss grew to $43 billion. Further research is needed to link the outcomes of such studies to economic evaluations focusing on specific interventions. Based on our findings, we suggest that studies should strive towards more comprehensiveness in what they include and more standardization in terms of how to include relevant costs and (health) benefits. Future costs and productivity costs are two areas in which standardization is clearly required. We also emphasize the need for a presentation of all elements of costs and health effects in future studies in a manner that allows readers to scrutinize the data and methods used, and facilitates transferability of results. Adopting reporting standards such as Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement would be an improvement in this regard (70).

We note that inclusion of particular costs and benefits may have distributional consequences, also in the context of deciding on interventions aimed at the prevention and mitigation of potential outbreaks. For instance, including productivity losses in the evaluation of an intervention may favor interventions saving or targeted at

younger, productive individuals, who participate in the paid labor force. Such distributional consequences should receive due attention, but are not solved by simply ignoring real costs like productivity costs. The increased costs of prolonging life also deserve mentioning in this context. These costs entail both costs of consuming health care in added life year but also the consumption of non-medical goods. It should be noted that these costs currently often are not included in economic evaluations (71).

3. Case study focusing on wider costs and benefits: Costs and benefits of early response in the Ebola virus disease outbreak in Sierra Leone

3.1 Background

The West African Ebola virus disease (EVD) outbreak was the largest EVD outbreak since the virus was discovered. The outbreak mainly affected Guinea, Liberia, and Sierra Leone which together reported 28,616 confirmed, probable and suspected cases and 11,310 deaths (72). Disruptive effects also affected health-seeking behavior and healthcare delivery (73–76). As the case counts grew, the outbreak drew international attention. In August 2014 the WHO published the Roadmap for response, outlining three phases of response initiatives to combat the outbreak (77). In October 2014, during the first phase, the UN Mission for Ebola Emergency Response (UNMEER) was launched (77). UNMEER had several aims: that 70 percent of cases would be isolated and that 70 percent of the burials would be conducted in a safe manner(78). Approximately two months after the UNMEER initiated interventions were implemented, the national weekly case counts decreased (79). Although the response operations seemed to effectively control the outbreak, critical voices raised an issue with the timeliness of the responses. Both the recognition of the outbreak and the implementation of the interventions came too late according to critics (80–82). The EVD epidemic highlighted the importance of surveillance systems for early detection as the virus remained undetected for the first three months of the EVD outbreak (82,83).

Previous studies have estimated the effectiveness of various interventions, both real and hypothetical aimed at mitigating the outbreak (84,85,94,95,86–93). In an early stage of the outbreak Rivers *et al* explored several different interventions and found that those would not effectively control the outbreak (87). Kucharski *et al* estimated the number of averted cases due to the introduction of additional hospital beds in Sierra Leone, and found that the increased capacity averted approximately 56,000 cases (94). Barbarossa *et al,* estimated the effect of the response efforts on the number of cases and concluded that a five-week earlier implementation would halve the outbreak size (95). Other studies have investigated the health effects of the EVD outbreak caused by disruption of the health care system (96–98). Apart from interventions, the economic effect of the outbreak has also been studied (99–101). Bartsch *et al* performed a cost of illness study comprising EVD treatment costs and productivity losses, suggesting that the total cost of the epidemic in Sierra Leone was approximately 30 million US$ (99). Additionally, Kirigia *et al* estimated future production losses due to EVD mortality to approximately 60 million international$ in Sierra Leone (100). Finally, The World Bank estimated the outbreaks' impact on the GDP of the outbreak-affected economies affected to be 2.8 billion US$, where Sierra Leone was most affected and incurred a loss of 1.9 billion US$ (101).

Although studies have investigated the effects of the outbreak in different intervention scenarios little work has been performed on the combination of potential health benefits and cost savings of earlier interventions. In this study, we focus on providing estimates of costs and health consequences of the outbreak and the potential benefits of an earlier response. Moreover, this study also provides relevant input for discussions on more general investments to strengthen relatively weak health systems (102). To enable comparability, we measure health losses in Disability Adjusted Life Years (DALY) and take into account the costs associated with an outbreak both within and outside the healthcare sector. DALYs are a summary measure of health that comprise both length and quality of life (103), being widely used in cost-effectiveness studies which facilitates comparison with similar studies. Furthermore, DALYs lost because of early death are closely linked to productivity

losses as health facilitates productivity. Given that the EVD outbreak affects people in their working age/productive years, an exclusive focus on the costs incurred within the health system would result in an incomplete picture of the impact of earlier response (104).

3.2 Methods

To estimate the incremental health benefits and potential costs of earlier interventions in the scenario of the EVD outbreak in Sierra Leone we used a compartment model to describe the transmission under the baseline scenario- the actual outbreak -, and several counterfactual scenarios. The counterfactual scenarios mimic earlier interventions varying from one day earlier up to four weeks earlier. We attached treatment costs and production losses to the transmission model compartments. We also attached disability weights to the compartments, from which DALYs were calculated. The sum of costs and DALYs were calculated under the baseline and the two counterfactual scenarios. We assessed the uncertainty of our results with respect to the uncertainty surrounding input parameters and carried out a sensitivity analysis for several key parameters.

Transmission model

To explore the potential benefits of earlier response we used an extended SEIR compartment model, based on the model of Kucharski *et al* (94). The model aims at describing the natural course of the disease and incorporating setting specific context such as hospitalization in either holding centers or treatment centers, which is then run on a district level. Figure 3.1 depicts the model schematics: upon contracting the virus the individual leaves the Susceptible compartment (S) and enters the latent compartment (E). From the E compartment the individuals' transition to the infectious compartment (I). When entering the I compartment, the individuals are infectious to others. As not all cases are assumed to be reported, the I compartment is differentiated in reported cases and cases not being reported. We assumed that the infection rate is the same for both I compartments and from there on infected individuals may die or recover from the EVD. If the infected individuals are reported then, if district beds are available, they are hospitalized. During hospitalization, they are assumed not to be infectious to others. During the outbreak, facilities with different functions existed such as holding centers and treatment centers. In our model we treated the different facilities as the same, assuming that the fatality rates did not differ. Within each district, homogenous mixing was assumed and no spatial interaction was accounted for. The whole population was assumed to be susceptible. Due to the small number of reported cases we excluded the Bonthe district.

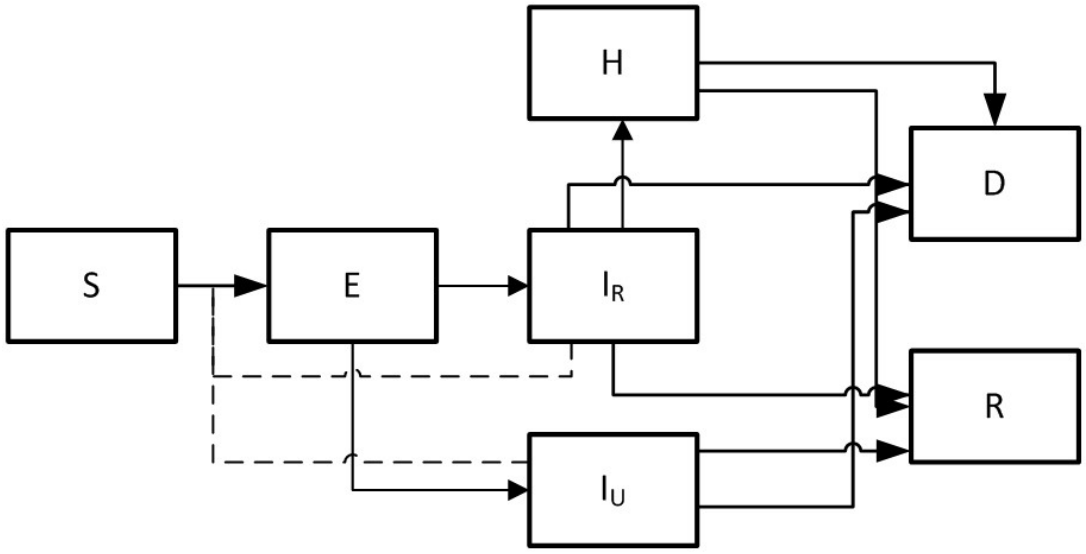


FIGURE 3.1 COMPARTMENT MODEL SCHEMATIC. *SOLID LINES INDICATE TRANSITION PATHS; DASHED LINES INDICATE TRANSMISSION ROUTES. WITH THE FOLLOWING COMPARTMENTS, SUSCEPTIBLE (S), EXPOSED (E), INFECTIOUS AND REPORTED (I_R), INFECTIOUS AND NOT REPORTED (I_U), HOSPITALIZED (H), DEAD (D) AND LASTLY RECOVERED (R)*

The transmission rate and parameters capturing the effect of the interventions implemented during the outbreak were fitted to the reported number of cases by weighted least squares, from the WHO's situation reports (72). The parameters were fitted separately for each district, to reduce identifiability issues we derived some parameter values from other studies (see supplementary material for more information). In Table 3.1 the parameters used in the model that are not district dependent are presented.

Table 3.1. Parameters estimated and fixed with their respective source.

Parameter	Description	Value	Reference
a_2	Maximum value of transmission rate	Estimated	See supplementary material
a_1	Slope of transmission rate parameter	Estimated	
a_t	Midpoint of transmission rate parameter	Estimated	
b_1	Slope of intervention rate parameter	Estimated	
b_t	Midpoint of intervention rate parameter	Estimated	
$1/\sigma$	Latent period	10.4 days	(104)
$1/\gamma_{CR}$	Time to recovery in the community	11.7 days	(104)
$1/\gamma_{CD}$	Time to death in the community	6.8 days	(104)
$1/\gamma_{HR}$	Discharge rate	11.6 days	(104)
$1/\gamma_{HD}$	Time to death for hospitalized	5.2 days	(104)
ϱ	Proportion reported	83%	(104)
$1/\omega$	Time to notification	4.8 days	(104)
$1/\eta$	Hospitalization rate	4.6-1.3 days	See supplementary material
δ_C	Fatality rate in the community	91.9%	(104)
δ_H	Fatality rate for hospitalized	60.3%	(104)

We allowed the infection rate to vary to accommodate different outbreak paces between districts. After the 1st of October 2014, the date of the UNMEER implementations (105), we introduced the effect of interventions in the model. We allowed the effect of the interventions to vary between districts. As the weekly number of reported cases declined at different speeds we did not force a linear decrease on the effect of the interventions.

Translating morbidity and mortality effects into DALYs and costs

The health loss due to EVD expressed in DALYs is the sum of health losses during an illness and the health lost because of an early death. To estimate health losses we attached disability weights from the Global Burden of Disease (GBD) study to the relevant compartments (106). Health losses because of early death were assumed to be equal to Health Adjusted Life Expectancy (HALE) estimates for Sierra Leone from GBD. To estimate the remaining HALE for each case the observed age distribution of reported cases was applied to the final outbreak size (91). The full societal costs as a consequence of EVD include not only direct costs such as treatment costs for EVD but also indirect costs such as production losses, due to sickness and death at a young age. As in Bartsch *et al* two treatment options were included: supportive and extensive supportive care (99). Supportive care consists of paracetamol, oral rehydration salts, metoclopramide for nausea. Extensive care adds morphine for pain, diazepam for convulsions, Ringer's lactate against shock and broad-spectrum antibiotics. As no proportion of the severity of cases was available a random number was drawn from a uniform distribution from 0 and 1 for each run representing the proportion of cases receiving supportive care. For treatment costs, the costs estimated by Bartsch *et al* were used (99). For reasons of international comparability, we calculated the production losses according to the Human capital method (107). GDP per capita was used as a proxy for annual production losses and was multiplied by the HALE lost for early deaths to estimate lifetime production losses. An implicit assumption here is that life years spent in poor health do not result in productivity gains in our estimation. For recoveries, the productivity loss from Bartsch *et al* due to absenteeism was used (99). Costs are all expressed in 2014 US dollars.

Table 3.2. Costs and health parameters included, mean and interquartile in brackets. CI. By age groups and costs groups. Expressed in 2014 $US.

	Age group:			Reference:
Cost group:	<15 years	15–44 years	≧45 years	
Supportive care:				
Patient recovers	431 (413–450)	446 (428–466)	447 (428–464)	(99)
Patient dies	178 (163–195)	185 (169–202)	185 (168–202)	(99)
Extensive supportive care:				
Patient recovers	598 (576–622)	830 (800–862)	830 (801–859)	(99)
Patient dies	238 (217–259)	321 (292–351)	322 (291–351)	(99)
Personnel costs:				
Patient recovers	59 (57–61)	59 (57–61)	59 (57–61)	(99)
Patient dies	21 (19–23)	21 (19–23)	21 (19–23)	(99)
Productivity losses due to:				
Absenteeism	23 (22–24)	23 (22–24)	23 (22–24)	(99)
Mortality	42 747.2 (12 355.9-128 273.4)	29 640 (7 599.2-90 040.3)	13 227.5 (2 934.1-42 393.5)	Calculated
Disability weights:				
Acute phase of illness	0.133 (0.088-0.19)			(99)
Post-sequale	0.219 (0.148-0.308)			(99)
Mortality, HALE (range)	51.3 (48.11 – 53.51)	34 (24.76 – 43.84)	13.92 (7.32 - 21.38)	(99)
Duration of illness:				
Acute phase, recover	15.1 (14.6 – 15.6) days			(99)
Acute phase, death	8.2 (7.9 – 8.4)			(99)
Post-sequale	0.75 years (0.417–1.135)			(99)

Interventions and counterfactual scenarios

To explore the potential benefits and costs of timely interventions we created counterfactual scenarios of earlier interventions. In our initial analysis we compare the baseline scenario - interventions as they were implemented by the UNMEER - to a counterfactual scenario of interventions taking place four weeks earlier. We then continued to investigate the effect on health and costs with interventions taking place between the baseline scenario and four weeks earlier in steps of one day. The counterfactual scenarios were modeled by moving the time of interventions in the transmission model four weeks earlier. This affected the transmission parameter and also the hospitalization rate and the case fatality rates for those hospitalized.

Assessment of uncertainties of transmission models

We assessed the uncertainty of our outcomes by taking into account the uncertainty around the input parameters of the compartment model and our health and cost estimates. In our main scenario of a four week earlier counterfactual we implemented a stochastic model using the tau-leaping approximation of the Gillespie's algorithm with a time step of .01 days (107,108). The approximation treats individuals as discrete units and translates the rates into probabilities allowing for stochasticity in all transitions. We performed several univariate sensitivity analysis to explore the impact of key input parameters on our outcomes. We varied the proportion of underreporting by ten percentage points, the time for cases to be reported, the time to hospitalization and the timing of interventions by one day each.

3.3 Results

Model fit

Figure 3.2 shows the fit of the reported cases of the models median and interquartile range by district and nationally against the reported number of weekly cases. Our model estimated 8 609 (3882-8609) reported cases which is a bit lower than the number actually of reported cases, with the largest discrepancy being in the Western Area Rural district reported cases. Distinct temporal differences between districts can be observed such as in Kailahun and Kenema, which experienced a peak of reported cases earlier than other districts. These two districts displayed a decrease in cases before the implementation of the UNMEER interventions. For the fitted parameter values, see supplementary materials.

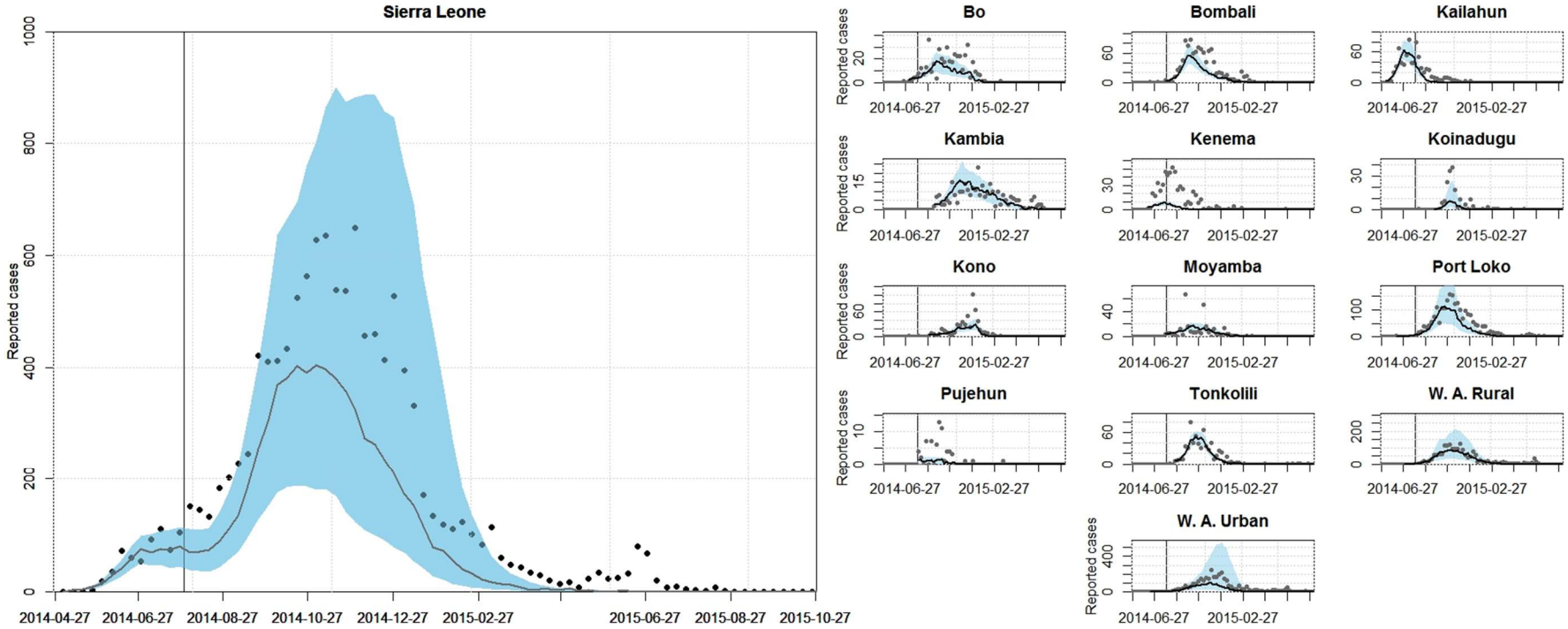


FIGURE 3.2 **STOCHASTIC MODEL FIT ON THE NATIONAL AND DISTRICT LEVEL.** SOLID LINE SHOWS THE MEDIAN NUMBER OF REPORTED CASES OF 1500 MODEL RUNS. BLUE AREAS ARE THE INTERQUARTILE RANGE. REPORTED CASES BY THE WHO PATIENT DATABASE ARE GIVEN AS BLACK DOTS. VERTICAL LINE SHOWS THE DATE OF IMPLEMENTATION OF INTERVENTIONS

Effect of earlier interventions

Districts with a large number of cases and exponential growth showed the greatest savings of costs and health. In a large number of the districts, the time of interventions and the decrease of cases correlated well. Four weeks earlier interventions resulted in cost savings and health gains compared to the baseline scenario. The savings in both costs and health were largely due to the averted mortality as seen in Table 3.3. Our result suggests that interventions implemented four weeks earlier would have halved both the costs and the health losses.

Table 3.3. Incremental results of scenarios compared to baseline. Means and 95% quantiles.

	4 weeks earlier (IQR)
Cases averted	10257 (4353 - 18813)
Deaths averted	8835 (3766 - 16316)
DALY s gained (thousand)	455.8 (194.1 - 841.11)
DALYs due to morbidity	0.23 (0.1 - 0.41)
DALYs due to mortality	455.57 (194 - 840.7)
Costs saved (million US$)	202.82 (87.42 - 373.86)
Costs from treatment	1.77 (0.86 - 2.52)
Costs from productivity losses	201.05 (86.56 - 371.34)

Figure 3.3 shows the incremental benefits of intervening earlier, from one day to 8 weeks, using the deterministic model. At four weeks, the same number of days earlier as in our main scenario, the estimated benefits gained from earlier interventions were estimated to 182 million US$. One week later would have averted 32 million US$ and 47 thousand DALYs less. Conversely, implementation one week earlier would yield an additional 25 million US$ and 38 thousand DALYs gained. Beyond our main scenario intervention date, the incremental benefits are diminishing in returns.

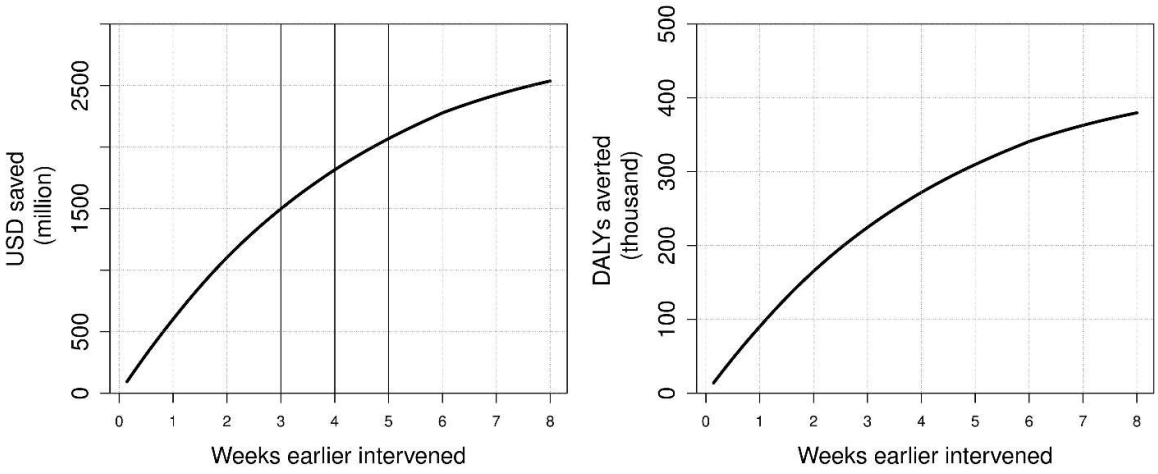


FIGURE 3.2 BENEFITS OF EARLIER INTERVENTIONS IN ONE-DAY INCREMENTS. *LEFT-HAND PANEL SHOWS THE COSTS SAVED, RIGHT-HAND PANEL SHOWS THE DALYS GAINED*

From the univariate sensitivity analysis, presented in Figure 3.4, we found that the parameter with the greatest impact is time to hospitalization. Reducing the time of intervention by one day would avoid 500 cases and reducing the time to hospitalization by one day would avoid 3,671 cases, for the time to notification the estimate is 668 cases avoided. When decreasing the underreporting by one percentage point it showed a smaller effect of 28 cases avoided. The relative decrease in values is substantially larger for the time to notification and hospitalization than for the timing of interventions.

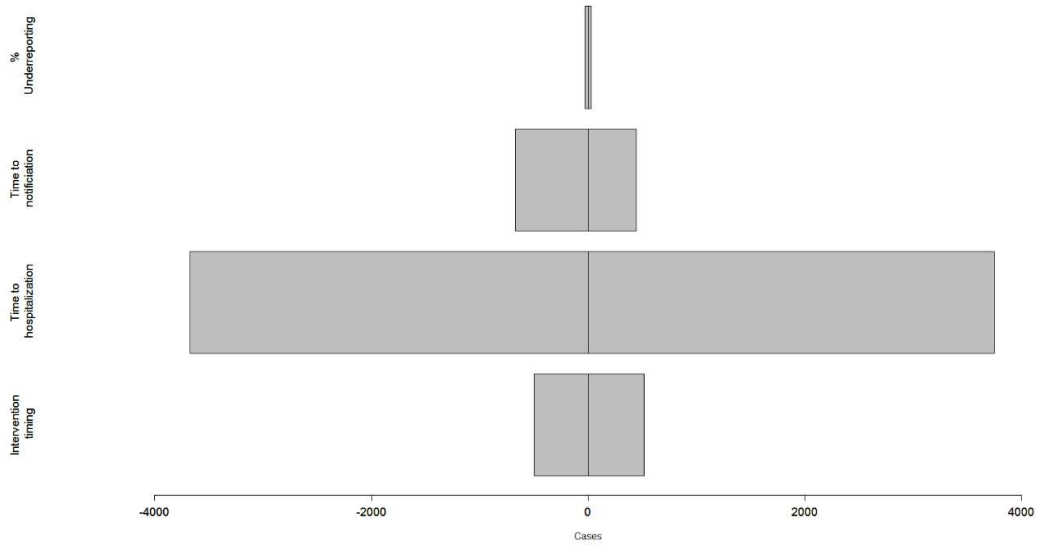


FIGURE 3.3 SENSITIVITY ANALYSIS OF KEY PARAMETERS. *THE PARAMETERS OF INTEREST ARE LOCATED ON THE Y-AXIS AND DIFFERENCE IN CASES COMPARED TO THE BASELINE SCENARIO ON THE X-AXIS. ESTIMATES ARE ON THE LEFT-HAND SIDE VARIED WITH TEN PERCENTAGE POINTS LESS FOR THE PERCENTAGE OF UNDERREPORTED, ONE DAY LESS FOR THE TIME TO NOTIFICATION, TIME TO HOSPITALIZATION AND TIME OF INTERVENTION. RIGHT-HAND SIDE SHOWS THE DIFFERENCE IN CASES FROM AN INCREASE OF THE SAME AMOUNTS FOR THE SAME PARAMETER VALUES*

3.4 Discussion

This study estimated the costs and health losses of the EVD outbreak in Sierra Leone from a societal perspective and provided estimates of the benefits from earlier interventions. The results suggest that timely interventions can reduce the loss of health and drastically reduce the economic impact of outbreaks. This emphasizes the importance of timely interventions. The largest contribution to the total cost in all scenarios was productivity losses, which arise from mortality at a young age. In our deterministic analysis, we showed that much benefit may be gained by even earlier interventions, albeit at a diminishing rate.

Before we highlight some implications of our findings, we note some limitations of this study. Importantly, several assumptions had to be made due to lacking data or poor quality data. Models previously used for EVD (e.g. (109)), allowed for explicit modeling of several transmission routes. To avoid fitting several transmission parameters and identifiability problems we did not model funeral transmissions or hospital transmissions explicitly. Evidently, funeral transmissions were an important driver of the outbreak and a facilitator of super-spreading events (110). We assumed in our model that infectiousness remains the same throughout the symptomatic period, which may not be fully accurate and may rather be increasing closer to death (111). The implication of this assumption is that we may have underestimated the benefits of earlier interventions, as the infected are hospitalized sooner after interventions and transmission rates are lower in hospitalized settings. Our model assumed homogenous mixing within compartments, meaning that all individuals have the same probability of contact. In reality, this assumption may not hold as individuals mix within their respective contact network primarily which may limit spread. For the current purpose, we did not include transmission caused by district interaction of individuals in different districts. This may again have underestimated the impact of the health gained and costs saved due to earlier interventions, as earlier interventions may prevent infected individuals from spreading the virus to other districts. Underreporting is assumed to occur during an EVD outbreak, however, few studies have provided concrete evidence of the proportion of underreporting. We, therefore, assumed a moderate estimate (compared to estimates by the CDC) whereby for each reported case, 2.5 cases were not reported (112). As uncertainty exists regarding the interventions performed, assumptions had to be made to calculate the effects of the interventions. We assumed that the decline in transmission after the 1st of October 2014 was solely caused by the interventions, and not taking into account independent behavior which was not due to for example information campaigns or community leader engagement. We did not differentiate between different types of interventions as this was not our aim, we were interested in the total effect. However, in our sensitivity analysis we saw that time to hospitalization proved very important in limiting the number of new cases. Another limitation is in the use of a single date to account for the interventions performed by the UNMEER. This assumes that the interventions and the effects were more homogenous than in reality. Our estimate of the production losses is much larger than that of the cost of illness study (99). Our approach estimated the years of productivity lost due to EVD mortality as the HALE lost multiplied by average annual GDP of Sierra Leone and also included the latest data on reported cases. The total estimated economic loss in the baseline scenario mounted to 635 million US$. This is a smaller estimate than previously estimated by the World Bank (WB) (101). The difference is due to the choice of approach, as the WB applied a macroeconomic level to determine the GDP loss in short and medium term. Our focus remained on individual costs to the health care system and the long-term production losses arising from deaths. An underexplored issue here is which approach is most suitable to estimate these productivity costs. In economic evaluations sometimes the human capital approach is replaced with the friction cost method, under the assumption that replacement of ill or deceased workers (through a reshuffling of labor or employing previously unemployed) will help to reduce total productivity costs (e.g. (113)). In countries and circumstances like the outbreak studied, it is unclear whether similar mechanisms exist and would lower productivity cost estimates. If we would assume this to be the case and production levels would be restored after 1 or 5 years,

production costs would be estimated to be 7.07 (3.08-13.08) and 34.14 (14.61-63.29) million US$ respectively.

The consequences of this outbreak proved devastating. However, it has been shown that EVD can be stopped in an early phase. Illustrated by the example of Nigeria, where quick response and actions managed to halt the outbreak containing the number of cases to 19 with seven deaths (114), however, this occurred at a later phase when the outbreak was known and the responders ready. Swift detection and isolation saved not only lives but was done at a cost of approximately 13 million US$ using the existing Polio surveillance infrastructure. This cost estimate is approximately 6 percent of the cost *savings* with interventions four weeks earlier in Sierra Leone. This study does not provide guidance on which preventive measures are best suited to preventing or limiting outbreaks. However, we do know that the virus was first discovered after several months of circulating in the population which advocates for systems capable of detecting emerging viruses before they spread more widely. The most important result from this study is that is considerable gains to be made from timely interventions, and that the losses primarily occurred outside the healthcare sector. To improve the capabilities for handling the next outbreak preferably before a new outbreak occurs. Timeliness is not only important in intervening, but also in the context of clear policy action.

4. The economics of improving global infectious disease surveillance

4.1 Background

Infectious diseases remain a serious public health problem worldwide. With the global increase in population density, urbanization, and global travel and trade, the threat of widespread outbreaks of high threat infectious diseases has increased relentlessly (2), as evidenced by recent examples of Ebola, Zika, and Lassa fever. Furthermore, although the most important causes of death have shifted to non-communicable diseases, in some poorer parts of the world communicable diseases remain the most important cause of death (106). Epidemics and pandemics pose an enormous threat on the world, for instance through the potential to cause millions of deaths over a short time and disrupt health systems and economies. Crucial in the prevention of and reaction to these threats is infectious disease surveillance. Surveillance has been defined as the 'systematic ongoing collection, collation and analysis of data and the timely dissemination of information to those who need to know so that action can be taken'. The core functions of these systems include case detection, case registration, case confirmation, reporting, data analysis and interpretation, and feedback (115). Traditional surveillance is primarily focused on monitoring of trends of endemic diseases, but the threat of new emerging infectious diseases (which often originate from animal populations) creates a need to continuously improve disease surveillance systems to prevent and act upon disease outbreaks (116). New diagnostic tools such as Next Generation Sequencing (NGS) are being explored as options to improve disease surveillance as such tools allow to trace and link sources of disease transmission and facilitate a better understanding of how viruses and bacteria pass from animal to humans.

How to set-up and improve disease surveillance and how to prioritize investments are questions that need input from different scientific disciplines. Here, we focus on some economic considerations when deciding on such matters. The motivation follows from the specific characteristics of disease surveillance which make an economic evaluation, where costs and benefits are compared to evaluate whether investments provide good value for money, a complex task. Related to this are difficulties in financing disease surveillance. Since infectious disease surveillance has characteristics of (global) public goods, collective action may be necessary to obtain surveillance on a level optimal for society. In the ensuing, we first describe the benefits of disease surveillance, followed by how current disease surveillance can be improved, as well as the crucial role of real-time data sharing. Then we turn our attention to how to finance disease surveillance and how to create an incentive structure that facilitates the production and sharing of information. Last, we describe the difficulties and potential improvements of the (economic) evaluation of disease surveillance.

4.2 The benefits of improving disease surveillance

The best recognized purpose of disease surveillance is the (early) detection of epidemics and other health problems in communities (117). Effective detection can result in fewer cases and deaths and thereby yield substantial health benefits and limit social and economic damage (118). Surveillance information can also be used to understand the natural history of diseases and to monitor ongoing diseases, and subsequently to estimate the size of ongoing and new health problems. Such information is crucial for the prioritization of research and allocation of (financial) resources. Better insight in health problems or threats further generates new research questions and can be used to evaluate former and current interventions and control strategies (119). Ultimately, better functioning disease surveillance systems are pivotal to policy decisions to mitigate or prevent disease outbreaks, by providing timely and useful evidence (117). When the public is aware of the regular monitoring and controlling of threats, surveillance can create greater peace of mind through increasing the perception of health security (115) , (120). Indeed, people may attach value to the provision of services which may never actually call upon, such as disease surveillance, as some sort of standby response capability or 'option demand' (121).

A plethora of unknown diseases escape routine surveillance, and there are regions of the world where the laboratory capacity necessary to conduct surveillance does not yet exist or is suboptimal. Compared to traditional laboratory tools, NGS tools can be used for a wide variety of disease pathogens, and so differ from traditional laboratory methods which target single pathogens or a limited group of pathogens. With NGS, the same platforms and sometimes even the same protocols can be used for analysis of viruses, bacteria, genes, parasites. Therefore, there is the potential for cost saving through economies of scale. Sequence information generated by NGS in case of outbreaks of viral infectious diseases can be used to detect outbreaks, but also simultaneously assess modes of transmission and alert to specific viral mutations that may increase the risk for humans. Combined diagnostic and genetic information from NGS has the potential to differentiate viruses in great detail which may lead to better understanding of the origin source and evolution of circulating viruses in animal and/or human populations and can be used to identify points of intervention. In current surveillance, the same goals can be reached through a series of analyses, whether or not on a routine basis. Consequently, with using new disease surveillance tools such as NGS the set of policy options available also is expanded when outbreak is detected early (122).

The power of the adaptation of genomic research in disease surveillance could be increased by incorporating concepts from 'One Health' (123). As the majority of emerging infectious diseases are zoonotic the integration of surveillance capacities across human and animal health sectors should be a priority. Another source of improvement can be sought in the incorporation of digital disease detection (123). With increased potential for obtaining large amounts of information from the internet (for instance through social media) in very short times, real-time information can be gathered that are relevant in the surveillance of diseases (124), (125). In general, sharing data in a timely manner, preferably real-time, is expected to greatly enhance and accelerate the understanding of diseases and their patterning. However, data sharing is a complex task in view of the range of both government and nongovernment stakeholders to provide and receive data, and to facilitate data sharing (126). Furthermore, recent infectious disease outbreaks suggest that such (international) cooperation cannot be taken for granted (127). A model for improving disease surveillance is set by the Collaborative Management Platform for detection and Analyses of (Re-) emerging and foodborne outbreaks (COMPARE). COMPARE is a project to develop a global platform for sharing and analysing NGS data (128). COMPARE's vision is to build a platform for detection and typing of many different pathogens, and for assessing the causes of unexplained illness combined, through fast-tracking NGS. The project aims to develop a data sharing infrastructure that is customizable so groups of users can share data rapidly when needed while retaining ownership.

4.3 Financing disease surveillance

An important characteristic of surveillance and interventions in the area of infectious diseases are generated externalities, outcomes beyond the scope of those pursuing the activity. Although this might be an important opportunity for collaboration, the risk is that actors will consider only their own costs and benefits, leading to underprovision of disease surveillance activities. Public goods are a special case of the situation where externalities exist and refer to goods which are both non-rivalrous and non-excludable. The first implies that consumption of the good does not reduce the quantity available to others. The second implies that people cannot be prevented from consuming the good. When the benefits of the good are quasi-universal in terms of countries, people, and generations, the good can be specified as global public good (129). Infectious disease surveillance is sometimes described as a (global) public good. For example, people cannot be excluded from benefiting from a reduction in risk of infectious disease when its incidence is reduced (non-excludability), and one person benefiting from this reduction in risk does not prevent anyone else from benefiting from it as well (non-rivalry). In this example, the surveillance would also be global when the disease easily spreads to other countries and has the potential to become pandemic. Non-excludability and thereby inability to demand payment furthermore eliminates the commercial incentive for producing pure public goods in the private market. As a consequence, the market fails to provide these goods in the quantity optimal for society. This market failure can be used as an argument for governmental

interference and financing, for instance through taxation. For global public goods this is however harder to do, because no global government exists (130). Global public goods are often financed by international organizations, national governments, or transnational corporations. Funding may be achieved in voluntary or coordinated contributions, ear-marked national taxes coordinated between countries, taxes imposed and collected on a global level, or marked based mechanisms (131). The purity of the public good characteristics of infectious disease surveillance have been questioned (131). For instance, property rights can be used to exclude others from using the information that can be gathered from surveillance. However, the concept of public goods can still be useful to promote and justify public interference and public funding of disease surveillance at least at a national level and, where possible, on a global level.

Clearly, different countries have different policies regarding spending on public health. They have different priorities and different current standards of care and pose different requirements on new investments and have different views on affordability. Little information is available on how much countries currently actually spend on infectious disease surveillance. Hossain and colleagues (132), for instance, found that low- and middle-income countries spent an annual median of $0.04 per capita on vaccine-preventable disease surveillance. The Organization for Economic Cooperation and Development (OECD) provides estimates of spending on epidemiological surveillance and risk and disease control programmes[1] for 2016 ranging from 0.06% (Sweden) to 0.74% (Korea) of total healthcare expenditures. These investments are relatively small compared to its spending levels on curative care (133), (134). Whether investments in disease surveillance are 'too low' compared to a socially optimal level is a difficult question to answer. However, recent research on the willingness-to-pay (WTP) for disease surveillance in the EU found that on average people are willing to spend €264 per year which roughly translates into 5% of total health spending. Based on this estimate it could be argued that within the EU currently too little is spend on disease surveillance. The comparison needs to be taken with caution, however, since the category of spending on epidemiological surveillance and risk and disease control programmes in the OECD studies does not exactly match with the early warning system for infectious disease surveillance as valued in the WTP study. For instance, the first also includes activities for diseases other than infectious diseases, although the latter system might capture broader activities. Nevertheless, the magnitude of the difference between WTP and current spending is large and therefore presumably remains after correcting for classification differences.

4.4 Disease surveillance as an insurance policy

A necessary prerequisite for any improvement in disease surveillance by investing in new technologies such as NGS is that there are appropriate incentives for individuals, researchers, business and governments to produce and share information. However, currently there are limited incentives for researchers to share data and there is a lack of appropriate infrastructure for data sharing, which requires a clear governance structure that ensures a balance between privacy and access, as well as adheres to national and international ethical and legal requirements (135). Furthermore, individuals, businesses, and governments might prohibit extensive data sharing based on concerns about economic consequences from being a source of an outbreak. They may also wish to retain ownership of potential intellectual property and secure access to interventions developed from the data (127). An example regulation to enhance equitable data and benefits sharing is the Nagoya Protocol which states that samples are owned by the countries in which these are found, and bilateral arrangements are required for sharing of these to be legal. Although the protocol promotes fair and transparent sharing of resources, the implementation is criticized for having a negative impact on public health (136). Other issues specifically hampering the sharing of microbial genetic resources related to ownership were mostly related to possible financial and reputational losses or due to

[1] Spending on epidemiological surveillance and risk and disease control programmes available for 17 OECD countries.

exposure of sensitive information (137). However, solutions have been proposed for many of the issues currently limiting the timely sharing of data in genomics research (122).

One way to think about creating appropriate incentives is by analogy with setting up an insurance scheme. In general, surveillance has similarities to insurance. When buying insurance, people pay for the loss they are expected to bear in case the insured event occurs, plus an additional amount to compensate for the risk they face. When people buy health insurance, for instance, they pay for protection of excess financial losses in case of healthcare need and an additional amount for risk avoidance and peace of mind regarding the possibility of unexpected large costs. In the same way with surveillance there is pooling of risk as well as the value of the peace of mind from knowing that large outbreaks of infectious diseases are less likely (115). In case of surveillance systems, this is more complex. Investing in surveillance does not result in having resources available to compensate those suffering from the negative event, but is intended to prevent these events and limiting damage in case they occur by intervening early. While in health insurance one is mainly concerned with moral hazard due to insurance resulting in more and possible unnecessary healthcare, an insurance scheme in the context of disease surveillance is mainly aimed at reducing the cost of sharing information. For instance, an insurance scheme might incentivise farmers or companies to share samples of their livestock in an earlier stage of an epidemic even though this might reveal that their farm is the source of a pathogen resulting in culling of their livestock. Without an insurance scheme that would compensate for this culling, this farmer might take the risk and not share data. Furthermore, with surveillance the focus is on multiple dimensions of the event in different areas (e.g. population health, animal health) and not only on the financial consequences. This greater complexity also makes the provision of surveillance, compared to insurance, more difficult.

Although recent global health crises have shown the potential of infectious diseases to become pandemic, the highest impact of infectious diseases is observed in low- and middle-income countries, and so the highest burden is imposed on the poor. Following from this, investments in disease surveillance in developing countries are often initiated as a form of development aid. The Bill and Melinda Gates Foundation and Welcome Trust, for instance, are important philanthropic funders of infectious disease surveillance in developing countries. The activities funded by such philanthropic donors may be conducted by academic organisations, which are themselves interested in the data from surveillance for research purposes. International disease surveillance increasingly involves national governments, international organizations, non-governmental organizations and professional groups and the private sector (129). There is an oft-repeated call for global collaboration to improve incentives for better disease surveillance. The WHO is largely seen as the organization that should have a main role in the further improvement of infectious disease surveillance (138). Other international collaborations on a smaller scale are the European Centre for Disease Prevention and Control (ECDPC) and the US Centers for Disease Control and Prevention (CDC).

From the global public good perspective it can be argued that financing by more developed countries is in the interest of those countries and is not necessarily development aid. One of the difficulties of international collaboration on infectious disease surveillance, however, is that different countries typically have different priority diseases and thereby different surveillance priorities due to the various threats to different population groups. Where rich countries may fear the importation of new viruses, poor countries suffer from common infections which give rise to diarrhoea and respiratory diseases (129). Improved affordability of newer catch-all tools that can provide diagnosis for most common diseases and rule out emerging diseases would reduce these differences in approaches and stimulate international collaboration. On a different note, Morton and colleagues paid attention to this when initiating a model based on which could be decided how development aid in global health should be spent (139). In this model, a framework is proposed wherein donor countries subsidize interventions up to the point that these interventions are cost-effective based on the receiving country's decision rules (where only interventions with a cost-effectiveness ratio below the threshold are adopted). Models like this can be a useful tool to arrange levels of

spending for different organizations and countries to obtain an optimal allocation of resources. The absence of hard evidence on cost effectiveness of disease surveillance however complicates the use of such analytical models.

4.5 The cost effectiveness of disease surveillance

From an economic perspective, deciding on how to improve and invest in disease surveillance (and how to intervene in case of outbreaks) should be done using evidence on cost-effectiveness to make optimal use of scarce resources. Especially in the case of public financing, a proper justification of how resources are spent is crucial. However, assessing the cost-effectiveness of health system interventions such as disease surveillance is difficult as quantifying the benefits is not straightforward (128). Methods of economic evaluation have been developed and most successfully applied in cost-effectiveness of clinical interventions, targeted at specific patient groups (140). In these economic evaluations there is a clear link between the costs of an intervention and the health benefits of the target patient group as the intervention often works through a biological mechanism. In case of disease surveillance and response, behavioural responses with respect to the policies play a crucial role which makes the outcome less predictable (141). Furthermore, treatments are often evaluated in isolation and are assumed to have little impact on economic activities outside the healthcare sector. In case of healthcare emergencies such as epidemics or pandemics, however, this assumption is likely to be violated as outbreaks not only influence human health, health spending and labour market participation but also animal health and have broader disruptive effects on international trade and tourism (142), (143), (144), (145).

In general, surveillance data results in health improvements only when combined with other programs as effective policy responses require a well-functioning health system and intra-governmental coordination. Therefore, it is difficult to quantify to what extent disease surveillance systems are effective and have an impact in case of emerging disease outbreaks. Moreover, the impact of disease surveillance is not limited to a specific disease area which makes evaluation more difficult. This is especially the case for disease surveillance using NGS which has the potential to serve as catch-all model for pathogen detection, for instance when using sewage sample sequencing as a target (146), (147), (148). As this allows detection of a range of different pathogens, this information may be used to strengthen multiple programs within the healthcare system. However, this multiplicity of impacts violates a key assumption in traditional cost effectiveness analyses that interventions are independent (14). Also the range of the different sectors involved

Textbox 1: The economic evaluation of Pulsenet

PulseNet is a surveillance system designed to identify and facilitate investigation of foodborne illness outbreaks. This molecular subtyping network of public health and food regulatory agency laboratories provides stakeholders information to improve decision making and provides powerful incentives for the industry. It furthermore enhances the focus of regulatory agencies and limits the impact of outbreaks.

In an economic evaluation the health and economic impacts associated with PulseNet were studied (151). Effectiveness was measured as a reduction of reported illness due to improved information, enhanced accountability of the industry, and more rapid recalls. Economic costs comprised programs costs and medical costs and productivity costs averted due to reduced illness.

Based on data collected between 1994 and 2009 it was estimated that the system reduced the number of illnesses from Salmonella by 266.522, from Escherichia coli (E. coli) by 9.489, and from Listeria monocytogenes by 56. This reduced medical and productivity costs with $507 million. Direct effects from improved recalls additionally reduced illnesses from E. coli by 2.819 and Salmonella by 16.994, which further reduced costs with $37 million. Annual costs for PulseNet to public health agencies were $7.3 million.

further complicates the measurement of benefits from improved infectious disease surveillance. And, although it is relevant for policymakers to include these benefits in an economic evaluation, there are difficulties in measuring and valuing benefits of surveillance such as an increased feeling of security (128), (149) No study so far has evaluated disease surveillance systems taking into account its unique characteristics. Although there have been several estimates of the costs of surveillance and response activities, these studies were restricted to pre-defined preparedness or response activities for endemic diseases and single pathogen models (128), (150), (151) (see Textbox 1 for an example). Previous economic evaluations in the area of disease outbreaks have focused mainly on evaluating pharmaceutical interventions and did not make a direct link with disease surveillance systems (62), (12).

The difficulties related to quantifying the impact of surveillance work also through in measuring its costs. For instance, costs considered should include as well the costs that rise from detected cases (including false positives), further creating the additional complexity that additional cases detected can cause both an increase and decrease of the cost-effectiveness of the system. Costs of improving disease surveillance using NGS tools can be substantial. For instance, a cost comparison stud found NGS tools between 1.6 and 4.3 times more expensive than conventional methods. This study further found decreasing costs at increased uptake, implying economies of scale, originated from the ability to negotiate price reductions for larger quantities and spread of fixed costs such as the purchase of sequencers (152). In general, further cost reductions in using NGS are expected as the technology becomes more mainstream, both through learning effects where methods are applied more efficiently and increasing economies of scale. This development is expected to be comparable to how traditional methods have developed over the past (152). When it comes to the application of One Health surveillance, integrating surveillance from different sectors, some actually estimate cost-savings (153). This practice is comparable to improved data-sharing within sectors in general, as discussed before.

Note that hidden costs here may be the costs for the development of incentive-structures for data-sharing to actually happen and facilitation of data-sharing, such as the COMPARE platform, which can be difficult to quantify and attribute to separate surveillance systems and activities, actually generating some sort of health system strengthening of health system strengthening. This relates to an important further aspect specifically relevant in global health which is seeking an optimal balance between funding disease specific (vertical) interventions and (horizontal) health system strengthening. Morton and colleagues developed an allocation model focused on choosing the optimal balance between investing in vertical and horizontal programs (14). The model was further expanded to allow for different types of health system strengthening (154). These models explicitly take into account that investments in health systems will increase benefits of other programs. For example, more information on emerging infectious diseases could improve vaccination strategies. Such models are important since another bottleneck so far has been the absence of a sound methodological framework that captures the unique characteristics of disease surveillance. Uncertainty is another very important characteristic in the case of infectious diseases and needs to be considered in the evaluation. Potential elements to capture uncertainty in such a framework may be the ‘value of information’ and the ‘real option concepts. Value of information focuses on uncertainty surrounding decisions and the role additional information can play in reducing uncertainty (155). Disease surveillance systems generate information which can reduce uncertainty (NB: NGS could also increase uncertainty due to the complex nature and quantity of the information).

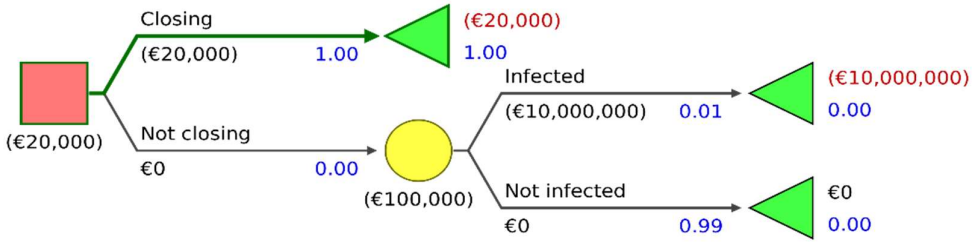
In Textbox 2 we explain the value of information using a stylized example of a policymaker facing the decision whether to close live poultry markets. This example clearly shows how information can aid policymakers to optimize outcomes, though also reveals other practical difficulties. How, for example, to get the industry to cooperate with such a policy and how to divide the burden and consequences among those involved. Pooling of risks through insurance could be an option here. Comparable solutions have already been developed and applied in the market of livestock which also suffer from the risk of epidemic disease. Problematic here are the limited incentives for the market to prevent and control infections when it is

known that potential losses will be reimbursed. Such moral hazard is however inherent to insurance and options to limit this, such as the deductible, can be applied (156).

Textbox 2: Value of information and the closure of live poultry markets

We can demonstrate the concept of value of information with a simple example. Imagine a policymaker in Guangzhou, a city in the province Guangdong in China, facing the decision whether to temporarily close its 100 live poultry markets after influenza A(H7N9) virus emerged. Currently there is no information on the market where the virus emerged. It is assumed that, when markets are closed, the risk of infection is reduced to zero.

The costs of keeping an infected market open are estimated to be €10.000.000, a combination of the monetary value of lost life-years after transmission to humans and economic consequences in the poultry industry. The costs of temporarily closing a market are estimated to be €20.000. As represented in the figure below, the expected value of not closing the market is -€100.000 (0.01*-€10.000.000 + 0.99*€0). The expected value of closing a market is -€20.000. In this problem setting the decision maker would choose to close the market since this is economically preferred. With 100 markets this would lead to expected costs of €2.000.000.



Suppose that NGS can be introduced which can trace the origin of the virus. This enables the policymaker to close only the market with infected poultry. The expected value would be -€20.000 (1*-€20.000 + 99*€0). The value of perfect information is the expected value with perfect information minus the expected value without only probabilistic information, which is €1.800.000 (-€20.000 + €2.000.000). A policymaker would be willing to pay a maximum of €1.800.000 for NGS in this scenario.

Decision tree was prepared with freeware Silver decisions from: http://silverdecisions.pl/SilverDecisions.html?lang=en

The real option valuation framework has its origins in financial economics and also focuses on decision uncertainty (157). While the focus in the value of information framework is on how more information reduces uncertainty of key decision parameters, the real option approach focuses on the dynamic character of uncertainty by valuing the option to postpone an investment provided that some initial investment is made to ensure such options are available. Examples of the application of this approach in the area of infectious diseases are studies by (158) and (159). Attema and colleagues use the approach to value stockpiling of antiviral drugs as a precautionary measure against a possible influenza. Megiddo and colleagues value the option of delaying antibiotic introduction. In the context of disease surveillance, investing in NGS would retain the option of intervening early in the event of an emerging disease outbreak. All these models capture some features of disease surveillance networks but none of these frameworks capture the system as a whole. Equally, none of these frameworks have been applied in the context of evaluating disease surveillance systems.

Another issue is the choice of appropriate perspective and decision rules to use in the context of economic evaluations of disease surveillance. Two main perspectives used in this context are the healthcare perspective and the societal perspective. When taking the former perspective, only costs that fall on the health care budget and only health benefits, for instance expressed in terms of Quality-Adjusted Life-Years (QALYs), are considered relevant. Under the goal of health maximization, the decision rule then requires the cost-effectiveness, in terms of incremental health care costs per QALY, of the new intervention (like surveillance), is positive relative to currently funded care. If, and only if that is the case, funding the new intervention, at the expense of existing care, would result in more health produced, and hence would be recommended. Compared to this, a full welfare economic assessment is attempted when taking the societal perspective, which prescribes that all costs and benefits, regardless of where, when, in what form, or in whom they occur, should be included in the analysis. Then, the ultimate decision rule is whether incremental benefits outweigh incremental costs, hence creating more societal welfare. This decision rule can be reformulated as requiring that the incremental cost-effectiveness ratio should be lower than the consumption value of health gains (160). Given the broad impact of prevention in the form of disease surveillance, which could include more health, less uncertainty and anxiety, less production losses and economic disruption, taking a societal perspective in assessing the value for money of better disease surveillance appears to be most appropriate. This more comprehensive form of assessment avoids aspects of real value to be ignored, recognizes the broad impact (in different sectors) of disease surveillance, and facilitates comparisons across interventions (also in different sectors).

This leaves the question of the societal value of an improved surveillance system. In terms of the value of health, several studies have been performed and a recent review indicated an average value of a QALY of around €75.000 (161). This figure only captures the value of health gains. The aforementioned study covering several countries within the European Union (EU) into the valuation of an improved surveillance system, indicated an average willingness to pay of around €22 per month per household (162). This is a high figure, which likely includes valuation of improved safety, reduced productivity losses, and all other elements relevant to individuals. Figures like this suggest that truly effective surveillance systems may well offer value for money from a societal perspective, given the broad range of benefits they potentially offer.

5. Conclusions and recommendations

5.1 Conclusions

Pandemics and major outbreaks have the potential to cause large health losses and major economic costs. In order to prioritize preventive and responsive interventions it is important to understand the costs and health losses interventions may prevent. In chapter 2 we reviewed the literature, investigated the type of studies performed, the costs and benefits included, and the methods employed against perceived major outbreak threats. We searched PubMed and SCOPUS for studies concerning the outbreaks of SARS in 2003, H5N1 in 2003, H1N1 in 2009, Cholera in Haiti in 2010, MERS-CoV in 2013, H7N9 in 2013, and Ebola in West-Africa in 2014. We screened titles and abstracts of papers, and subsequently examined remaining full-text papers. Data were extracted according to a pre-constructed protocol. We included 34 studies of which the majority evaluated interventions related to the H1N1 outbreak in a high-income setting. Most interventions concerned pharmaceuticals and did not look at interventions that strengthen health systems such as improving disease surveillance. Included costs and benefits, as well as the methods applied, varied substantially between studies. Most studies used a short time horizon and did not include wider costs and benefits and thus did not apply a societal perspective in practice. Overall, we conclude that the evidence base regarding the cost-effectiveness of interventions targeted at preventing or mitigating the effects of major outbreaks at this stage is biased towards specific settings and outbreaks and methodologically diverse and often fail to include relevant societal costs and benefits.

In chapter 3 we presented a case study focusing on the 2014-2016 Ebola virus disease (EVD) outbreak in West Africa and estimated the costs and health effects from a societal perspective of earlier interventions in Sierra Leone. A deterministic and a stochastic compartment model describing the EVD outbreak was estimated using a variety of data sources. Costs and Disability-Adjusted Life Years were used to estimate and compare scenarios of earlier interventions. Four weeks earlier interventions would have averted 10,257 (IQR 4,353–18,813) cases and 8,835 (IQR 3,766–16,316) deaths. This implies 456 (IQR 194-841) thousand DALYs and 203 (IQR 87-374) million $US saved. The greatest losses occurred outside the healthcare sector illustrating that earlier response in an Ebola outbreak saves lives and costs and suggest that investments in healthcare system facilitating such responses are needed and can offer good value for money.

In chapter 4, we described and discussed several economic issues raised by the prospect of improved surveillance. First, we made the case that improving disease surveillance crucially depends on real-time data sharing and that new technologies such as Next Generation Sequencing (NGS) can facilitate and act as a 'catch-all' platform suitable for surveillance of known and unknown disease pathogens resulting in economies of scale. Next, we argued that infectious disease surveillance can be typified as a global public good, due to the characteristics of non-exclusivity and non-rivalry in consumption. Public provision is therefore important and probably even required to achieve (cost)-effective disease surveillance. From an economic point of view it is desirable that once information is produced it is shared as widely as possible. Unfortunately the incentive structures which are necessary to ensure the production of information, typically hindering sharing – as once information is shared, it is harder for the generator of the information to capture the value for himself. Consequently, the most important obstacles to enable effective disease surveillance are financing and removing barriers for producing and sharing information. Research suggests that people are willing to invest in disease surveillance to a level beyond the current level of investment (162). To make optimal use of scarce resources, further investments in disease surveillance should be based on sound economic evaluations. However, an evaluation framework that captures the specific characteristics of upgrading infectious disease surveillance using NGS does not yet exist.

5.2 Recommendations

The threat of new emerging infectious diseases creates a need to continuously improve disease surveillance systems to prevent disease outbreaks (116). We described that infectious disease surveillance can be typified as (global) public goods, due to the characteristics of non-excludability and non-rivalrousness in consumption. Considering the substantial positive externalities of disease surveillance, market failure and as a consequence underprovision of disease surveillance are likely. Hence we argue for public financing of investments in surveillance. (Partial) public provision is important and presumably even required to enable cost-effective disease surveillance, due to public good characteristics of surveillance, since otherwise optimal levels for society are unlikely to be reached. Higher prevalence and burden of infectious diseases in low- and middle-income countries, combined with less financial resources available for disease surveillance in these countries demands financial support by higher-income countries. Financing surveillance also introduces questions on how much we are willing to spend on further investments. Considering current spending on disease surveillance there is potential for substantial investments in disease surveillance. Upgrading disease surveillance using NGS seems a logical step forwards given the 'catch all' potential of NGS and increasing returns to scale as a result of that especially if prices of NGS technologies will decrease due to more competition between producers of NGS technologies.

To make optimal use of scarce resources, further investments in disease surveillance are preferably based on sound economic evaluation. However, assessing cost effectiveness of disease surveillance not only requires estimates of effectiveness which is difficult to estimate but also a different analytical framework. In chapter 4 we highlighted methods which together with current practice of economic evaluation of individual interventions focusing on wider costs and benefits from a societal perspective, could form the basis of such a framework. The analyses presented in Chapter 2 illustrate the relevance of taking a broad societal perspective. The key mechanism by which disease surveillance creates value is by producing information. However, information, as well as having value, also has a cost of production, and hence there have to be appropriate incentives to create that information. Generally the cost of sharing information is much less than the cost of producing it in the first place, and so from an economic point of view it is desirable if once information is produced it is shared as widely as possible. Crucial prerequisite for cost-effective upgrading of disease surveillance is that data sharing, being on a local, national or global level, should be incentivised rather than leading to shooting the messenger where the bearer of bad news is being blamed. I. Appropriate reward and regulatory mechanisms are critical to the creation and efficient use and diffusion of innovative technologies for disease surveillance, and for the optimal use of the information which these products will generate.

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Appendix A: EBOLA health economic model

Transmission model

Equation set 1 describes the equations governing the transmission model. In the susceptible compartment β is the force of infection, φ is the effectiveness parameter of the interventions whose value before the time of intervention is fixed to 1 and thereafter decreases. In the compartment of the latent stage (E compartment) σ is the time individuals spent in the phase of being infectious but not showing symptoms or being infectious to others. The proportion of ρ is set to move to the infectious compartment and eventually become reported cases, while the remaining proportion transitions to the infectious compartment and will not become reported cases. The I_C compartment represents individuals that are infectious to others but not reported. The infected compartment has a recovery rate of γ_{CR} and the proportion $1\text{-}\delta_{C,\ while}$ the proportion δ_C dies at rate γ_{CD}. The I_{R0} compartment contains those infected that will become but are not yet reported. They become reported cases at rate ω and die and recover at the same rate and proportion as those in the I_C. After the transition to the $I_{R1,}$ the infected in the model are considered reported; they die and recover at the previously mentioned proportion and rates minus the time spent in the $I_{R0,}$ but they may be hospitalized if beds are available at rate η. When hospitalized, compartment H, a proportion of $1\text{-}\delta_H$ individuals recover and are discharged at rate γ_{HR}; the other proportion dies at rate γ_{HD}. Values used from the literature are available in table 3.1 and estimated values are available in table S2.

$$
\begin{aligned}
\frac{dS}{dt} &= -\frac{1}{N}(\beta\varphi I_C S + \beta\varphi I_R S),\\
\frac{dE}{dt} &= \frac{1}{N}(\beta\varphi I_C S + \beta\varphi I_R S) - \sigma E,\\
\frac{dI_C}{dt} &= (1-\rho)\sigma E - (1-\delta_C)\gamma_{CR} I_C - \delta_C \gamma_{CD} I_C,\\
\frac{dI_{R0}}{dt} &= \rho\sigma E - \omega I_{R0} - (1-\delta_C)\gamma_{CR} I_{R0} - \delta_C \gamma_{CD} I_{R0},\\
\frac{dI_{R1}}{dt} &= \omega I_{R0} - (1-\delta_C)(\gamma_{CR}-\omega) I_{R1} - \delta_C(\gamma_{CD}-\omega) I_{R1} - \eta I_{R1},\\
\frac{dH}{dt} &= \eta I - (1-\delta_H)\gamma_{HR} H - \delta_H \gamma_{HD} H,\\
\frac{dR}{dt} &= (1-\delta_C)\gamma_{CR} I_C + (1-\delta_C)\gamma_{CR} I_{R0} + (1-\delta_C)(\gamma_{CR}-\omega) I_{R1} + (1-\delta_H)\gamma_{HR} H,\\
\frac{dD}{dt} &= \delta_C \gamma_{CD} I_C + \delta_C \gamma_{CD} I_{R0} + \delta_C(\gamma_{CD}-\omega) I_{R1} + \delta_H \gamma_{HD} H,
\end{aligned}
\qquad (1)
$$

and the total population (N) being:

$$N = S + E + I_C + I_{R0} + I_{R1} + R \qquad (2)$$

And β being:

$$\beta(t) = \frac{a_2}{1 + e^{a_1(t-a_t)}} \quad (3)$$

And φ being:

$$\varphi(t) = \begin{cases} 1, & for\ t < intervention\ start \\ (1 - \frac{1}{1 + e^{b_1(t-b_t)}}), & for\ t \geq intervention\ start \end{cases} \quad (4)$$

To allow the infection rate to vary due to reasons other than the interventions of UNMEER, the rate was modeled through a sigmoid function. The intervention efficacy was modeled as a logistic function multiplied by the transmission parameter after the date of the intervention of the 1st of October 2014. The logistic function allows for a gradual implementation in both time and efficacy.

The parameter η, time to hospitalization among reported cases, was modeled as a linear function of time as in Kucharski *et al* (77). Data was gathered from WHO situation reports (52), and for months where estimates were missing, we assumed the closest value available. The values ranged from 4.6 days in the early epidemic to 1.3 days in the late epidemic. To reduce computational load, the bed capacity restraints of hospitalization was controlled through equation 5, where H_{max} is the maximum bed capacity at a given time for a given district. When comparing the model with the term in equation 5 to the model with bed constraints modeled through roots, the two models corresponded well.

$$\eta = \eta - \frac{\eta}{((\widehat{H}_{t,j} + 1) - H_{t,j})^2} \quad (5)$$

Parameter inference

For fitting the model, we used data from the patient database provided by the WHO website. The data are the weekly reported cases counts on a district level which we fitted against the weekly difference of the I_{R1} compartment. We fixed the following parameters with values observed by the WHO Ebola Response Team (89). The time of the latent phase as 10.4 days, the time from onset to death in the community: 6.8 days, onset to recovery in the community: 11.7 days, onset to notification to authorities for the reported cases: 4.8 days, hospitalization to death: 5.2, hospitalization to recovery and discharge: 11.6. Time to hospitalization was modeled as a linear function using data reported by the WHO situation reports (52), resulting in a range of 4.6-1.3 days from the beginning of the outbreak to the end of the outbreak. Reported opening dates and bed numbers from the Humanitarian Data Exchange were cleaned and checked for inconsistency by comparing it to various sources such as NGOs, Situation Reports by UNMEER and Sierra Leone's Ministry of Health. In the case of fatality rates we used observed values of 60.3 percent for hospitalized cases, 91.9 percent non-hospitalized cases (74). The model accounts for underreporting using an estimate of 83% of the cases being reported, an empirical estimate of underreporting (89). An estimate smaller than for example the estimates in the study by Kucharski *et al* and the estimate of the CDC (77,98). The transmission parameter was modeled as a time-dependent logistic function in order to handle the temporal heterogeneity of districts transmission. Resulting parameter values by district are available in table S2.

Table S2. District specific parameters

District	a_2	a_1	a_t	b_1	b_t
Bo	0,3899	137,0676	-0,0037	0,2387	241,5276
Bombali	0,5067	242,2816	-0,0019	0,0015	279,8948
Kailahun	0,5000	50,0000	-0,0390	0,0127	739,2832
Kambia	0,5091	35,2471	-0,0024	1,8922	436,6217
Kenema	0,5468	60,5284	-0,0274	0,3494	741,8758
Koinadugu	0,7352	20,6048	0,0909	0,0978	173,9795
Kono	0,6307	299,6713	0,0061	1,9659	247,7990
Moyamba	0,7034	445,4053	0,0032	0,0005	741,9642
Port loko	0,4008	1,0003	0,0037	0,0018	218,6708
Pujehun	0,2204	160,1710	-0,1313	0,6885	326,8079
Tonkilili	0,5686	56,6040	-0,0005	0,0061	154,0043
Western area rural	0,5056	500,0000	-0,0005	0,0181	251,7345
Western area urban	0,4876	492,1892	-0,0004	0,0261	239,8340

Remaining HALE

We used disability weights from the GBD for suffering from EVD of 0.133 (0.088-0.19) and for a period of post EVD weights of 0.219 (0.148-0.308). The length of the period on which the post EVD weight was applied was done in a similar manner as in the Global Burden of Disease study to 0.75 years (0.417–1.135). As was the acute phase of EVD of 15.1 (14.6 – 15.6) days for recoveries and 8.2 (7.9 – 8.4) days for the deceased. From the GBD we also used remaining HALE in age groups of five years as shown in article table S2. We assumed a normal distribution from which we sampled individual HALE estimates. The lifetime production losses were estimated by multiplying the individual HALE and the annual production losses. For the production losses, we used the annual GDP per capita from the World Bank. The distribution between the age groups among the recovered and fatalities was determined by applying the observed distribution of the WHO response group (74). Among the distribution of recovered by age groups of <15, 15-44, and ≥45 was 12.6%, 73.1%, 14.3% respectively. For deaths by age groups 14.2%, 56.5%, 29.3% respectively.