Deliverable

14.1 Framework for assessing the cost effectiveness of COMPARE

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Contents

Deliverable description

Work Package 14 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. This first deliverable corresponds to the first objective of the Work Package: To identify the important elements in calculating costs and benefits of COMPARE and related methods and tools (both regarding the system itself and from the societal perspective). It presents the methodological approach implemented so far, describes the elements of the COMPARE system and the results of the literature review conducted to date.

1. Introduction

This is the first 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 consortium partners Civic Consulting and Erasmus University Rotterdam.

In this deliverable, we present a description of the elements of the COMPARE system and the results of the research concerning possible components of the methodological framework for the cost-effectiveness analysis. This corresponds to the first of the five objectives specified for the activities of Work Package 14, namely "To identify the important elements in calculating costs and benefits of COMPARE and related methods and tools both regarding the system itself and from a societal perspective."

The document is structured as follows:

- Section 2 presents the methodology for the research conducted to date, describing our approach for conducting exploratory interviews and identifying and reviewing literature;
- Section 3 describes the elements of the COMPARE system;
- Section 4 presents results of the literature research concerning the main components of the methodological framework for the cost-effectiveness analysis;
- Finally, Section 5 describes the next steps to be followed in this Work Package.

2. Methodological approach

This section describes the methodological approach adopted for preparation of this deliverable.

2.1 Exploratory interviews

Exploratory interviews were conducted with selected stakeholders involved in the COMPARE project. The interviews were aimed at gaining a better understanding of the objectives, activities and progress made in the various Work Packages (WP) in view of identifying the key elements of COMPARE and associated cost and benefit types. The main topics covered by the interviews included:

- What are the key elements and objectives of each WP and the progress made to date?
- What are the main institutions/stakeholders that are currently involved in the activities of the WP?
- Which types of costs are accruing in the WP?
- What types of benefits are expected to result from WP activities?
- What are possible indicators for measuring the effectiveness of a system like COMPARE?

A questionnaire was developed ahead of the exploratory interviews, with questions adapted to the specificities of each Work Package. The semi-structured interviews were conducted face-to-face at the General Meeting in Copenhagen on 8 and 9 March 2016. Interviews were recorded and summary notes drafted following the interview, highlighting the key points of each discussion.

Below, we provide a list of the interviews conducted so far. The results of the interviews, along with the review of key COMPARE documents, are presented in Section 3.

Table 1: List of exploratory interviews conducted to date

Interviewee	Organisation	Work Package	Date of interview
Alisdair Wotherspoon	(Formerly) UK Food Standards Agency	Expert Advisory Panel (EAP) – Food Safety	8 March 2016
Amie Adkin	EFRA/APHA	Work Package 1	8 March 2016
Sandra Diaz Sanchez	University of Castilla-La Mancha	Work Package 1	8 March 2016
Martin Beer	Friedrich Loeffler Institut	Work Package 2	9 March 2016
Constance Schultsz	Academic Medical Center (University of Amsterdam)	Work Package 3	9 March 2016
Sebastien Matamoros	Academic Medical Center (University of Amsterdam)	Work Package 3	9 March 2016
Victoria Janes	Academic Medical Center (University of Amsterdam)	Work Package 3	9 March 2016
Guy Cochrane	European Molecular Biology Laboratory (EMBL)	Work Package 9	8 March 2016
Ole Lund	Technical University of Denmark (DTU)	Work Package 9	8 March 2016
Istvan Csabai	Magyar Tudomanyos Akademia Wigner Fizikai Kutatokozpont	Work Package 9	8 March 2016

Source: Civic Consulting

2.2 Literature review

The literature review served to collect information about the use of next-generation sequencing in the four key sectors covered by COMPARE (human health, food safety, animal health and wildlife), and to examine previous cost-benefit and cost-effectiveness analyses of current systems for pathogen identification and outbreak prevention in these sectors. For comparison purposes, we also considered methodological guidance documents and meta-analyses regarding economic analyses conducted in the four sectors.

Relevant articles, reports and studies were identified through search engines and specialised databases and journals, including Google, Plos One, Google Scholar, PubMed, PubMed Health, DOAJ (Directory of Open Access Journals), NICE (National Institute for Health and Care Excellence) and the Cochrane Library. A series of search term combinations were used, containing the key words “Next Generation Sequencing”, “Costs”, “Benefits”, “Cost effectiveness analysis”, “Cost-benefit analysis”, “Molecular typing”, “Pathogen”, “Food”, “Pathogen identification”, etc. In addition, relevant articles and reports were identified in the course of the exploratory interviews with Work Package leaders and retrieved from previous studies and other research conducted by the consortium partners. In total, 105 documents were identified, and subsequently included in our database and tagged according to content. The tags used correspond to main themes and/or subjects of the research and are as follows:

- *Animal health* - Documents relating to animal health, including detection and response to (re) emerging infections and epidemiological analyses;
- *Barriers* - Documents relating to data protection and other potential barriers to open data sharing (PEARL);
- *Benefits* - Documents identifying or analysing potential benefit types of COMPARE;
- *Case studies* - Documents relating to potential case studies to be used (e.g. H5N8 virus);
- *CBA* - Documents on cost benefit analyses and methodological guidance;
- *CEA* - Documents on cost effectiveness analyses and methodological guidance;
- *COMPARE* - Documents about the COMPARE project, official documents of the consortium, milestones and deliverables of other Work Packages;
- *Costs* - Documents identifying or analysing potential cost types of COMPARE;
- *Country*, e.g. "*UK*" - Documents relating to an element existing in a specific country (e.g. a surveillance system or data platform);
- *Data platform* - Documents relating to the data and information platform used for sharing of NGS data, the planned COMPARE platform and other relevant data sharing platforms;
- *Data sharing* - Documents relating to the need for sharing genomic information and possible implications;
- *Food safety* - Documents relating to food safety, including foodborne pathogen surveillance, outbreak detection and epidemiological analyses;
- *Methodology* - Other methodological guidance (not specifically related to CBA/CEA), or previous studies providing insight on methodologies to be applied;
- *NGS* - Documents about Next Generation Sequencing;
- *Public health* - Documents relating to public health, including frontline diagnostics and epidemiological analyses;
- *Risk assessment* - Documents about risk assessment, risk-based strategies of sample and data collection;
- *Sample processing* - Documents about harmonised standards for sample processing and sequencing;
- *Societal impact* - Documents analysing the potential wider societal impacts of COMPARE;
- *Wildlife* - Documents relating to wildlife, including detection and response to (re-) emerging infections and epidemiological analyses.

In a next step, key documents were selected based on their relevance to the cost-effectiveness framework to be developed for the COMPARE system, i.e. we identified literature focusing on previous cost-benefit or cost-effectiveness analyses of surveillance and response platforms and related costs and benefit types. Based on these criteria, ten articles were retained for further review.

The selected documents were then systematically examined by the study team, with particular attention paid to the components of the methodological frameworks applied in the studies. For each article a review template was completed, which served as basis for the subsequent synthesis of results, as presented in Section 4.

3. Description of the COMPARE system

3.1. Rationale of COMPARE

Whole genome sequencing (WGS) allows the entire DNA-profile of pathogens to be "mapped out at one time."[1] Like older sequencing technologies, Next Generation Sequencing (NGS) begins with the collection and extraction of DNA from a sample. Then, "random DNA fragments are created that contain adapter sequences that are complementary to platform-specific PCR and sequencing primers. DNA is fragmented, and additional processing (e.g. end-repair, A-tailing, "barcoding") is completed. In most cases, PCR amplification of the library is needed before sequencing."[2] The library is then sequenced using one of several NGS platforms available. Replacing first-generation platforms that used Sanger-based chemistries and capillary-based instruments, NGS technologies involve the parallel sequencing of millions of DNA fragments at the same time. The technological advances of NGS have led to a sharp drop in costs of DNA sequencing, accompanied by a massive surge in output data which is expected to continue rising to unprecedented levels in the coming years.[3]

The success of NGS is largely contingent upon collaboration by members of the international scientific community. By openly and rapidly sharing the results of NGS analysis, sequence data "can be exchanged and compared between laboratories and over time, in combination with other associated data or 'metadata' (…) (e.g. data on sample type and process, clinical, microbiological, epidemiological and other data)."[4] In 2015, the World Health Organisation (WHO) issued a statement calling for researchers to share preliminary results related to public health emergencies immediately following quality control.[5] A number of open-access databases are already in place to facilitate the sharing of genomic data, focusing on specific pathogens (such as the Global Initiative on Sharing All Influenza Data -GISAID- which gathers sequence data of influenza viruses from outbreaks around the world)[6] or on specific sectors (such as the US Genome Trakr Network which collects and shares genomic data from foodborne pathogens).

The COMPARE system is intended as a global platform to enable the open sharing of genomic information across sectors, countries and pathogen types. COMPARE aims at improving the rapid identification, containment and mitigation of emerging infectious diseases and foodborne outbreaks through:

- Developing a cross-sector and cross-pathogen analytical framework and globally linked data and information sharing platform;

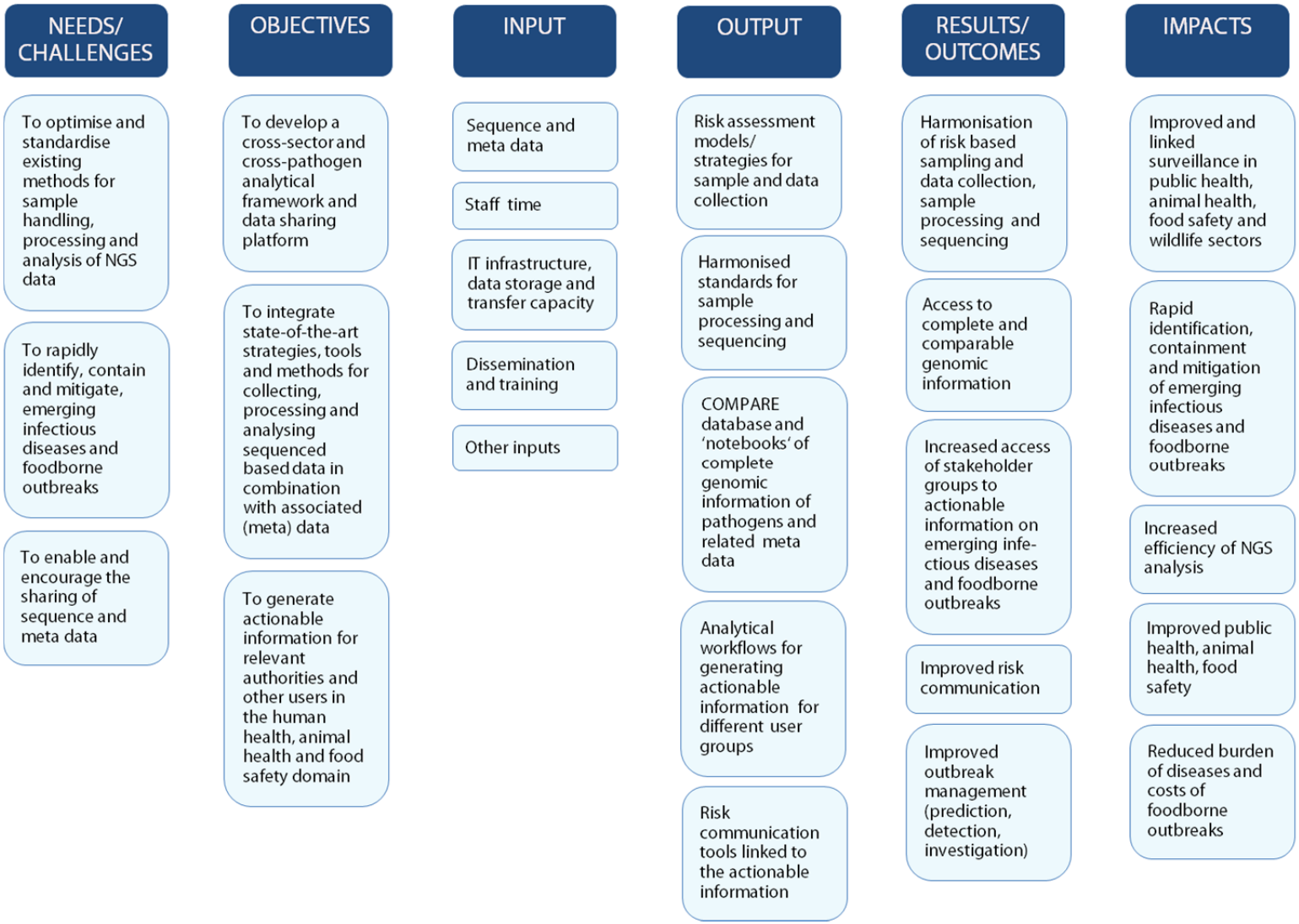
[1] DTU National Food Institute, "Large EU project to head up global fight against infectious diseases," 20 January, 2015. Available at http://www.food.dtu.dk/english/News/2015/01/Large-EU-project-to-head-up-global-fight-against-infectious-diseases?id=aecff2b3-aa21-4c03-babd-5b751e85810c.
[2] Christensen Kurt, Dmitry Dukhovny, Uwe Siebert, and Robert Green, "Assessing the Costs and Cost-Effectiveness of Genomic Sequencing", Journal of Personalized Medicine, Vol. 5, No. 4, 2015, pp. 470–486. http://www.mdpi.com/2075-4426/5/4/470.
[3] Compare proposal, p.44
[4] Ibid, p. 2
[5] World Health Organisation, "Developing global norms for sharing data and results during public health emergencies: Statement arising from a WHO Consultation held on 1-2 September 2015", available at http://www.who.int/medicines/ebola-treatment/blueprint_phe_data-share-results/en/
[6] See http://platform.gisaid.org/epi3/frontend#3fc16c

- Integrating state-of-the-art strategies, tools and methods for collecting, processing and analysing sequence-based data in combination with associated meta-data; and
- Generating actionable information for relevant authorities and other users in the human health, animal health and food safety domain.[7]

The rationale of the COMPARE system can be illustrated through an intervention logic, which is depicted in the figure on the following page. It indicates the existing needs/challenges to which the COMPARE system responds, the objectives it aims to achieve, the inputs used, and the expected outputs, results and impacts. While an intervention logic is a dynamic tool which may evolve as the analysis advances, it is useful for illustrating the expected causal chain of the intervention, which will have to be taken into account for the analysis of the system's costs and benefits.

[7] Compare proposal, p. 2

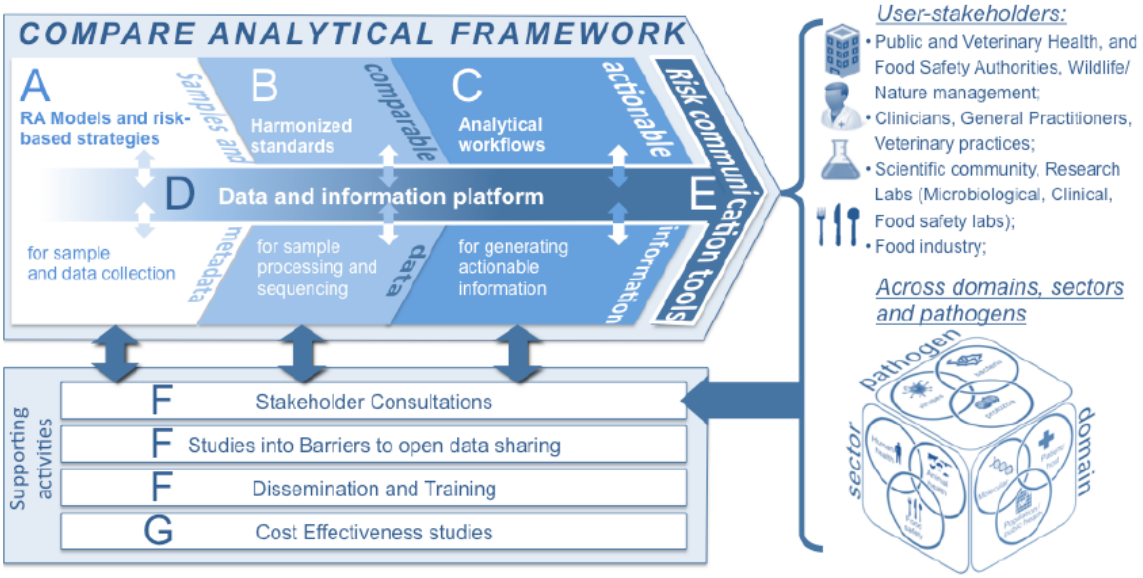
Figure 1: Indicative intervention logic for the COMPARE system



3.2. Elements of the COMPARE system

The figure below illustrates the elements of the COMPARE system according the project proposal. The elements correspond to the steps involved in NGS-based analysis: from surveillance and sampling (A) to processing and sequencing (B), resulting in actionable information (C). Enabling this process, the data and information platform (D) provides the technical infrastructure for uploading, sharing and analysing the sequence data. Risk communication tools (E) such as templates and standard messages serve to provide guidance to authorities for communicating results obtained through the system. A cost-effectiveness analysis (G), as well as complementary research on barriers to open data sharing, consultations, and training and dissemination activities (F) support the project and the system's uptake by user groups.

Figure 2: Key elements of COMPARE



Source: COMPARE proposal.

As the figure indicates, a diverse range of stakeholders are involved in the core elements of COMPARE (or will be once the system is fully operational). They include users acting as data providers, and others who are primarily information users, and many who are likely to function as both.[8] Users include professionals working in the public health, food safety, animal health and wildlife involved at various levels of research. Public authorities and private companies are also expected to use and benefit from the system. The different elements of the system (excluding management and supporting activities) are described in more detail in the following paragraphs, which also outlines for each element the progress made since project start:

The first element (A) in the figure relates to the *risk-assessment models and risk-based strategies*, which guide and structure sample and data collection for NGS-based analyses. In the absence of COMPARE, no established

[8] Compare proposal, p.11

methodology for the risk assessment of outbreaks exists that takes into account NGS data.[9] Among research conducted since the start of COMPARE, the project has developed an inventory of existing sampling protocols to map the type of samples that are currently recommended for known diseases in the public and animal health sectors.[10]

With the second element of the system (B), COMPARE aims to *harmonise and standardise the methods and protocols used for handling, processing and sequencing samples*. Since the start of the project, "an inventory of commonly used protocols with respect to collection, handling, transport and storage of samples was conducted (…) [Experiments were then] designed to investigate the influence of diverse treatments and handling procedures such as fixation, storage temperature and duration on different sample matrices."[11] Pipelines for sampling processes prior to sequencing were developed and are currently undergoing testing for different matrices. Finally, initial Laboratory Operating Procedures (LOPs) have been prepared, based on the best results obtained for the "quality and quantity of extracted nucleic acids (…) [and] sequence reads."[12]

Using the high-quality, comparable data obtained through standardised methods to be developed in the previous step, a third element (C) aims to develop *analytical workflows for processing this information and providing users with actionable information*. The overall objective is to develop and apply the analytical tools that allow sequence- and meta-data to be interpreted and used for taking well-informed decisions in frontline diagnostics, foodborne pathogen surveillance, outbreak detection, and epidemiological analysis. The work conducted to date has included the construction of a "database of reference genomes covering some of the most important foodborne pathogens of public health relevance", based on publicly available genomes.[13]

The *data and information platform* (D) provides the technical backbone for the elements previously described, enabling the rapid sharing and analysis of pathogen genomics data. A number of informatics tools have already been launched, including COMPARE Data Hubs, which allow project "partners to share data rapidly (…) using a confidential 'quarantine' period prior to full public release."[14] The COMPARE-VM cloud compute environment was also set up, "providing a selection of bioinformatics tools used by software engineers (…) for the development of computational analysis workflows to be deployed across COMPARE data."[15] Based on these developments and existing infrastructure, the completed COMPARE platform is conceived as a portal "in which partners, [external] researchers and users … report their data sets into the system and … query, analyse and visualise COMPARE data, global public data of relevance and connected external data resources."[16]

The fifth core element (E) is a *risk communication toolbox* which is intended to support the "development of communication messages about findings, outbreaks, and new opportunities discovered (…) through COMPARE

[9] Compare proposal, p.27
[10] Compare booklet– Update Year 1, p.4
[11] Ibid, p.5
[12] Ibidem.
[13] Ibid, p.9
[14] Ibidem.
[15] Ibidem.
[16] Compare proposal, p. 46

(…).”[17] The toolbox is aimed at stakeholders directly or indirectly involved in risk communication, who have been identified in the research conducted over the past year.[18]

The following table presents the COMPARE system in more detail, differentiating between the COMPARE framework (the essential elements including management of the system) and the supporting activities. For each element, information is provided regarding the related work packages and activities.

Table 2: Overview of elements of the COMPARE system and related Work Packages and activities

Level	Element	Corresponding Work Package	Activities
Compare framework	**A. Risk-assessment models and risk-based sample and data collection strategies**	WP1 RA and risk-based sample and data collection	Develop and maintain: - Generic and spatial risk assessment framework - Generic food chain risk assessment framework - Tools for epid. transmission modelling and rapid RA - Risk based sampling strategies for unusual clinical symptoms - Targeted sampling strategies for early detection - Risk-based sampling algorithms and protocols - Food level sampling strategies for surveillance
	B. Harmonized standards for sample processing and sequencing	WP2 harmonised standards sample processing and sequencing	Develop and maintain: - Harmonized standards for sample handling - Standardised processes for sample processing - Selection of Next Generation Sequencing platforms - Basic bioinformatics toolbox - Harmonized standards for metadata collection - Historic and prospective biobanks as reference - Quality management and ringtrials
	C. Analytical tools and methods for sequence-based pathogen and outbreak detection and analyses	WP3 Analytical workflows frontline diagnostics (underpinning research studies in WP6)	Develop and maintain: - Workflows for integration of NGS in clinical laboratory diagnostics - Framework for prediction - Tools for identification of hospital clusters and nosocomial transmission
		WP4 Analytical workflows foodborne outbreaks (underpinning research studies in WP7)	Develop and maintain: - Methods for sequence based surveillance of food-borne pathogens - Framework NGS and analysis tools food-borne outbreaks - Tools for source attribution
		WP5 Additional tools for detection of and response to (re-) emerging infections (underpinning research studies in WP8)	Develop and maintain: - Analytical framework for detection of (re)emerging pathogens in meta-genomic datasets - Tools for rapid sequence based detection of strain specific clusters - Tools for phylogenetic and phylogeographic analysis - Tools for detecting SNPs in pathogen NGS data - Tools for prediction of phenotype changes
	D. Data information	WP9 Data and Information sharing	Develop and maintain: - COMPARE data resource component

[18] Compare booklet – Update Year 1, p.12
[18] Compare booklet – Update Year 1, p.12

	sharing platform	platform	- COMPARE workflow engine - User spaces for COMPARE workflow development - COMPARE portal - Long-term sustainability
	E. Risk communication toolbox	WP10 Risk Communication	Develop and maintain: - Stakeholder Analysis - Targeted messages for risk communication - COMPARE risk communication tool box
	M. Management	WP15 Consortium Management	- Installment and maintenance of management bodies - Implementation of internal management procedures - Periodic technical and financial reporting - Knowledge and contract management
Supporting activities	**F1. Consultations**	WP11 User-Stakeholder Consultations	- Establishment of the Expert Advisory Panels - Implementation of EAP meetings (by Executive Board) - Establishment and consultation of Online User Panel
	F2. Research on barriers to open data sharing	WP12 Barriers	- Establishment of the Expert Advisory Panel Barriers - Analysing legal limitations, conditions in open data sharing - Constructing an ethical framework and charter - Developing standard procedures for data shipment - Data sharing guidelines - Support for COMPARE and workpackage leaders
	F3 Training and dissemination	WP13 Dissemination & Training	- Developing and maintaining user-stakeholder database - Producing and distributing promotion materials - COMPARE public website and Twitter-account - international conferences, seminars and symposia - Production and distribution of e-learning material - Establishment of COMPARE helpdesk - COMPARE workshops - Expert (practical) courses and researcher exchange
	G. Cost-effectiveness analysis	WP14 Cost effectiveness	- Identify the important elements - Identify develop costing methodologies - Define the baseline - Value safety methodology in several countries. - Estimate the cost-effectiveness of COMPARE - assess options for refining selected elements of COMPARE

Source: Civic Consulting, adapted from COMPARE proposal.

4. Framework of analysis

For assessing the cost-effectiveness of COMPARE – as for any cost-effectiveness or cost-benefit analysis – a methodological framework has to be defined before research on costs and benefits can be conducted. Essential components of such a framework include:

- *Perspective of the analysis* – determines the scope of the analysis and which costs and benefits are included;
- *Timeframe of the analysis* –influences whether certain costs and benefits are considered or not (e.g. the long-term benefits of an intervention);
- *Unit of effectiveness* – measures a quantifiable outcome central to the objectives of the program/intervention;
- *Baseline* – is the comparator (also known as the counterfactual scenario) against which an intervention is measured;
- *Cost types* – have to be determined for collecting, quantifying and assessing related data about the intervention;
- *Benefit types* – have also to be determined for collecting, quantifying and assessing related data about the intervention;
- *Method(s)* – are adopted for establishing cost-effectiveness or cost-benefit ratios, based on the cost and benefit data collected.

In line with the methodology suggested in the Work Package description, we conducted a literature review to examine previous cost-benefit and cost-effectiveness analyses of systems for pathogen identification and outbreak prevention and of whole genome sequencing with the aim of identifying approaches that could inform the development of the methodological framework for assessing the cost-effectiveness of COMPARE.

Section 4.1 below presents the results of this review. Section 4.2 provides an analysis of the results of the literature review according to the above listed methodological components.

4.1. Results of the literature review

As indicated before, a total of ten key articles and other documents were selected for in-depth review based on their relevance to the cost-effectiveness framework to be developed for the COMPARE system. The selected documents were then systematically examined by CIVIC and EUR, with particular attention paid to the components of the methodological frameworks applied in the studies. The results are presented in the following review templates, which provide for each document bibliographical information, an abstract and other key information, including regarding the specified methodological components.

Title		COST-EFFECTIVENESS ANALYSIS OF DIAGNOSTIC OPTIONS FOR *PNEUMOCYSTIS* PNEUMONIA (PCP)
Authors		Harris, Julie R.; Marston, Barbara J.; Sangrujee, Nalinee; DuPlessis, Desiree; Park, Benjamin
Abstract		Diagnosis of Pneumocystis jirovecii pneumonia (PCP) is challenging, particularly in developing countries. Highly sensitive diagnostic methods are costly, while less expensive methods often lack sensitivity or specificity. Cost-effectiveness comparisons of the various diagnostic options have not been presented. We compared cost-effectiveness, as measured by cost per life-years gained and proportion of patients successfully diagnosed and treated, of 33 PCP diagnostic options, involving combinations of specimen collection methods [oral washes, induced and expectorated sputum, and bronchoalveolar lavage (BAL)] and laboratory diagnostic procedures [various staining procedures or polymerase chain reactions (PCR)], or clinical diagnosis with chest x-ray alone. Our analyses were conducted from the perspective of the government payer among ambulatory, HIV-infected patients with symptoms of pneumonia presenting to HIV clinics and hospitals in South Africa. Costing data were obtained from the National Institutes of Communicable Diseases in South Africa. At 50% disease prevalence, diagnostic procedures involving expectorated sputum with any PCR method, or induced sputum with nested or real-time PCR, were all highly cost-effective, successfully treating 77–90% of patients at $26–51 per life-year gained. Procedures using BAL specimens were significantly more expensive without added benefit, successfully treating 68–90% of patients at costs of $189–232 per life-year gained. A relatively cost-effective diagnostic procedure that did not require PCR was Toluidine Blue O staining of induced sputum ($25 per life-year gained, successfully treating 68% of patients). Diagnosis using chest x-rays alone resulted in successful treatment of 77% of patients, though cost-effectiveness was reduced ($109 per life-year gained) compared with several molecular diagnostic options. For diagnosis of PCP, use of PCR technologies, when combined with less-invasive patient specimens such as expectorated or induced sputum, represent more cost-effective options than any diagnostic procedure using BAL, or chest x-ray alone.
Metho-dological framework	***Type***	Cost-effectiveness analysis
	Sector	Human health
	Timeframe	Unknown (not relevant)
	Perspective	Health care payer in developing countries (typically the government)
	Unit(s) of effectiveness	Diagnostic options were ranked with respect to the proportion of PCP patients successfully treated and the total diagnostic and treatment cost per life-year gained (i.e. the sum of the total diagnostic costs and total treatment costs, divided by the number of ill patients successfully treated)
	Baseline	Comparison between different options
	Cost types	Materials and personnel time
	Benefit types	Correct diagnosis, successful treatment, life years gained
	Method(s) used	The proportion of ill patients successfully treated is represented by the number of patients successfully treated divided by the number ill, while the proportion unnecessarily treated is equal to the number of well persons treated divided by the total number of well persons. Total

	treatment costs are equal to the total number of well persons and ill patients who receive treatment, multiplied by the estimated treatment cost. Finally, the total diagnostic and treatment cost per life-year gained (the cost-effectiveness ratio) is equal to the sum of the total diagnostic costs and the total treatment costs, divided by the number of ill patients successfully treated. The incremental cost-effectiveness ratios of the most effective options were then calculated.
Results	Three metrics are relevant in this analysis for decision-making and policy concerning diagnostic testing for PCP: (a) proportion of PCP patients successfully treated, (b) proportion of well persons unnecessarily treated, and (c) the total diagnostic and treatment cost per life-year gained. An ideal test will maximize the first metric and minimize the second, at the smallest – and most feasible, for the implementing clinic or geographic region under consideration – value of the third. Because all laboratory-based diagnostic procedures considered in this analysis were highly specific, the effect of (b) is negligible for this analysis; thus, we presented the results as a function of (a) and (c). Our results indicate that PCR methodologies are so sensitive that, specimen type notwithstanding, they represent the most cost- effective diagnostic options for PCP. When PCR methodologies are available, they mitigate the need for obtaining highly invasive specimens, such as BAL, which increase procedural sensitivity at substantial increases in cost. However, if both PCR and machinery for sputum induction are unavailable at a given site, the next-best option could be ES/TBO, which is relatively inexpensive and simple in terms of specimen collection and laboratory require- ments for diagnosis. Although the use of chest x-ray alone for diagnosis can lead to the successful detection and treatment of high proportions of patients, the cost per life-year gained exceeds that of other equally-sensitive or more sensitive methods for diagnosing disease. In general, the decision about which test is most useful in a given region will depend on the estimated prevalence of PCP among persons tested, local technical capacity, and available financial resources.
Other notes	Indirect costs were not included in the model (buildings, equipment, technical know-how needed to carry out more advanced molecular diagnostics that are not in place in all countries or unevenly distributed geographically). We did not account for differing diagnostic or treatment costs in different countries or among different patient groups, which could affect overall cost or cost-effectiveness of different diagnostic options. However, it is worth noting that, although the costs of all procedures might differ by country, the relative cost of procedures is unlikely to differ greatly.

Title		AN ECONOMIC EVALUATION OF PULSENET
Authors		Scharff, Robert L; Besser, John; Sharp, Donald J; Jones, Timothy F; Dms, Peter Gerner-smidt; Hedberg, Craig W
Abstract		The PulseNet surveillance system is a molecular subtyping network of public health and food regulatory agency laboratories designed to identify and facilitate investigation of foodborne illness outbreaks. This study estimates health and economic impacts associated with PulseNet. The staggered adoption of PulseNet across the states offers a natural experiment to evaluate its effectiveness, which is measured as reduction of reported illnesses due to improved information, enhanced industry accountability, and more-rapid recalls. Economic impacts attributable to PulseNet include medical costs and productivity losses averted due to reduced illness. Program costs are also reported. Better information and accountability from enhanced surveillance is associated with large reductions of reported illnesses. Data collected between 1994 and 2009 were assembled and analyzed between 2010 and 2015. Conservatively, accounting for underreporting and underdiagnosis, 266,522 illnesses from Salmonella, 9,489 illnesses from Escherichia coli (E. coli), and 56 illnesses due to Listeria monocytogenes are avoided annually. This reduces medical and productivity costs by $507 million. Additionally, direct effects from improved recalls reduce illnesses from E. coli by 2,819 and Salmonella by 16,994, leading to $37 million in costs averted. Annual costs to public health agencies are $7.3 million. The PulseNet system makes possible the identification of food safety risks by detecting widespread or non-focal outbreaks. This gives stakeholders information for informed decision making and provides a powerful incentive for industry. Furthermore, PulseNet enhances the focus of regulatory agencies and limits the impact of outbreaks. The health and economic benefits from PulseNet and the foodborne disease surveillance system are substantial.
Metho-dological framework	***Type***	Economic evaluation
	Sector	Food safety
	Timeframe	Data collected between 1994 and 2009, assembled and analyzed between 2010 and 2015
	Perspective	Society (benefits) and public health agencies (costs)
	Unit(s) of effectiveness	Reduction of reported illnesses
	Baseline	Pre-PulseNet situation in states: “This study estimates health and economic impacts associated with PulseNet. The staggered adoption of PulseNet across the states offers a natural experiment to evaluate its effectiveness …”
	Cost types	Program costs (laboratory setup, isolate testing, outbreak response borne by government and industry)
	Benefit types	Improved information, enhanced industry accountability, more rapid recalls, cost savings due to averted medical costs and productivity losses, improvements in outbreak detection, reduction in foodborne illness.
	Method(s) used	Probabilistic models (to estimate the number of cases prevented through recalling products) and regression analysis (to capture indirect effects of the system on incidence of illness): Two approaches were used to assess the number of illnesses averted due to PulseNet. First, a “Recall” model was developed to assess the direct effects of faster identification of outbreaks on consumption of contaminated product and the resultant illness reduction. Second, a “Process Change” model was designed to capture the indirect effects from enhanced outbreak

	identification on illnesses averted due to new incentives and information used by industry and government. A comprehensive Monte Carlo analysis using @Risk, version 5.7.1, was performed to account for uncertainty in both the illness and economic models. Credible intervals are reported for terminal values across alternative models. A conservative cost of illness analysis is then used to produce summarymeasures for burden of illness averted. Data for this study were assembled and analyzed between 2010 and 2015.
Results	Annually, averted illnesses attributable to improved industry processes resulted in $14–$647 million in median reduced direct and indirect costs, yielding a societal return of $3–$90 for every $1 invested by public health agencies. The direct effects from improved recalls yielded up to $29 million, with a societal return of up to $5 for every $1 invested by public health agencies (…) This evaluation of PulseNet demonstrated significant economic and public health benefits from the system. These benefits are driven by improvements in outbreak detection, which provide industry and government with valuable information, while exposing food producers to increased threat from litigation and reputation losses. This ultimately leads to adjustments in processes that reduce foodborne illness. The measurable costs of the program, in contrast, are very modest.
Other notes	The study does not include all economic costs: e.g. welfare losses from premature death and reduced quality of life due to illness are not monetised, and indirect costs from PulseNet (e.g. costs to other government agencies, costs of recalls) (…) Also complicating the analysis is the fact that outbreak identification and the media attention surrounding it leads to enhanced illness reporting by the public. Theoretically, this will affect the analysis in two ways. First, because reported illnesses are used as a dependent variable in one part of the analysis, enhanced reporting without a control for media effects introduces omitted variable bias into the model. Properly controlled, the process model would likely yield larger reductions in foodborne illness than it currently predicts. Second, enhanced reporting will affect the degree to which illnesses are underreported and underdiagnosed. As a result, in the adjusted model only, the effects of PulseNet may be overstated. The net effects of these biases are unclear, but do not undermine the principal conclusion.

Title		ASSESSING THE COSTS AND COST-EFFECTIVENESS OF GENOMIC SEQUENCING
Authors		Christensen, Kurt; Dukhovny, Dmitry; Siebert, Uwe; Green, Robert
Abstract		Despite dramatic drops in DNA sequencing costs, concerns are great that the integration of genomic sequencing into clinical settings will drastically increase health care expenditures. This commentary presents an overview of what is known about the costs and cost-effectiveness of genomic sequencing. We discuss the cost of germline genomic sequencing, addressing factors that have facilitated the decrease in sequencing costs to date and anticipating the factors that will drive sequencing costs in the future. We then address the cost-effectiveness of diagnostic and pharmacogenomic applications of genomic sequencing, with an emphasis on the implications for secondary findings disclosure and the integration of genomic sequencing into general patient care. Throughout, we ground the discussion by describing efforts in the MedSeq Project, an ongoing randomized controlled clinical trial, to understand the costs and cost-effectiveness of integrating whole genome sequencing into cardiology and primary care settings.
Metho-dological framework	***Type***	Randomized controlled clinical trial to understand the costs and cost-effectiveness of integrating whole genome sequencing into cardiology and primary care settings
	Sector	Human health
	Timeframe	Ongoing (2015)
	Perspective	Societal (health care expenditure)
	Unit of effct.	Cost per QALYs, using SF-6D values (index measure of health ranging from 0 to 1 that can be used to generate QALYs)
	Baseline	WGS patients prior to disclosure of WGS results / Non-WGS patients
	Cost types	Costs for garnering informed consent, costs of genomic sequencing, costs of confirming variants via Sanger sequencing, medical care costs following disclosure of results, patient out-of-pocket expenses (e.g. time off work, patient copayments, transportation costs).
	Benefit types	Number of pathogenic and likely pathogenic monogenic findings for participants, health related quality of life, early identification and prevention of potential threats
	Method(s) used	Cost-effectiveness will be assessed using incremental cost-effectiveness ratios (ICERs) by dividing the differences in costs by the differences in QALYs when comparing both randomized groups. We will also conduct subgroup analyses and secondary analyses to assess whether benefits, harms, and ICERs of WGS differ between by cohort (primary care versus cardiology) and to assess the impact of having a monogenic finding disclosed.
	Results	Study ongoing
	Other notes	Evaluation conducted alongside the MedSeq Project, an ongoing randomized clinical trial of whole genome sequencing in cardiology and primary care settings. Patient participants in both the cardiology and primary care trials are randomly assigned to receive a family history assessment with or without WGS. The laboratory delivers a genome report to physician participants that balances the needs to enhance understandability of genomic information and to convey its complexity. Using varied data sources, including surveys, semi-structured interviews, and review of clinical data, the attitudes, behaviors and outcomes of physician and patient participants are measured at multiple time points before and after the disclosure of these results.

Title		INVESTMENT IN PREVENTING AND PREPARING FOR BIOLOGICAL EMERGENCIES AND DISASTERS: SOCIAL AND ECONOMIC COSTS OF DISASTERS VERSUS COSTS OF SURVEILLANCE AND RESPONSE PREPAREDNESS
Authors		Rushton, J., Upton, M.
Abstract		Biological emergencies such as the appearance of an exotic transboundary or emerging disease can become disasters. The question that faces Veterinary Services in developing countries is how to balance resources dedicated to active insurance measures, such as border control, surveillance, working with the governments of developing countries, and investing in improving veterinary knowledge and tools, with passive measures, such as contingency funds and vaccine banks. There is strong evidence that the animal health situation in developed countries has improved and is relatively stable. In addition, through trade with other countries, developing countries are becoming part of the international animal health system, the status of which is improving, though with occasional setbacks. However, despite these improvements, the risk of a possible biological disaster still remains, and has increased in recent times because of the threat of bioterrorism. This paper suggests that a model that combines decision tree analysis with epidemiology is required to identify critical points in food chains that should be strengthened to reduce the risk of emergencies and prevent emergencies from becoming disasters.
Metho-dological framework	***Type***	Theoretical analysis
	Sector	Animal health
	Perspective	Societal
	Cost types	Costs of control and eradication measures, protective measures at borders, strategies for wildlife disease control, surveillance measures that require the implementation and use of improved database technology, response mechanisms to disease outbreaks and simulation exercises, socio-economic impacts of disease outbreak, financial investment in the development of programmes for the control, eradication and prevention of transboundary disease, contingency funds, vaccine banks.
	Benefit types	Faster detection of transboundary diseases, reduced impact of biological disaster, reduced likelihood of outbreaks, quick control and eradication of diseases with minimal costs
	Results	Based on earlier work, the authors (1, 21) suggest that decision tree analysis (9, 33) combined with epidemiological analysis would be the best method for developing a strategy to confront biological disasters. This approach could perhaps be taken a step further by using an optimisation process, such as dynamic programming, to determine a unique solution (26). However, given the number of unknowns for a biological disaster, it is unlikely that optimisation would be possible. Furthermore, the value of models used for the prediction of solutions is questionable (14, 27, 28). Figure 2 presents a simple representation of the model proposed above. The value of such modelling is the actual process of working through the problems and issues rather than the identification of a final solution. It has been suggested that determining the critical risk points and the most costly aspects of a biological disaster would help in prioritising human and economic resources used to confront biological disasters. It is suggested that a balance of active and passive measures should be employed, but that because of the unknown level of threat from bioterrorism, the need to strengthen internal surveillance measures and policies to address the needs of countries with unknown animal disease status is a priority.

Title		COSTS AND BENEFITS OF A SUBTYPE-SPECIFIC SURVEILLANCE SYSTEM FOR IDENTIFYING ESCHERICHIA COLI O157:H7 OUTBREAKS
Authors		Elbasha, Elamin H.; Fitzsimmons, Thomas D.; Meltzer, Martin I.
Abstract		We assessed the societal costs and benefits of a subtype-specific surveillance system for identifying outbreak-associated Escherichia coli O157:H7 infections. Using data from Colorado, we estimated that if it averted five cases annually, the system would recover all its costs.
Metho-dological framework	***Type***	Cost-benefit analysis
	Sector	Food safety
	Timeframe	The life span of the subtype-specific surveillance system in Colorado is 5 years, yielding benefits over the lifetime of people affected by it.
	Perspective	Societal
	Unit(s) of effectiveness	N/A
	Baseline	No subtype-specific surveillance system
	Cost types	Labor and equipment costs (equipment, laboratory scientist, analysing isolates, investigating an outbreak, present value of outbreak costs, annual operating costs)
	Benefit types	Economic savings from E.coli O157:H7 cases averted (medical costs + productivity losses + lost lifetime earnings)
	Method(s) used	We estimated two threshold numbers of cases that must be averted for the costs to be equal to the benefits of the system. The first threshold number was calculated by assuming the system averts a constant number of cases every year. The second number was calculated under the assumption that the system averts only a given number of cases in the first year and no cases in subsequent years. If the estimated threshold is below a reasonable number, the system is cost beneficial. A reasonable number is calculated by consulting the literature and expert opinion.
	Results	If 15 cases were averted by the recall of the 25 million pounds of potentially contaminated beef, the Colorado system would have recovered all costs for the 5 years of start-up and operation by detecting a single outbreak (Table 3). In comparison, the outbreak-related 1993 recall of 255,000 regular (0.1-lb) hamburgers in Washington State was estimated to have prevented 800 cases. The discounted average cost of an E. coli O157:H7 infection of $7,788 (Table 3) was a relatively conservative estimate compared with that of $38,000 (in 1995 dollars) by Buzby et al. The major differences are the probability of death and the economic value of life used in the estimation. If other benefits of the system (e.g., obviating the need to investigate sporadic cases) are included, the system becomes even more cost beneficial. Unproductive extensive traceback investigations of sporadic E. coli O157:H7 infections have been conducted. Investigating such sporadic cases can be very costly (Table 1), and a subtype-specific system can reduce such costs. (…) Despite its limitations, this study has important implications for public health policy. From a societal perspective, a surveillance system does not need to prevent a large number of cases to yield return on the resources invested in it.
	Other notes	This study was limited by lack of data that would have enabled us to estimate attack rates from the outbreak, cases averted by the meat recall, and the benefit to society (money saved) by establishing the system.

RAPID, COMPREHENSIVE, AND AFFORDABLE MYCOBACTERIAL DIAGNOSIS WITH WHOLE-GENOME SEQUENCING: A PROSPECTIVE STUDY		
Authors		Pankhurst, Louise J., del Ojo Elias, Carlos, Votintseva, Antonina A., Walker, Timothy M., Cole, Kevin, Davies, Jim, Fermont, Jilles M., Gascoyne-Binzi, Deborah M., Kohl, Thomas A., Kong, Clare, Lemaitre, Nadine, Niemann, Stefan, Paul, John, Rogers, Thomas R., Roycroft, Emma, Smith, E. Grace, Supply, Philip, Tang, Patrick, Wilcox, Mark H., Wordsworth, Sarah, Wyllie, David, Xu, Li, Crook, Derrick W.
Abstract		Slow and cumbersome laboratory diagnostics for Mycobacterium tuberculosis complex (MTBC) risk delayed treatment and poor patient outcomes. Whole-genome sequencing (WGS) could potentially provide a rapid and comprehensive diagnostic solution. In this prospective study, we compare real-time WGS with routine MTBC diagnostic workfl ows.
Metho-dological framework	***Type***	Prospective, comparative study (including a micro-costing analysis)
	Sector	Human health
	Timeframe	Reference year 2014
	Baseline	Routine laboratory diagnostic workflows
	Cost types	Costs associated with staff time, error rates, equipment, and consumables
	Benefit types	Rapid identification and control of outbreaks, lower cost per culture-positive specimen
	Method(s) used	To assess the financial viability of WGS-based diagnostics, we did a microcosting analysis at a local clinical laboratory (John Radcliffe Hospital, Oxford, UK) and regional reference laboratory (Birmingham Heartlands Hospital Trusts, Birmingham, UK). We collected data using questionnaires based on standard operating procedures, expert consultations, and interviews with laboratory staff . Questionnaires were completed by clinical scientists doing mycobacterial processing and financial managers, who collected costs associated with staff time, error rates, equipment, and consumables (appendix). We obtained basic cost data (staff time, consumables, and equipment only) via interview with clinical scientists for second-line phenotypic DST (done at the National Mycobacterial Reference Laboratory, London, UK). We annualised costs using the throughput of the Birmingham regional reference laboratory for 2014.
	Results	Costs (calculated with reported throughput for 2014) for routine diagnostic workflows were £518 per culture- positive specimen, consisting of MGIT culture for all samples received, species identifi cation for culture- positive specimens, and MIRU-VNTR and DST for MTBC-positive specimens. For WGS-based diagnosis, consisting of MGIT culture for all samples received and WGS for culture-positive specimens, the per-culture- positive specimen cost would be £481, which is 7% cheaper than are routine diagnostics. To do DST as per present workfl ows alongside WGS would cost £540 per culture-positive specimen, which is 4% more expensive than are routine diagnostics (table 3). Increasing sample throughput decreased costs overall (table 3, appendix). Variation in sequencing batch size, throughput, error rates, equipment, consumables, and overhead costs could alter overall WGS costs by up to 17% (appendix). (…)An often cited obstacle to clinical implementation of WGS is cost. For the laboratories and workfl ows costed here, high WGS costs for NTM diagnosis were outweighed by savings made in MTBC diagnosis, leading to an overall saving of 7% per year for a reference centre. If present DST workfl ows are continued alongside WGS, costs would be 4% greater per year than with present workfl ows alone. However, these additional costs would be mitigated by replacement of any molecular DST done alongside phenotypic DST with WGS. The cost-effectiveness of replacement of phenotypic with other rapid genotypic assays in terms of patient care has already been shown and is

probably similar for WGS. The decentralised-sequencing, centralised-analysis model used in this study minimises computational and technical support costs. WGS costs could fall further when implemented diagnostically, which will need less skilled staff than at present. However, availability of skilled staff is likely to remain a key limitation of adoption of WGS in low-income settings.

AN ECONOMIC EVALUATION OF THE CONTROL OF THREE NOTIFIABLE FISH DISEASES IN THE UNITED KINGDOM

Authors		Dominic Moran, Abdulai Fofana
Abstract		We summarised the challenges faced in an ex ante cost–benefit appraisal of United Kingdom government spending on disease surveillance for three notifiable fish diseases: infectious salmon anaemia (ISA), viral haemorrhagic septicaemia (VHS) and infectious haemorrhagic necrosis (IHN). We used a social cost–benefit analysis and adopted a national perspective. We compared costs of current public and private surveillance effort with the benefits stated in terms of the avoided private and social costs of potential disease outbreaks. Spending on ISA and VHS were predicted to be efficient; the benefit–cost ratios were always 3.2 for ISA and 5.8 for VHS for all nine scenarios examined for each infection. However, the benefit–cost ratio for IHN was predicted never to exceed 1.6, and was <1.0 in five of the nine scenarios-so spending on IHN would be harder to justify.
Metho-dological framework	***Type***	Cost–benefit
	Sector	Animal health
	Perspective	Social perspective (national)
	Unit(s) of effectiveness	Monetary
	Baseline	Existing surveillance policy
	Cost types	Eventual outbreak cost, impacts across the industry plus social or welfare costs to wider society, costs of implementing surveillance
	Benefit types	Monetary (avoided private and social costs of potential disease outbreaks)
	Results	The surveillance-and-control programme for ISA and VHS seem to be providing acceptable rates of return on investment of public funds. For ISA, public spending yielded £3.2, £3.6 and £ 4.3 in scenarios LRO, MRO and HRO, respectively, for every £1 invested. In the case of VHS, for every £1 invested would yield £5.7, £5.8 and £6.8 in scenarios LRO, MRO and HRO, respectively. Control and surveillance expenditure on IHN was less favourable with comparatively low BCRs of 0.80 for scenarios LRO and MRO and BCR of 1.00 in scenario HRO.

ECONOMIC EVALUATION OF THE SURVEILLANCE AND INTERVENTION PROGRAMME FOR BLUETONGUE VIRUS SEROTYPE 8 IN SWITZERLAND

Authors		B. Häsler, K.S. Howe, E. Di Labio, H. Schwermer, K.D.C. Stärk
Abstract		Empirical analyses founded on sound economic principles are essential in advising policy makers on the efficiency of resource use for disease mitigation. Surveillance and intervention are resource-using activities directed at mitigation. Surveillance helps to offset negative disease effects by promoting successful intervention. Intervention is the process of implementing measures (e.g. vaccination or medication) to reduce or remove a hazard in a population. The scale and ratios in which the two are combined affect the efficiency of mitigation, its costs, benefits, and thus net effect on society's well-being. The Swiss national mitigation programme for bluetongue virus serotype 8 was used as case study to investigate the economic efficiency of mitigation. In 2008, Switzerland implemented a vaccination programme to avoid and reduce disease and infection in its ruminant population. To monitor the vaccination programme and the vector dynamics, a surveillance system consisting of serological and entomological surveillance was established. Retrospective analyses for the years 2008–2009 and prospective analyses for the years 2010–2012 were conducted to investigate if the mitigation programme was economically beneficial. In the retrospective analysis, the implemented programme (=comparative scenario) was compared to a hypothesised baseline scenario of voluntary vaccination and surveillance. In the prospective analysis, the comparative scenario assumed to continue was compared to two baseline scenarios: one of voluntary vaccination combined with surveillance and one of no vaccination combined with surveillance. For each scenario, monetary surveillance, intervention and disease costs were calculated. The comparison of baseline and comparative scenarios yielded estimates for the total benefit (=disease costs avoided), margin over intervention cost and the net value of the programme. For 2008–2009, in aggregate, the mean biannual total benefit was 17.46 m Swiss francs (CHF) (1CHF = 0.66D at the time of analysis) and the mean net benefit after subtraction of the intervention and surveillance cost was 3.95 m CHF. For the three years 2010–2012, overall net costs were estimated at 12.93 m and 8.11 m CHF, respectively, for comparison of the implemented mitigation programme with the two baseline scenarios. It was concluded that the surveillance and intervention programme implemented in 2008–2009 was economically beneficial, while its continuation in the same form in 2010–2012 would produce net costs. These costs were due to the mean intervention cost remaining constant at a level of approximately 11 m CHF per year while the mean total benefit would be gradually reduced in 2010–2012 due to the reduced occurrence of disease in a fully vaccinated population.
Metho-dological framework	***Type***	Cost-benefit
	Sector	Animal health
	Timeframe	1 year (retrospective analysis) and two years (prospective analysis)
	Perspective	Societal
	Unit(s) of effectiveness	Monetary
	Baseline	Scenario of voluntary vaccination and surveillance
	Cost types	Production losses, expenditures for palliative treatment and export, and costs in case of an outbreak

Benefit types	Disease costs avoided
Results	The results showed that the implementation of the mitigation programme was beneficial overall for the years 2008–2009, but produced net costs in future years.

A QUALITATIVE APPROACH TO MEASURE THE EFFECTIVENESS OF ACTIVE AVIAN INFLUENZA VIRUS SURVEILLANCE WITH RESPECT TO ITS COST: A CASE STUDY FROM SWITZERLAND

Authors		B. Häsler, K.S. Howe, R. Hauser, K.D.C. Stärk
Abstract		The aim of the project was to apply cost-effectiveness analysis to the economic appraisal of avian influenza virus (AIV) surveillance, using the implemented surveillance programme in Switzerland as a case study. First a qualitative risk assessment approach was used to assess the expected impact of surveillance on the transmission and spread of AIV. The effectiveness of surveillance was expressed as the difference in defined probabilities between a scenario with surveillance and a scenario without surveillance. The following probabilities were modelled (i) transmission of highly pathogenic AIV (HPAIV) from wild birds to poultry, (ii) mutation from low pathogenic AIV (LPAIV) into HPAIV in poultry, and (iii) transmission of HPAIV to other poultry holdings given a primary outbreak. The cost-effectiveness ratio was defined conventionally as the difference in surveillance costs (C) divided by the change in probability (P), the technical objective, on the presumption that surveillance diminishes the respective probabilities. However, results indicated that surveillance in both wild birds and poultry was not expected to change the probabilities of primary and secondary AIV outbreaks in Switzerland. The overall surveillance costs incurred were estimated at 31,000 D/year, which, to be a rational investment of resources, must still reflect the value policy makers attribute to other benefits from having surveillance (e.g. peace of mind). The advantage of the approach adopted is that it is practical, transparent, and thus able to clarify for policy makers the key variables to be taken into account when evaluating the economic efficiency of resources invested in surveillance, prevention and intervention to exclude AIV.
Metho-dological framework	***Type***	Cost-effectiveness
	Sector	Animal health
	Perspective	Direct surveillance costs only
	Unit(s) of effectiveness	Change in probability
	Baseline	Scenario without surveillance
	Cost types	Organisation, material, sample taking, laboratory analysis and labour
	Benefit types	Difference in different types of transmission probabilities
	Method(s) used	Because of the lack of quantitative data, a qualitative risk assessment approach based on the framework outlined by the World Organisation for Animal Health (Anon., 2010b) was used. It included a release and exposure assessment as described below. The HPAIV outbreaks could either stem from an introduction of LPAIV and subsequent mutation into HPAIV or the transmission of HPAIV via wild birds or illegal trade to poultry. The difference in probabilities of primary and secondary outbreaks between a scenario with surveillance and a scenario without surveillance was compared to the costs of surveillance for the year 2009. To estimate the probabilities of primary and secondary outbreaks, detailed steps for transmission and mitigation measures were described. They were the same for both commercial and backyard holdings. Pathway 1 was to determine the probability of HPAIV transmission from wild birds to commercial and backyard poultry holdings with and without wild bird surveillance. Pathway 2

	described the chain of events to determine the probability that LPAIV introduced by wild birds or illegal trade and transmitted to poultry holdings mutates into HPAIV. The starting point for LPAIV in poultry was a combination of the probabilities of a primary outbreak in commercial and backyard holdings found through illegal trade or wild birds. Because more than one factor contributes to the probability estimate of the starting point (additive effect), the highest probability was considered. Pathway 3 was to determine the probability of HPAIV transmission from an infected poultry holding to other commercial or backyard holdings with and without wild bird surveillance in place. Pathway 4 was to determine the probability of HPAIV transmission from an infected poultry holding to other commercial or backyard holdings with and without poultry surveillance in place. A workshop was held with four Swiss AIV experts to discuss and agree all steps of the pathways and estimate probabilities and uncertainties using data from the scien- tific literature whenever possible.
Results	The annual surveillance costs were estimated to be 20,000 for wild bird and 11,000 for poultry surveillance. But because the difference in estimated probabilities was zero, it follows that cost-effectiveness ratios in any conventional sense are formally undefined. (...) The surveillance costs were less than one quarter of the approximately D134,000 spent annually on salmonella surveillance in poultry in Switzerland, and so is a relatively small sum. Nevertheless, for the existing policy to have any real economic value, the implicit value of non-monetary benefits that accrue from the surveillance programme still must be considered at least to cover its cost. Otherwise the resources expended, however modest in financial terms, are being used wastefully. Conceivably, surveillance is val- ued for the peace of mind it provides, a kind of insurance in the minds of the general public should expert opinion be shown in error about its negligible actual efficacy and contribution to protection against AIV.
Other notes	The use of a modified risk assessment approach to determine the effectiveness of surveillance for CEA has two important advantages. It is based on the well- established risk assessment framework suggested by the World Organisation for Animal Health (Anon., 2010b), and it allows investigation of the relationship between transmission pathways and mitigation measures. Thus it provides information about the effectiveness of surveillance and, at the same time, highlights critical points in the transmission–mitigation interaction. In this study, however, the results showed that surveillance in both wild birds and poultry had no perceptible impact on the estimated probabilities of primary and secondary outbreaks of AIV. Possibly, four qualitative probability categories were not enough to detect small differences. However, the use of more categories is not recommended due to considerable uncertainty and lack of data. If data are abundant and accurate, the expansion of the number of probability categories or the use of a quantitative approach should be considered to increase the precision of the model.

MODELING THE COST-EFFECTIVENESS OF THE INTEGRATED DISEASE SURVEILLANCE AND RESPONSE (IDSR) SYSTEM: MENINGITIS IN BURKINA FASO		
Authors		Zana C. Somda, Helen N. Perry, Nancy R. Messonnier, Mamadou H. Djingarey, Salimata Ouedraogo Ki, Martin I. Meltzer
Abstract		Effective surveillance for infectious diseases is an essential component of public health. There are few studies estimating the cost-effectiveness of starting or improving disease surveillance. We present a cost-effectiveness analysis of the Integrated Disease Surveillance and Response (IDSR) strategy in Africa.
Metho-dological framework	***Type***	Cost-effectiveness
	Sector	Human health
	Timeframe	Pre-IDSR period (1996-2002) and post-IDSR period (2003-2007)
	Perspective	Health care provider
	Unit(s) of effectiveness	Number of cases, deaths or sequelae averted
	Baseline	Outbreaks before implementation
	Cost types	Personnel, transportation items, office consumable goods, public awareness campaigns, laboratory and response materials and supplies, meningitis case management and capital.
	Benefit types	Cases, deaths or sequelae averted
	Method(s) used	To model the cost-effectiveness of IDSR, we used data from Burkina Faso because that country had fully established IDSR leadership and structures at the national level by 2002, with implementation at regional and district levels in 2003. Burkina Faso had data, collected using the IDSR-supported surveillance systems, on several meningitis outbreaks. The nature of disease surveillance systems makes it impossible to have a randomly controlled experiment to measure the impact of IDSR on public health outcomes. We were unable to readily collect comparable data from another country (e.g., one without IDSR systems, or one that implemented IDSR systems after Burkina Faso), and thus we were unable to conduct a comparison between countries. We therefore relied on observational (before- and-after) data from outbreaks of meningococcal meningitis to assess the possible impact of IDSR-related activities in Burkina Faso. We assumed that any correlations between the start of IDSR activities, which includes both surveillance and response to disease activity detected, and changes in the epidemiology of meningitis outbreaks were due primarily to IDSR. With this assumption, we calculated, on an outbreak basis, costs per case, per death and per sequelae prevented.
	Results	IDSR implementation was correlated with a median reduction of 2 weeks to peak of outbreaks (25th percentile 1 week; 75th percentile 4 weeks). IDSR was also correlated with a reduction of 43 meningitis cases per 100,000 (25th–40: 75th-129). Assuming the correlations between reductions in time to peak of outbreaks and cases are related, the cost-effectiveness of IDSR was $23 per case averted (25th-$30; 75th – cost saving), and $98 per meningitis-related death averted (25th-$140: 75th – cost saving). The median cost of operating IDSR was $0.01 per capita (25th: $0.01; 75th: cost saving). We cannot absolutely claim that the measured differences were due to IDSR. We believe, however, that it is reasonable to claim that IDSR can improve the cost-effectiveness of public health surveillance.

4.2 Methodological framework

As indicated in the review templates presented in the previous sub-section, all listed articles define each of the components of the methodological framework indicated at the beginning of this section. In the following, we analyse for each component the different approaches taken, and put them into perspective by comparing them to the suggested approaches presented in relevant guidance documents for cost-effectiveness and cost-benefit analysis.

3.2.1 Perspective of the analysis

The perspective from which the analysis is conducted constitutes the starting point of any economic evaluation.[19] The choice of the point of view determines the scope of the analysis and which costs and benefits are included. While a narrow perspective considers only the direct costs of an intervention and the resulting benefits for its users, a wider point of view takes into account the social, health and economic costs and benefits accruing to society as a whole.

Among narrow approaches, a common perspective adopted in health economics is that of the single benevolent decision-maker, whose aim is to maximise population health based on the available resources. The benefits taken into account are those that accrue to the target population; the costs are those provided for in the health budget.[20] At the other end of the spectrum, a societal approach considers the costs of an intervention that accrue to individuals beyond those directly involved, as well as indirect impacts of the policy/programme. For example, from this perspective the opportunity costs and the effect on income resulting from health improvements might be considered. According to the WHO Guide to Cost-Effectiveness Analysis, most cost-effectiveness guides argue that a societal perspective is the appropriate one to adopt in health economics, i.e. one which includes all costs regardless of who pays them, and resources used or created by health interventions should be valued at the benefit foregone because society could not use the resources in their next best use (health-related or otherwise). [21] While a narrow perspective can make sense if decisions are taken at a micro level for a detailed patient population (e.g. decisions regarding which chemo-therapy a cancer patient should receive), the limitations of a narrow perspective become more obvious if policies are to be evaluated with more diverse consequences. In the UK, where a narrow perspective is usually adopted when evaluating curative health care interventions, there have been calls to broaden the perspective when public health interventions are assessed.[22] In practice, about 50% of all genomic economic evaluations adopt a wider societal perspective.[23] Indeed, as Buchanan et al. note, "the correct perspective to use in economic evaluations of genomic

[19] World Health Organisation, Evaluating the Costs and Benefits of National Surveillance and Response Systems: Methodologies and Options, 2005.
[20] 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. pp 18-19.
[21] Edejer T et al , 2003. pp 18-19.
[22] Marsh, Kevin, Ceri J Phillips, Richard Fordham, Evelina Bertranou, and Janine Hale, "Estimating Cost-Effectiveness in Public Health: A Summary of Modelling and Valuation Methods", Health Economics Review, Vol. 2, No. 1, 2012, p. 17. Health Economics Review.
[23] Buchanan, James, Sarah Wordsworth, and Anna Schuh, "Issues Surrounding the Health Economic Evaluation of Genomic Technologies", Pharmacogenomics, Vol. 14, No. 15, 2013, pp. 1833–47. http://www.futuremedicine.com/doi/abs/10.2217/pgs.13.183\nhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3909837&tool=pmcentrez&rendertype=abstract.

interventions remains uncertain." A guidance document by the WHO on Evaluating the Costs and Benefits of National Surveillance and Response Systems observes that most studies are likely to adopt an approach falling between the decision-maker's narrow perspective and the wider societal one.[24]

Among the articles reviewed, the narrowest perspective is applied in the cost-effectiveness analysis of diagnostic options for Pneumocystis Pneumonia (PCP).[25] Here, the costs and benefits are calculated specifically from the point of view of the health care payer in developing countries (typically the government). However, a majority of the reviewed studies adopted a wider approach to their analysis. Some of these mixed the narrow and societal approaches, including the costs of a specific system and comparing these with the benefits accruing to users/patients and the wider societal impacts. For instance, the evaluation of PulseNet calculated the costs of the system borne by public health agencies, while assessing benefits such as cost savings due to averted medical costs and productivity losses, improvements in outbreak detection, reduction in foodborne illness.[26] Similarly, the study assessing the costs and benefits of a subtype-specific surveillance system for identifying E.coli outbreaks analysed the costs of the surveillance system, juxtaposing these with the economic savings obtained from the E.coli cases averted as a result of the system, including medical costs and productivity losses.

3.2.2 Timeframe of the analysis

Similarly to the choice of perspective, the timeframe and timing chosen to conduct a cost-benefit/cost-effectiveness analysis has an influence on the inclusion and calculation of various costs and benefits. Evaluating an intervention for a typical (or reference) year may bias the outcome against programmes that take a number of years to start providing benefits its users. On the other hand, a long evaluation period is less feasible in practice due to the short time horizon in which health decisions are often taken.[27]

The methodological guidance documents reviewed provide several reasons for selecting longer timeframes for economic evaluations of genomic technologies or surveillance and response systems. These are summarised below:

- The information provided by genomic interventions can have long-term implications that are not observed in the short-term; therefore studies that focus on the short-term costs and consequences of genomic interventions may misestimate cumulative costs and effects over longer timeframes; [28]
- New features of surveillance and response systems may take time to become effective; oftentimes there is a gap between the time when data is collected and when it is used for research/policy purposes;
- For surveillance systems designed to detect outbreaks of new diseases (which are rare events), the reference period should be long enough to allow for the possibility of these events to occur;

[24] World Health Organisation, Evaluating the Costs and Benefits of National Surveillance and Response Systems: Methodologies and Options, 2005.
[25] Harris, Julie R., Barbara J. Marston, Nalinee Sangrujee, Desiree DuPlessis, and Benjamin Park, "Cost-Effectiveness Analysis of Diagnostic Options for Pneumocystis Pneumonia (PCP)", PLoS ONE, Vol. 6, No. 8, 2011.
[26] Scharff, Robert L, John Besser, Donald J Sharp, Timothy F Jones, Peter Gerner-smidt Dms, and Craig W Hedberg, "An Economic Evaluation of PulseNet", American Journal of Preventive Medicine, 2015.
[27] See also: 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.
[28] Buchanan, James, Sarah Wordsworth, and Anna Schuh, "Issues Surrounding the Health Economic Evaluation of Genomic Technologies", Pharmacogenomics, Vol. 14, No. 15, 2013, pp. 1833–47.

- The reference period should also be long enough for estimates of costs and benefits to be independent of epidemic-prone diseases with multi-year cycles and other characteristics particular to the reference period.[29]

As a result, the WHO Guide suggests that generalised cost-effectiveness analysis (GCEA) should evaluate interventions over a period of 10 years at full implementation, although the time horizon for the analysis should include all health effects that continue to occur beyond the reference period. While the feasibility of long reference periods depends also on data availability, this is a less relevant obstacle for hypothetical and modelling studies. When estimating the costs and effects over long time horizons, the choice of an appropriate discount rate for converting the values to their present worth is of key importance,[30] as this may significantly affect results.

A number of different timeframes were applied in the studies reviewed. A timeframe of five years was applied in the study on the costs and benefits of a subtype-specific surveillance system for identifying E.coli outbreaks. In the randomised controlled clinical trial conducted for the MedSeq project, the effects of WGS are estimated over a six-month period. The evaluation of PulseNet applies the longest timeframe of the studies reviewed, utilising data from a fifteen year period (between 1994 and 2009). For other studies, the timeframe is either unspecified or insignificant. For example, in the cost effectiveness analysis comparing various diagnostic options for PCP, the timeframe is considered to be largely irrelevant as long as the comparison is made at the same point in time for the different options.

3.2.3 Unit of effectiveness

The unit of effectiveness, also known as the measure of outcome, is a central component of the methodological framework used in conducting cost effectiveness analyses. It is a measure of a quantifiable outcome central to the objectives of the program/intervention.[31] The unit of effectiveness is used to calculate the denominator of the cost-effectiveness ratio, which in turn allows making comparisons between various interventions.

In health economics, units of effectiveness relate to improvements in health or in the quality of life. The most commonly used units in the area of human health include metrics such as disability-adjusted life years (DALYs) and quality-adjusted life years (QALYs).[32] Both QALYs and DALYs capture not only the impact of diseases on length of life but also multiple dimensions indicating health related quality of life. While QALYs are more popular when evaluating clinical interventions, DALYs are more frequently used for evaluating public health interventions.[33]

[29] World Health Organisation, Evaluating the Costs and Benefits of National Surveillance and Response Systems: Methodologies and Options, 2005.
[30] See also: Buchanan, James, Sarah Wordsworth, and Anna Schuh, "Issues Surrounding the Health Economic Evaluation of Genomic Technologies", Pharmacogenomics, Vol. 14, No. 15, 2013, pp. 1833–47.
[31] Cellini, Stephanie Riegg, and James Edwin Kee, "Cost-Effectiveness and Cost-Benefit Analysis", Handbook of Practical Program Evaluation, 2010, pp. 493–530.
[32] 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. p 50.
[33] Gold, Marthe R, David Stevenson, and Dennis G Fryback, "HALYS and QALYS and DALYS, Oh My: Similarities and Differences in Summary Measures of Population Health.", Annual Review of Public Health, Vol. 23, 2002, pp. 115–34. http://www.ncbi.nlm.nih.gov/pubmed/11910057.

As noted by Cellini and Kee (2010), while it is typical for a cost-effectiveness analysis to focus on a single primary outcome, one may also compute cost-effectiveness ratios for a number of other outcomes of interest.[34] Moreover, there is an ongoing debate about the appropriateness of using the narrow perspective (i.e. cost effectiveness) for evaluations related to genomics, with some literature suggesting that a broader perspective which takes into account also non-health outcomes may be more relevant than the use of QALYs.[35]

Among the cost-effectiveness analyses reviewed, several different units of effectiveness were selected. The assessment of costs and cost-effectiveness of genomic sequencing conducted alongside the MedSeq project used Quality Adjusted Life Years (QALYs) as the measure of outcome. In the economic evaluation of PulseNet, the effectiveness of the system is measured as a reduction of reported illnesses due to improved information, enhanced industry accountability, and more rapid recalls. Finally, in the cost-effectiveness analysis of diagnostic options for *Pneumocystis pneumonia*, the unit of effectiveness used was the number of life-years gained, although the options were also ranked with respect to the proportion of PCP patients successfully treated. The results of the literature review discussed above demonstrate that while QALY is considered to be the standard unit of effectiveness in health economics, in practice the measures of outcome used vary from study to study, reflecting the objectives of the intervention scrutinised and the effects captured.[36]

3.2.4 Baseline

Another key component of the methodological framework is the baseline – also known as the counterfactual scenario or the comparator – against which an intervention is measured. By comparing the proposed intervention to an alternative scenario, the difference that the intervention makes to a given outcome can be measured.[37] To fully capture the effect of the policy or programme, the outcomes/effects must be measured for both the intervention as well as the counterfactual.[38] The WHO guidance for evaluation of the costs and benefits of national surveillance and response systems lists three alternative counterfactual scenarios that may be used as a baseline:

- The *current system*;
- The *current system without the particular features under evaluation*; and
- The *null system*, i.e. the counterfactual situation in which no surveillance and response system is in place.

[34] Cellini, Stephanie Riegg, and James Edwin Kee, "Cost-Effectiveness and Cost-Benefit Analysis", Handbook of Practical Program Evaluation, 2010, pp. 493–530.
[35] Buchanan, James, Sarah Wordsworth, and Anna Schuh, "Issues Surrounding the Health Economic Evaluation of Genomic Technologies", Pharmacogenomics, Vol. 14, No. 15, 2013, pp. 1833–47. http://www.futuremedicine.com/doi/abs/10.2217/pgs.13.183\nhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3909837&tool=pmcentrez&rendertype=abstract.
[36] Babo Martins, Sara, and Jonathan Rushton, "Cost-Effectiveness Analysis: Adding Value to Assessment of Animal Health, Welfare and Production", Revue Scientifique Et Technique-Office International Des Epizooties, Vol. 33, No. 2201, 2014, pp. 1–18.
[37] World Health Organisation, Evaluating the Costs and Benefits of National Surveillance and Response Systems: Methodologies and Options, 2005.
[38] 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. pp 18-19.

In the first scenario, the intention is to evaluate ex-ante the new features of a particular system by using the current situation as a baseline for comparison. In the second scenario, the new features of the system are evaluated by comparing them (ex-post) with how the system functioned prior to their introduction. In the third scenario, the entire new system is evaluated against a counterfactual situation in which it is absent altogether. While this counterfactual allows the system to be evaluated as a whole, it is often difficult to estimate and quantify in detail what would have happened in its absence.[39]

Cellini and Kee (2010) define the baseline for the analyses as the status quo, or "the state of the world in the absence of the program or policy." According to this perspective, costs and benefits should only be considered in a cost-effectiveness or cost-benefit analysis if they would not have occurred in the absence of the intervention. In other words, when comparing the intervention to the status quo, only the marginal (or incremental) costs and benefits should be included in the assessment.[40] This approach is often taken in cost-benefit analyses and corresponds to recent guidance provided by the European Commission for cost-benefit analyses in a regulatory context.[41]

The different baseline scenarios used in the literature reviewed reflect the diversity of the research methods applied across the studies. In the PulseNet study, the evaluators make use of the staggered adoption of the program across different states (also known as a *phase-in* design[42]) to assess its effectiveness. Using this natural experiment, they are able to compare states in which PulseNet (the intervention) has been put in place with those states in which it has not yet been adopted. Although they do not benefit from the natural experiment as in the case of PulseNet, two of other studies use the status quo, or absence of a given system or technology, as a baseline scenario.[43]

In a cost-effectiveness analysis of options for diagnosing Pneumocystis Pneumonia (PCP), no single baseline is defined. Instead, a number of diagnostic options are compared and ranked against each other based on selected units of effectiveness (see section on units of effectiveness above). Finally, the MedSeq Project, an ongoing randomized controlled clinical trial, makes use of two groups of patients to assess the cost-effectiveness of genomic sequencing in cardiology and primary care settings. Among a group of patients, half is randomly assigned to receive a family history assessment using WGS; the other half receives a family history assessment without WGS. In the project, the cost-effectiveness is assessed using incremental cost-effectiveness ratios (ICERs) by dividing the differences in costs by the differences in QALYs before and after the treatment when

[39] World Health Organisation, Evaluating the Costs and Benefits of National Surveillance and Response Systems: Methodologies and Options, 2005.
[40] Cellini, Stephanie Riegg, and James Edwin Kee, "Cost-Effectiveness and Cost-Benefit Analysis", Handbook of Practical Program Evaluation, 2010, pp. 493–530.
[41] "... [O]nly incremental costs and benefits need to be estimated. When standard cost-benefit analysis is the methodology of choice, [it] is the sign of the net change in costs and benefits that matters for policy decision, not the aggregate (or cumulative) level of regulatory costs and benefits.", qoted from European Commission (2015), Better Regulation "Toolbox" complements the Better Regulation Guideline presented in in SWD(2015) 111, p 348.
[42] See Introduction to Evaluations, Abdul Latif Jameel Poverty Action Lab at https://www.povertyactionlab.org/research-resources/introduction-evaluations.
[43] Elbasha, Elamin H., Thomas D. Fitzsimmons, and Martin I. Meltzer, "Costs and Benefits of a Subtype-Specific Surveillance System for Identifying Escherichia Coli O157:H7 Outbreaks", Emerging Infectious Diseases, Vol. 6, No. 3, 2000, pp. 293–297.

comparing both randomized groups. Therefore, the baseline in the MedSeq project is the pre-treatment situation of the patients (in terms of QALYs).

3.2.5 Cost types

By definition, cost-benefit and cost-effectiveness analyses seek to collect, quantify and assess data about the costs of an intervention. Levin (1995) defines costs as the value of the resources that are given up by society to implement the intervention, while Cellini and Kee (2010) consider the overall costs of a program as any negative impacts of that program, added to actual budgetary outlays.

The WHO Guide to Cost-Effectiveness Analysis differentiates between the costs of providing health interventions and the costs of accessing health interventions. Broadly, the categories of costs involved in *providing* health interventions are the following:

- Labour;
- Capital (such as building space and equipment);
- Consumables (such as medical supplies and medication); and
- Overhead costs (such as electricity, water and maintenance).

The costs of *accessing* healthcare interventions accrue to patients and their families and consist of the resources used and time costs involved in seeking or obtaining the intervention.

Buchanan et al. (2013) do not distinguish between the provision of and access to the healthcare intervention, instead proposing *cost categories that correspond to the steps involved* in medical testing using whole genome sequencing. The study presents a list of the following cost categories that could be included in economic evaluations of genomic technologies:

- Costs related to patient recruitment;
- Costs related to sample collection;
- Costs related to sample testing;
- Costs related to data analysis, including informatics solutions, data libraries, data storage and quality assessment;
- Costs related to the communication of test results;
- Costs related to the actions taken based on the test results, including treatment, follow-up testing and monitoring;
- Training and infrastructure costs; and
- Indirect costs accruing to patients, such as productivity gains or losses.[44]

[44] 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.

On the other hand, Babo Martins and Rushton (2014) assert that methodological guidelines clearly establish the cost types that should be included in the assessment of human health interventions:

- Tests;
- Drugs;
- Personnel;
- Rent;
- Costs of patients' time;
- Costs associated with caregivers' time; and
- Direct non-health care costs.

These three examples illustrate the range of approaches for cost categorisation used in relevant analyses (for a more detailed overview, see Table 3 below). The difference in the choice of which costs and benefits to include in the analysis depends to some extent on the perspective taken. From the point of view of the healthcare provider/decision-maker, only the direct costs (and benefits) of the intervention are considered. For example, Scharff et al. (2015) focus on program costs and leave out the indirect costs of PulseNet, such as the costs borne by other government entities, administrative costs of litigation, costs associated with recalls, and costs of implementing and managing process changes. Other economic (societal) costs, such as the welfare losses from premature death and reduced quality of life due to illness are also excluded from the analysis.[45] Applying an even more narrow approach, Harris et al. (2011) consider only costs related to materials and personnel time dedicated to the diagnostic options assessed, excluding capital costs. In contrast, in a societal perspective, the wider social, health and economic costs (and benefits) are also taken into account regardless of who pays or benefits from the effects.[46] For example, Rushton and Upton (2006) adopt a wider approach and include costs related to control and eradication measures as well as socio-economic impacts of disease oubreak in their analysis.

Another factor that contributes to differences in categorisation is the variety of terms used for describing largely similar cost types. Cost types in a majority of the studies reviewed can be grouped into the four main cost categories proposed by the WHO Guide: labour, capital, consumables and overhead costs. First, all of the relevant studies systematically monetised staff time, focusing on various categories of personnel including laboratory scientists, healthcare workers, clinicians and nurses. Second, most of the analyses accounted for capital costs representing investments at a single point in time, including those related to the construction of the building/laboratory and the purchase of equipment. Third, some of the studies calculated the cost of consumables, a category encompassing materials that are used up as a good or service is provided. These are

http://www.futuremedicine.com/doi/abs/10.2217/pgs.13.183\nhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3909837&tool=pmcentrez&rendertype=abstract.

[45] Scharff, Robert L, John Besser, Donald J Sharp, Timothy F Jones, Peter Gerner-smidt Dms, and Craig W Hedberg, "An Economic Evaluation of PulseNet", American Journal of Preventive Medicine, 2015.

[46] Babo Martins, Sara, and Jonathan Rushton, "Cost-Effectiveness Analysis: Adding Value to Assessment of Animal Health, Welfare and Production", Revue Scientifique et Technique-Office International Des Epizooties, Vol. 33, No. 2201, 2014, pp. 1–18.

e.g. medical supplies or materials required for specimen collection and diagnostic test procedures. Finally, overhead costs are also considered in several of the documents reviewed.

In line with these results, we differentiate in the following overview five main cost categories: Staff costs, costs of consumables,[47] overhead costs, capital costs and other costs. While the definitions of costs types in the different studies largely overlap for the first four categories, the category 'other costs' is very diverse and depends on the subject area, perspective and level of detail used.

[47] We have included shipping costs into the 'consumables' category, as they can be a significant variable cost, often closely related to the number of laboratory test performed (as is the case with e.g. laboratory consumables such as chemicals, petri dishes, tubes and plates etc.)

Table 3. Overview of cost categorisation used in previous analyses and recommended in guidance documents

SOURCE	MAIN COST CATEGORIES				
	Staff costs	**Costs of consumables**	**Overhead costs**	**Capital costs**	**Other costs**
Harris et al. (2011), Cost effectiveness Analysis of Diagnostic Options for *Pneumocystis* Pneumonia (PCP)	Personnel time (laboratory workers, health care workers and clinicians)	Costs of required materials (for specimen collection and diagnostic test procedures)			
Scharff et al. (2015), An Economic Evaluation of Pulsenet	Cost of labour (technicians, technologists, epidemiologists)	Costs of shipping samples to the public health lab, cost of reagents used in the PFGE process		Annual amortized laboratory set up costs (construction of laboratory space, equipment costs)	
Christensen et al. (2015), Assessing the costs and cost-effectiveness of genomic sequencing	Staff time (nurse, medical scientist, laboratory director)				Costs of genomic sequencing Costs of confirming variants via Sanger sequencing Costs of variant interpretation Costs of medical care Patient out-of-pocket expenses (time off work, transport)
Elbasha et al. (2000), Costs and benefits of a subtype-specific surveillance system for identifying E.coli O157:H7 outbreaks	Labour costs (laboratory scientist)			Costs of sub-typing equipment	Costs of analysing isolates Medical costs Outbreak investigation costs

SOURCE	MAIN COST CATEGORIES				
	Staff costs	Costs of consumables	Overhead costs	Capital costs	Other costs
Hulme, C. (2006), Using Cost Effectiveness Analysis	Staff time	Consumables	Overhead costs, e.g. administrative support, computers, and database packages	Capital costs that represent investments at a single point in time	Out-of-pocket expenses
Cellini and Kee (2010), Cost-effectiveness and cost-benefit analysis	Personnel	Materials	Administration	Facilities, equipment	
Edejer et al. (2003), WHO Guide to Cost-Effectiveness Analysis	Labour	Consumables e.g. medical supplies and medication	Overhead costs such as electricity, water and maintenance	Capital such as building space and equipment	Costs of accessing health interventions
World Health Organisation (2005), Evaluating the Costs and Benefits of National Surveillance and Response Systems	Recurrent costs (personnel costs, supplies, operation and maintenance of capital costs, recurrent training costs, costs of surveillance, outbreak investigation and response)			Capital costs (buildings, vehicles, equipment, training)	

Source: Civic Consulting, based on the literature listed.

3.2.6 Benefit types

While ultimately the cost-effectiveness ratio(s) of the interventions/alternatives considered are based on one or several key measures of outcome (see section on unit of effectiveness above), the benefits of the intervention are likely to be more far-reaching and numerous in practice. The WHO Guide on evaluating the costs and benefits of national surveillance and response systems lists the following types of benefits that may arise as a result of such systems:

- Benefits derived from averting cases;
- Benefits derived from averting deaths;
- Benefits of fewer social and economic disruptions (including disruptions to trade and tourism) when epidemics are averted; and
- Social and psychological benefits stemming from less apprehension and greater peace of mind when large outbreaks of serious infectious diseases are rare or non-existent.[48]

Cellini and Kee (2010) suggest to identify and classify benefits (and costs) according to whether they are real benefits or merely transfers; direct or indirect; tangible or intangible; and financial or social. Based on these categories, the authors discuss the following examples of benefit types:

- Nonmarket goods and services such as social benefits that cannot be readily estimated using market prices and budgets;
- Cost avoidance or cost savings;
- Time saved; and
- Increased productivity.

Whether other benefits – e.g. changes in the value of property or in taxes – are taken into account, depends on the perspective and scope of the analysis. From a societal point of view, an increase/decrease in taxes is a transfer of wealth; from a narrower point of view, it may be considered to be a cost or a benefit.[49] Once again, the range of benefits considered depends on the perspective taken as well as the type of analysis undertaken (i.e. cost-effectiveness or cost-benefit). The reviewed cost-benefit analyses tended to quantify and monetise certain key benefits, describing additional benefits qualitatively.

In the analysis of a subtype-specific surveillance system for identifying E.coli outbreaks, the benefits considered are all expressed as cost savings due to cases averted, including medical costs, productivity losses and lost lifetime earnings.[50] In Rushton and Upton (2006), the authors describe benefits resulting from investment in preventing and preparing for biological emergencies and disasters. These include the faster detection of

[48] World Health Organisation, Evaluating the Costs and Benefits of National Surveillance and Response Systems: Methodologies and Options, 2005.
[49] Cellini, Stephanie Riegg, and James Edwin Kee, "Cost-Effectiveness and Cost-Benefit Analysis", Handbook of Practical Program Evaluation, 2010, pp. 493–530.
[50] Elbasha, Elamin H., Thomas D. Fitzsimmons, and Martin I. Meltzer, "Costs and Benefits of a Subtype-Specific Surveillance System for Identifying Escherichia Coli O157:H7 Outbreaks", Emerging Infectious Diseases, Vol. 6, No. 3, 2000, pp. 293–297.

transboundary diseases, reduced impact of biological disaster, reduced likelihood of outbreaks, and the quick control and eradication of diseases with minimal costs. Likewise, the economic evaluation of PulseNet identifies the following benefits of the system: improved information, enhanced industry accountability, more rapid recalls, cost savings due to averted medical costs and productivity losses, improvements in outbreak detection, and reduction in foodborne illness.

In the cost-effectiveness analyses reviewed the benefits considered were roughly equivalent to the unit of effectiveness selected, although in some cases additional benefits were listed. For instance, in Harris et al. (2011), the benefits of the diagnostic options are correct diagnosis, successful treatment and life years gained. In line with these benefits, diagnostic options were ranked with respect to the proportion of PCP patients successfully treated and the total diagnostic and treatment cost per life-year gained. In the evaluation conducted alongside the MedSeq project, the benefits of genomic sequencing identified related to the number of pathogenic and likely pathogenic monogenic findings for participants, health related quality of life, early identification and prevention of potential threats. In this case, the selected unit of effectiveness was QALYs (see section on unit of effectiveness above).

An approach to estimate the wider benefits of surveillance and detection systems from a more macro perspective focuses on the value of information that surveillance and detection systems provide. This information then may lead to the other outcomes, if e.g. better information leads to better diagnosis and better treatment. A framework to quantify the value of more and better information is the so-called value of information (VOI) framework. The VOI framework is developed within statistical decision theory and has been applied in healthcare and other fields. The key idea behind VOI is that the choice between several policy options is distinct from the choice of whether or not additional information should be collected by financing research in order to inform the choice between these policy options. The value of information is determined by assessing to what extent more information can result in better decisions that yield a higher expected return (e.g. through averted cases, reduced outbreaks and related gains in productivity, quality of life, etc.) compared to the situation in which is there is less information. Information is valuable because it reduces the expected costs of uncertainty surrounding various policy options. In addition, surveillance and detection systems like COMPARE may provide a sense of safety to populations, or a “greater peace of mind” as noted in the WHO Guide cited above. Although it is a difficult element to value, it is a relevant benefit from the perspective of policy makers as well as from a welfare economic perspective. The feeling of unsafety in countries facing a potential outbreak can be disruptive and unsettling. It is well known that the value of safety or avoiding losses can be high, but methods to determine these values are currently lacking (therefore, this aspect has been included in the methodological approach for this Work Package).

3.2.7 Methods used for calculating cost-benefit or cost-effectiveness ratios

The articles reviewed adopted different methods for calculating cost-benefit or cost-effectiveness ratios. In the cost-benefit analysis of a subtype-specific surveillance system for E.coli outbreaks, two threshold numbers were calculated, indicating the number of cases that had to be averted for the costs to be equal to the benefits of the system. The first number was calculated by assuming the system averts a constant number of cases per year, while the second threshold was calculated under the assumption that the system averts only a given number of cases in the first year and no cases in subsequent years. The average cost of an E. coli infection was estimated by using an infection outcome tree. The assessment was then conducted based on the idea that if the estimated

threshold is below a reasonable number (calculated based on literature and expert opinion), the system is cost beneficial.

The economic evaluation of PulseNet developed different types of models to estimate the effects of the network. First, a recall model was used to estimate the number of averted cases due to detection and recall, based on data on the rate of illness and amount of product recovered. Next, a process change (econometric) model tested the effect of PulseNet's implementation and testing intensity on the number of reported illnesses. Along with data on the expected costs per illness, the results from these models allowed the researchers to calculate the economic impacts of PulseNet and to contrast these with the program costs borne by public healthcare agencies.

Another cost-effectiveness analysis[51] used a model flow to calculate the proportions of ill patients treated successfully and unsuccessfully as well as those treated unnecessarily per diagnostic option and given prevalence rate. Assuming that patients successfully treated gain one life-year, the incremental cost-effectiveness ratios of the most effective options were calculated by adding up the total diagnostic costs and the total treatment costs, and dividing these by the number of ill patients successfully treated. Finally, in the ongoing MedSeq project, data from the randomised control trial is used to estimate the QALYs gained from genomic sequencing. The cost-effectiveness is then calculated by dividing the differences in costs by the differences in QALYs when comparing both randomized groups.

[51] Harris, Julie R., Barbara J. Marston, Nalinee Sangrujee, Desiree DuPlessis, and Benjamin Park, "Cost-Effectiveness Analysis of Diagnostic Options for Pneumocystis Pneumonia (PCP)", PLoS ONE, Vol. 6, No. 8, 2011.

5. Next steps

This section discusses the next steps to be carried out as part of Work Package 14.

5.1 Finalising the methodological framework

Based on the work presented in this deliverable, the methodological framework for assessing the cost-effectiveness of COMPARE will be finalised, including the final definition of the perspective of the analysis, the timeframe, the unit(s) of effectiveness, the baseline, the cost and benefits types and the method(s) used for calculating cost-benefit or cost-effectiveness ratios. We will consider whether one methodological framework will suit the different case studies foreseen, or whether the frameworks will differ depending on their scope. For example, while in some cases a timeframe of several years may be applied, in other cases such as for a specific disease outbreak the duration of the outbreak could be more appropriate. We will also decide whether case studies are retrospective or prospective in nature, and conclude whether or not scenario analysis and/or modelling techniques could be applied.

5.2 Selection of case studies

The case studies foreseen will be selected according to a set of criteria, such as the extent to which they are (potentially) within the scope of the COMPARE project, the coverage of relevant sectors (human health, food safety, animal health and wildlife), and the pathogen type (e.g. bacteria or virus). At this stage, the following potential case studies are under consideration:

- Outbreak of the Ebola virus in Western Africa (beginning in 2014);
- Outbreak of highly pathogenic avian influenza H5N8 virus in Asia and Europe (2014);
- Outbreak of Shiga toxin-producing E. coli in Germany (2011);
- Antimicrobial resistance; and
- Hospital infections and their transmission from patient to patient.

For the last two listed potential case studies, specific incidents, situations or countries would be selected. The Ebola and H5N8 virus outbreaks have been studied in-depth by various participants of the COMPARE project, which could increase the complementarity and cooperation between Work Packages. Finally, Civic Consulting conducted a detailed examination of the 2011 E.coli outbreak in Germany; the data collected through a large number of interviews and review of literature could serve as a starting point for the analysis of this food safety incident. To the extent that reviewed outbreaks have taken place before the COMPARE system was operational, a possible research aspect would be the extent to which NGS technologies were applied and their effects, and which additional effects a COMPARE like system could have had in this situation under certain assumptions.

5.3 Next deliverables

The next deliverables to be produced by Work Package 14 are as follows:

- Deliverable 14.2. State-of-the-art methodologies for the measurement and valuation of the elements specified in the framework. This will include a section on the system itself and on the wider framework (to be submitted in Month 30 of the project);
- Deliverable 14.3. A scientific paper describing the methodology and results of estimating the value of safety, with the results from several European countries (to be submitted in Month 45 of the project);
- Deliverable 14.4. Report on the (potential) cost-effectiveness of COMPARE, based on the case studies (scenario/pilot/retrospective studies). Each case study presented will include a section on elements related to the system and on the wider framework (to be submitted in Month 54 of the project);
- Deliverable 14.5. A report on the assessment of options for refining selected elements of COMPARE in view of improving the overall cost-effectiveness of the system, with recommendations (to be submitted in Month 60 of the project).

Annex: Literature reviewed for the first deliverable

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Adkin, Amie, *Work Package 1 : Risk Assessment and Risk-Based Strategies for Sample and Data Collection*, 2016.

Agra CEAS Consulting, *Prevention and Control of Animal Diseases Worldwide: Economic Analysis – Prevention versus Outbreak Costs*, 2007.

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Babo Martins, Sara, and Jonathan Rushton, "Cost-Effectiveness Analysis: Adding Value to Assessment of Animal Health, Welfare and Production", *Revue Scientifique Et Technique-Office International Des Epizooties*, Vol. 33, No. 2201, 2014, pp. 1–18.

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Bexton, Steve, Lidewij C Wiersma, Sarah Getu, Peter R van Run, Georges M G M Verjans, Debby Schipper, Claudia M E Schapendonk, et al., "Detection of Circovirus in Foxes with Meningoencephalitis, United Kingdom, 2009-2013.", *Emerging Infectious Diseases*, Vol. 21, No. 7, 2015, pp. 1205–8. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4480402&tool=pmcentrez&rendertype=abstract.

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Buchanan, James, Sarah Wordsworth, and Anna Schuh, "Issues Surrounding the Health Economic Evaluation of Genomic Technologies", *Pharmacogenomics*, Vol. 14, No. 15, 2013, pp. 1833–47.

http://www.futuremedicine.com/doi/abs/10.2217/pgs.13.183\nhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3909837&tool=pmcentrez&rendertype=abstract.

Canadian Agency for Drugs and Technologies in Health, *Next Generation DNA Sequencing: A Review of the Cost Effectiveness and Guidelines*, 2014.

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