

UPDATE, Spring 2018

Version 01, August 2018

COMPARE Quick Facts



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Project period 01 December 2014 – 30 November 2019

Funding €20 million (approximately)

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This project has received funding from the *European Union's Horizon 2020 research and innovation programme* under grant agreement No 643476.



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Note from Coordinators

At the time that information was gathered for this Update, COMPARE was finishing its General Meeting 2018. Members of the Consortium had gathered at the Technical University of Denmark to present the latest developments in the project, discuss the challenges they are facing, and identify the steps forward for the coming year.

For the past three (+) years, COMPARE has been developing an enabling system and tools for collaborative preparedness and outbreak research. We have developed a platform that

- Encourages collaborations between the users of next generation sequencing and bio-informaticians
- Shares validated workflows for disease preparedness research and outbreak research
- Is sector-, domain- and pathogen-independent (One Health)
- Is flexible, scalable and open-source
- Shares data and information
- Is built upon a sustainable infrastructure

We have made progress to establish an analytical framework and data exchange platform that will allow real-time analysis and interpretation of sequence-based pathogen data in combination with metadata.

- Generic models for sampling the hot-spot surveillance published
- Searchable inventories of protocols available
- COMPARE standard operating procedures and laboratory operating procedures (SOPs and LOPs) developed and available (summer 2018)
- Working datahubs with automated analysis
- Active data sharing and joint research across sectors, domains and pathogens
- Active machine-learning group on antimicrobial resistance
- Pilot studies in different fields
- Insight into barriers and possible solutions (we are a resource for others)
- Developing the cost and the value of prevention
- Published results, some in high-impact journals
- Invitations for collaboration based on these published results and presentations made at conferences
- Links to other H2020 initiatives (EJP One Health, ZIKALLIANCE, etc.)
- An involved and dynamic next-generation researcher community (Young COMPARE)

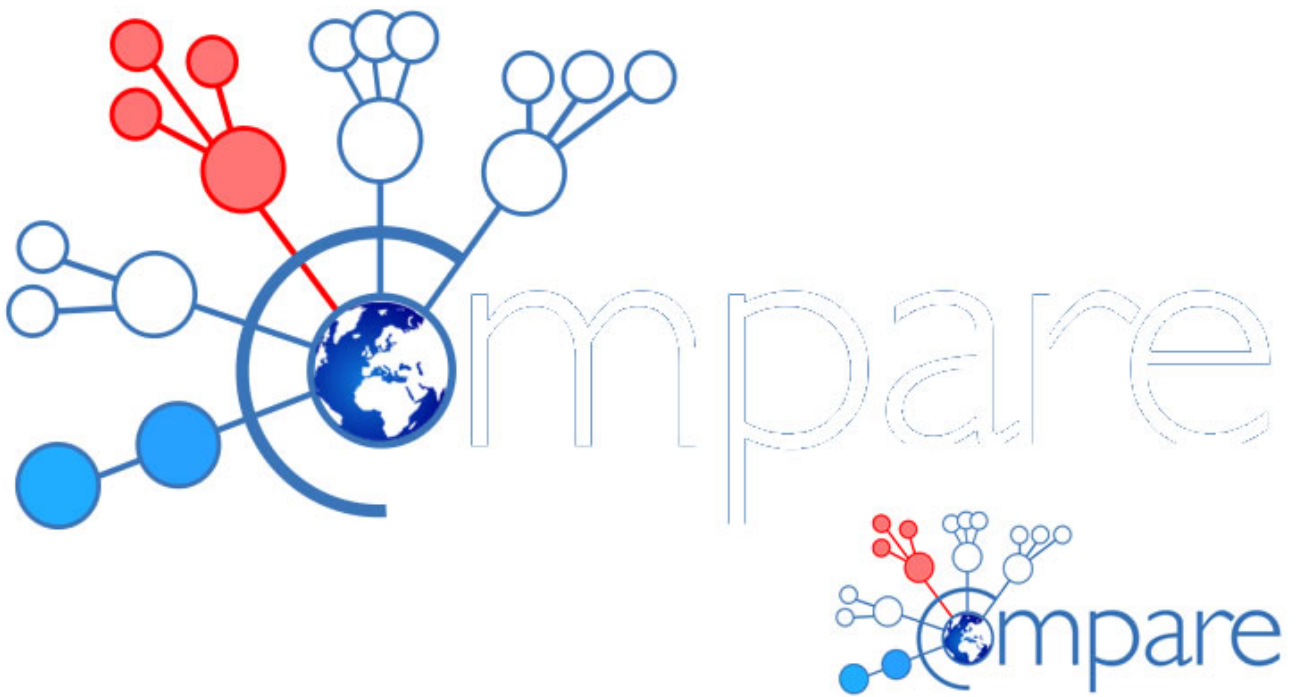
We stated in the Update Fall 2017 that we were looking to move our work and results beyond the Consortium and testing the waters beyond the comforts of our partners. That we should share the results of our pilot projects, expand the use of a standard SOP, link pipelines and workflows, and invite an outside stakeholder to develop and participate in a pilot.

Well, we have worked with the ECDC to develop a pilot with Member States, and during the summer 2018, the COMPARE-ECDC-EFSA Pilot on Salmonella will be launched. Besides testing the datahubs and workflows, we will also gain insight as to the how Member States will view security issues, what the individual Member State barriers may be and what other tools users want to have available.

We are excited at this opportunity to share and learn. We invite you to read further, and explore the work being done in the various pilots and under the different themes.



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



WP1 – Risk assessment and risk-based strategies for sample and data collection

In WP 1, a generic framework for the risk assessment is being developed.

Work is progressing well across WP 1, and in the last period there has been significant progress with developing those areas associated with the wildlife health theme and wildlife acting as reservoirs or vectors of disease. Wildlife is a particularly difficult population to accurately include in risk assessments and in designing appropriate risk-based surveillance and sampling. This is due to the nature of free-moving populations and lack of information regarding the distribution, population size and health status when compared to public health and livestock datasets. Within the generic risk assessment framework, progress has been made to model movement of wild boar based on species distribution maps and habitat suitability maps. An assessment of the spread of infection across Europe by such wildlife populations is nearly complete using African swine fever as the case study.

Estimated number of infected wild boar entering cell: Germany

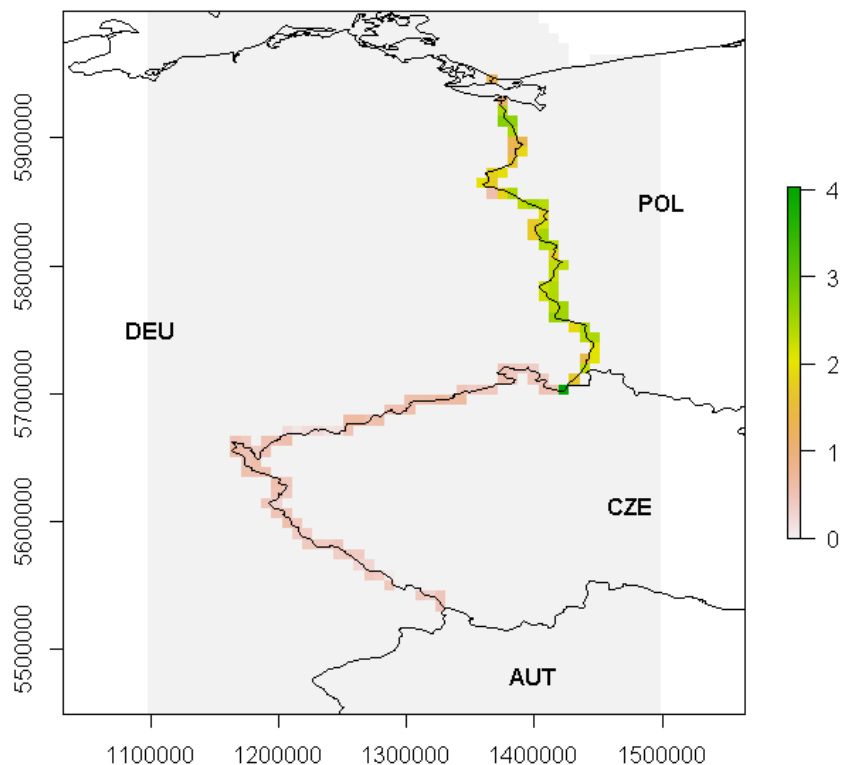


Figure 1: Estimated number of ASF-infected wild boar moving from other countries in to Germany, per year (preliminary results).

Each 10km² cell within greyed zone of Germany is coloured according to how many infected wild boar will reach that cell over one year, assuming that boar will perform both short-range movement within a cell and long-range

movement up to 50km. Since only Poland and Czech Republic have had cases of ASF, only cells along the border with these countries have non-zero numbers of infected wild boar crossing in to Germany. Countries are indicated by their ISO3 code.

To help in the design of risk-based surveillance and sampling protocols, the next version of the One Health combined flowchart has also been completed to provide guidance to clinicians, wildlife experts and other stakeholders. The flowchart can be used for outbreaks of unknown disease and increased risk of such outbreaks not covered by existing surveillance. Most epidemiological wildlife questions can be divided into two scenarios: (1) a morbidity or mortality event in wildlife occurs for which we would like to investigate the cause, and (2) wildlife are identified as a potential hazard associated with observed or predicted disease emergence in humans and/ or livestock. For each of these scenarios we aim to offer steps and guidance using the flowchart. Two requests to pilot the wildlife flowchart have been requested, one regarding neurological disease in foxes, and another about neurological disease in wolves.

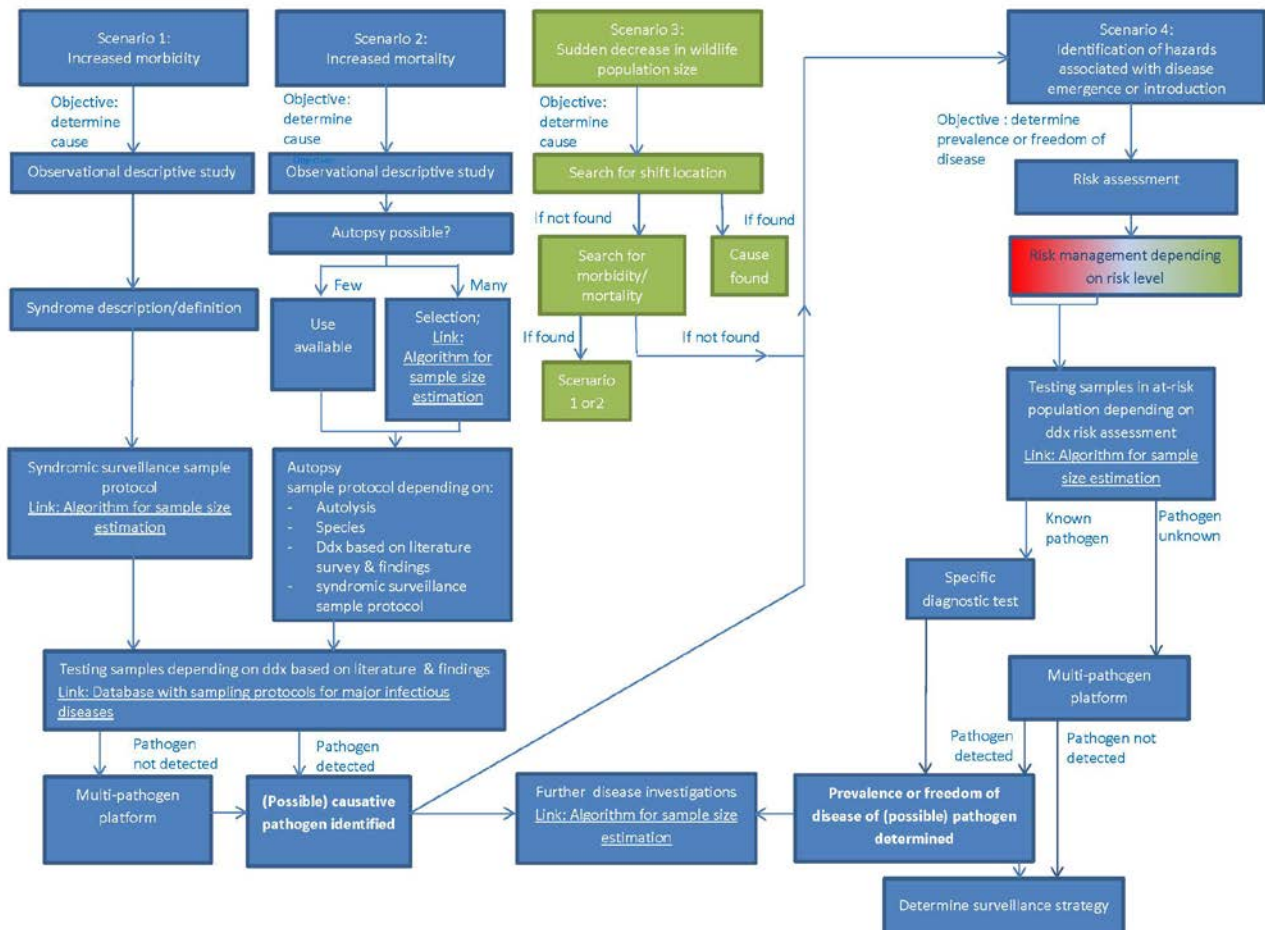


Figure 2: One Health sampling flowchart protocol for wildlife, livestock and public health.

WP2 – Harmonised standards for sample processing and sequencing

Workpackage 2 is addressing the harmonization of standards for sample handling as a basis for other tasks in the COMPARE project.

Many protocols have been collected for the sample processing and sequencing workflow (Deliverables D2.2 and D2.3) within WP 2. During reporting period, the "Report on sequencing workflow" was compiled and provided as D2.3 (due M36) as a continuation of the "Report on standard protocol sample processing" (D2.2, due M24). The corresponding LOPs are available on the closed COMPARE Share Site and will be made publicly available on the COMPARE website as COMPARE branded LOPs or approved branded SOPs during the next reporting period. An announcement as a journal article is planned.

WP2 is now focusing on the validation of sample processing workflows using ring trials (Task 7). The GMI Virus Proficiency Test with a dry and a wet lab part organized by RKI was finished in 2017, and was reported as Deliverable D2.5 during the reporting period. The next ring trial, on food metagenomics, was organized and prepared by partners UNIBO, DTU, FLI and ISS and will be conducted during the coming reporting period (D2.6, due M48).



Figure 3. Face-to-face Meeting of WP2 partners at the RKI in November 2017 to discuss the outcome of the already performed Virus PT and to plan the next metagenomics ring trial on food, for example.

Besides, many tasks were ongoing during the reporting period such as investigation of storage on the sequencing outcome (Task 1), matrix and pathogen tests to provide a largely matrix- and pathogen-independent sequencing workflow (Tasks 2 and 3), and bioinformatic analyses using SLIM and RIEMS (Task 4). With respect to the experience of COMPARE partners, esp. WP2, it is highly recommended to use blank samples with the preferred sample processing workflow to be aware of the contaminations that might be occur with the respective workflows. Furthermore, metagenomics sequence data should be interpreted

with caution and a confirmation of found (new) pathogens by PCR is highly recommended to avoid wrong interpretations.

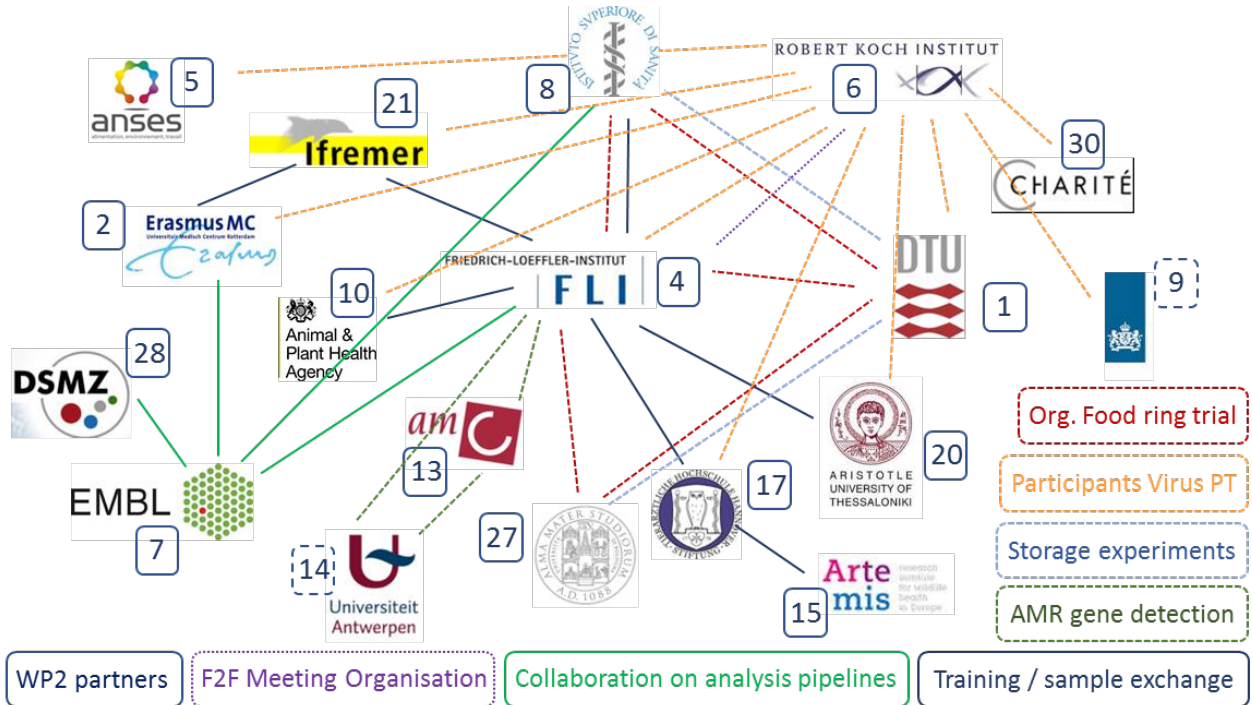


Figure 4. Overview of current and past collaborations among WP2 partners (all partner contributions to the last and the current Snapshot Reports are considered).

WP3/6 – Frontline diagnostics

In Workpackage 3/6 the objectives are to develop an analytical workflow for the use of single isolate and metagenomic NGS in human and veterinary clinical microbiology and to assess the feasibility of NGS/WGS/WCS for clinical diagnostic use and hospital epidemiology.

The WP3/6 has organized itself into ‘Work Bundles’, and the current achievements of the Work Bundles are described below.

During September 2017 to February 2018, two workflows for integration of NGS in clinical laboratory diagnostics have been developed. One to utilize NGS in clinical settings to study the epidemiology and population biology of bacterial clones that will identify antibiotic resistance genes (BacPipe) (**work bundle 1**) and one to detect viruses from metagenomics samples (RIEMS) (**work bundle 4**). These workflows will now be built into the COMPARE platform and evaluated further in WP3/6 and other WP members (WP4/7).

During this period, ResFinder and PointFinder databases have been expanded, and a code to output antibiograms based on AMR genes in WGS data has been developed (ResFinder 4.0). Also, datasets were collected to validate ResFinder 4.0 including both already available datasets and a new dataset representing all clinical isolates collected country-wide in Denmark in one day. In particular, this last dataset will reveal to what extent ResFinder 4.0 is applicable to real-life clinical settings. This validation is ongoing and all data will be shared with the respective providers using the COMPARE platform.

Machine learning and Hidden Markov model approaches have been used to predict fluoroquinolones and colistin resistance, respectively, from WGS data. For this, extensive data collection was done and additional data collection is ongoing (**work bundle 2**).

Within the **work bundle 3** framework, we have developed an outbreak detection module in BacPipe that allows to trace outbreaks in hospitals utilizing core-genome and whole-genome based phylogeny. Also, the wgMLST and cgMLST allelic databases for *S. aureus* were created and validated (Bionumerics and BigSDB).



WP4/7 – Foodborne pathogen surveillance, outbreak detection and epidemiological analysis

Workpackages 4 and 7 are focused on developing and validating cross-sector and cross-pathogen methods for sequence-based analysis within surveillance, outbreak investigation, epidemiological analysis, and source attribution of foodborne pathogens.

The COMPARE project and European Centre for Disease Prevention and Control (ECDC) has initiated a pilot project where WP4/7 and WP9 are especially active. The project concerns the sharing of whole genome sequence data between European public health laboratories and the ECDC for the purpose of real-time data sharing and faster detection and response to multi-country foodborne outbreaks. The pilot will concern genome sequences of *Salmonella enterica* and nine member states will take part.

The benchmarking study in WP4 Task 2.2 aiming at exploring different approaches and models for source attribution based on *Salmonella Typhimurium* sequencing data is progressing according to plan. Raw sequence data of 1 isolates from four datasets from four countries (Denmark, Germany, Italy and UK) are now available in the Vivaldi data hub. Metadata will be sorted and shared on the COMPARE share site soon. The raw data will be analysed using different CGE tools (by DTU) and also distance matrices based on cgMLST will be created (by SSI). Different institutions started exploring source attribution models based on the complete Danish dataset. Methods explored until now are: Machine learning, network analysis and Bayesian modelling.

The cross WP virus group did a norovirus ring trial. Two Human norovirus (HuNV) positive feces samples were sent to several institutes. One sample contained a GII.4 HuNV with a Ct value of 20 and a GI with a Ct value of 17.1. The samples were sequenced by the RIVM, IFREMER and Erasmus MC using their own protocols and sequencing platforms, but the same methods were used to analyze all NGS data. All institutes were able to obtain full genomes and the consensus sequences were identical. For all methods and institutes, the GI sample resulted in more reads than the GII sample. IFREMER consistently obtained high percentages of HuNV reads compared with non-HuNV reads. IFREMER used a sample preparation protocol that contained a centrifuge and filtration step to remove the bacteria and debris and an enzymatic step to remove DNA/RNA prior to the lysis of viral particles, in combination with Illumina sequencing with random primers. The used protocols as well as a more elaborate report will be made available to all COMPARE members. As a next step, we will prepare a more complex ring trial with different matrices containing several viruses at low concentrations.

WP5/8 – Detection and response to (re-) emerging diseases

The focus for this Workpackage is on harnessing the potential added value of NGS for emerging disease detection and research. The unique opportunity from the H5N8 outbreaks pushed these Workpackages (and the Consortium) to evaluate the methods and abilities to share data, analyse data and work across disciplines.

In Compare, we advocate a One Health approach to pathogen investigations, with harmonization of sampling from wildlife, domestic animals, and humans, and optimization of these sampling protocols for the early diagnosis of new infectious diseases. For pathogen investigations of wildlife, we need to account for specific challenges, including identification of the wildlife species involved, knowledge on specific causes of morbidity and mortality in wildlife, knowledge of size, structure, and demography of wildlife populations, and practical aspects of accessing and preserving samples in the field. In WP1 and WP2, we established algorithms and protocols for selecting and storing samples, as well as NGS pipelines. As part of WP8, the responsible partners for Task 2 are now in discussion on suitable subjects to develop and pilot early detections of emerging pathogens from wildlife reservoirs through these established protocols for strategic sampling and metagenomic analysis. The suggested pathogens so far include Anaplasma, canine distemper virus, CCHFV, influenza virus, lyssavirus, Mycobacterium, and Usutu virus. There is ample experience with these pathogens from earlier WP5/WP8 studies, as can be seen from several manuscripts published. At the same time, the Global Consortium on H5 Viruses continues to collect and sequence whole influenza virus genomes (Figure 5), release these immediately in public databases, and publish about the processed data.

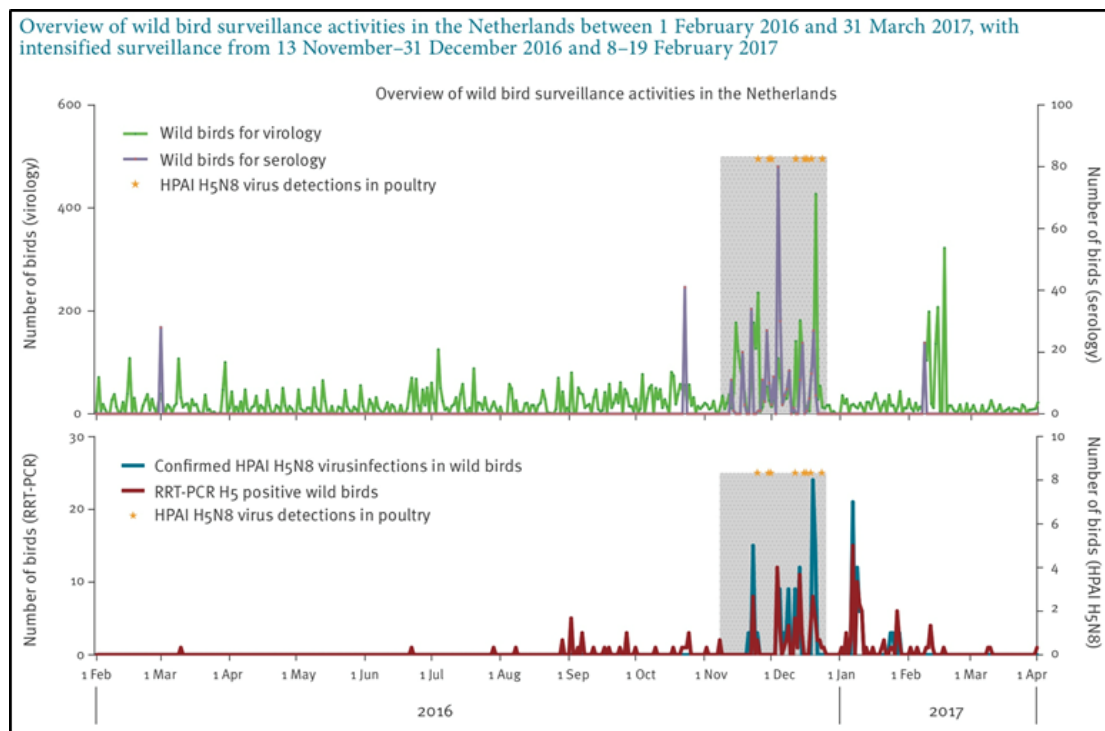


Figure 5. Demonstration of Dutch surveillance intensity.



Other WP5/WP8 highlights in this reporting period are the major progress of the Global Sewage project that has expanded to more than 250 cities in more than 100 countries and for which the first manuscript(s) on AMR are being prepared. The virus genomics component of the Global Sewage project is focused on optimizing both experimental and bioinformatics techniques. The ancient DNA data-mining project has revealed a second DNA virus in bronze/iron age humans, for which a manuscript is being prepared.



WP9 – COMPARE platform

Rapid sharing and analysis of pathogen genomics data is central to COMPARE, and in WP9, they have built the informatics to enable this.

Our work in the reporting period has focused on two areas: extension and improvement of the COMPARE platform's technical infrastructure and engagement across a number of COMPARE initiatives in which the platform is being used.

Infrastructure work has seen a number of developments that add resilience to the system, such as in the Kooplex management system for Notebooks and the SELECTA cloud compute workflow engine. We have undergone a round of upgrade in each the analysis workflows deployed in production, SLIM and CGE_DTU, resolving bugs and adding functionality, and have progressed on a number of further workflows and methods, including parasite analysis, RIEMS, EverGreen and KMA.

A number of functions have been added to the platform that are to be used by its operators, adding flexibility and increasing autonomous operation, including support for whole data hub-level (rather than project-level) triggering of analysis workflows. New user-facing functionality has been added across the platform, including sharing tools within the Notebook system and core genome MLST analysis for bacterial isolates.

We now see use of the COMPARE platform across a number of pilots and other initiatives within COMPARE and have engaged actively across the relevant working groups. This work includes ongoing support for all data hub operations, specific tools (such as the AMR antibiogram tools) and the Pathogen Portal.

We have been particularly active where demand has been greatest, including for the sewage metagenome project, AMR machine learning and in preparation for the major upcoming pilot for the ECDC and EFSA.

Data Hub/project	Topic	Associated Projects	Usage
dcc_sibelius	Pilot: Influenza H5N8	PRJEB12582, PRJEB9687, PRJEB9846	Seq Data for 13 samples: 9 COMPARE Influenza standard, 4 ENA default
dcc_berlioz	Pilot: Ebola	PRJEB10265	Seq Data for 57 samples: all COMPARE virus pathogen standard
dcc_liszt	Global Sewage	PRJEB13831	Seq Data for 179 samples: all COMPARE sewage standard
dcc_strauss	Kibera Sewage	PRJEB13833	No samples and no sequencing data
No hub since all public from onset	Copenhagen Sewage	PRJEB13832	Seq Data for 64 samples: all COMPARE sewage standard
dcc_vivaldi	EpiData (WP4 Foodborn pathogen surveillance and epidemiological analysis)	PRJEB14853, PRJEB15081, PRJEB15201, PRJEB16326, PRJEB18442, PRJEB22002, PRJEB21631	Seq Data for 1363 samples: 514 pathogen default standard, 849 GMI standard;
dcc_schubert	AMR working group; AMR machine learning	PRJEB18042 PRJEB14981 PRJEB21131 (list not complete here) PRJNA292666 PRJNA266657	Seq Data for 16404 samples: 168 ENA default, 166 pathogen default standard, 994 GMI standard; 15180 NCBI registered samples derived from a public project; 2139 AMR analysis files of which 365 AMR files are linked to COMPARE partners' own data (PRJEB projects) and 1774 AMR files were produced by AMC from publication results associated with the NCBI registered projects: around 200 E. coli MIC data and the rest are Salmonella. 1909 DTU_CGE analysis files
dcc_beethoven	Workflow Demonstrator	PRJEB11174, PRJEB13610, PRJEB2822	Data for 922 samples: extremely poor metadata, no checklist; 880 analysis files
dcc_brahms	Diagnostic metagenomics on clinical samples	PRJEB18065	Seq Data for 4 samples: COMPARE virus pathogen standard
dcc_handel	Virus metagenomics (NoV and HepA)	PRJEB14410, <u>PRJEB13141</u> , <u>PRJEB14042</u> , PRJEB14393, PRJEB13823, PRJEB15608	Seq Data 8 samples from <u>underlined projects</u> : GSC MixS human gut standard but poor metadata
dcc_puccini	Parasites (Comparative Genomics of Intestinal Protozoa)	PRJEB15112	No samples and data yet; checklist has been in place since 26 April 2017

Figures 6. Current data hub status.

WP10 – Risk communication tools

Workpackage 10 is designing and developing the appropriate risk communication tools and strategies for COMAPRE stakeholders. Workpackage 10 has completed extensive inventory on stakeholders to the COMPARE platform, and has developed a message mapping tool.

In the period from September 2017 to February 2018, WP10 advances have followed three main directions.

The first direction has concerned the message map, which has been now finalized and fully integrated with the dynamic stakeholder list and with narrative paradigms. Coordinated sets of messages related to different stakeholder groups are now available; these messages are generated according to the epidemic narrative paradigm (Figure 7) identified through a comprehensive narrative analysis, including 64 classic epidemic narrative schemes from novels, movies, short stories, paintings, and some examples of applications of these schemes in current narrative structures, such as comics, videogames, TV series.

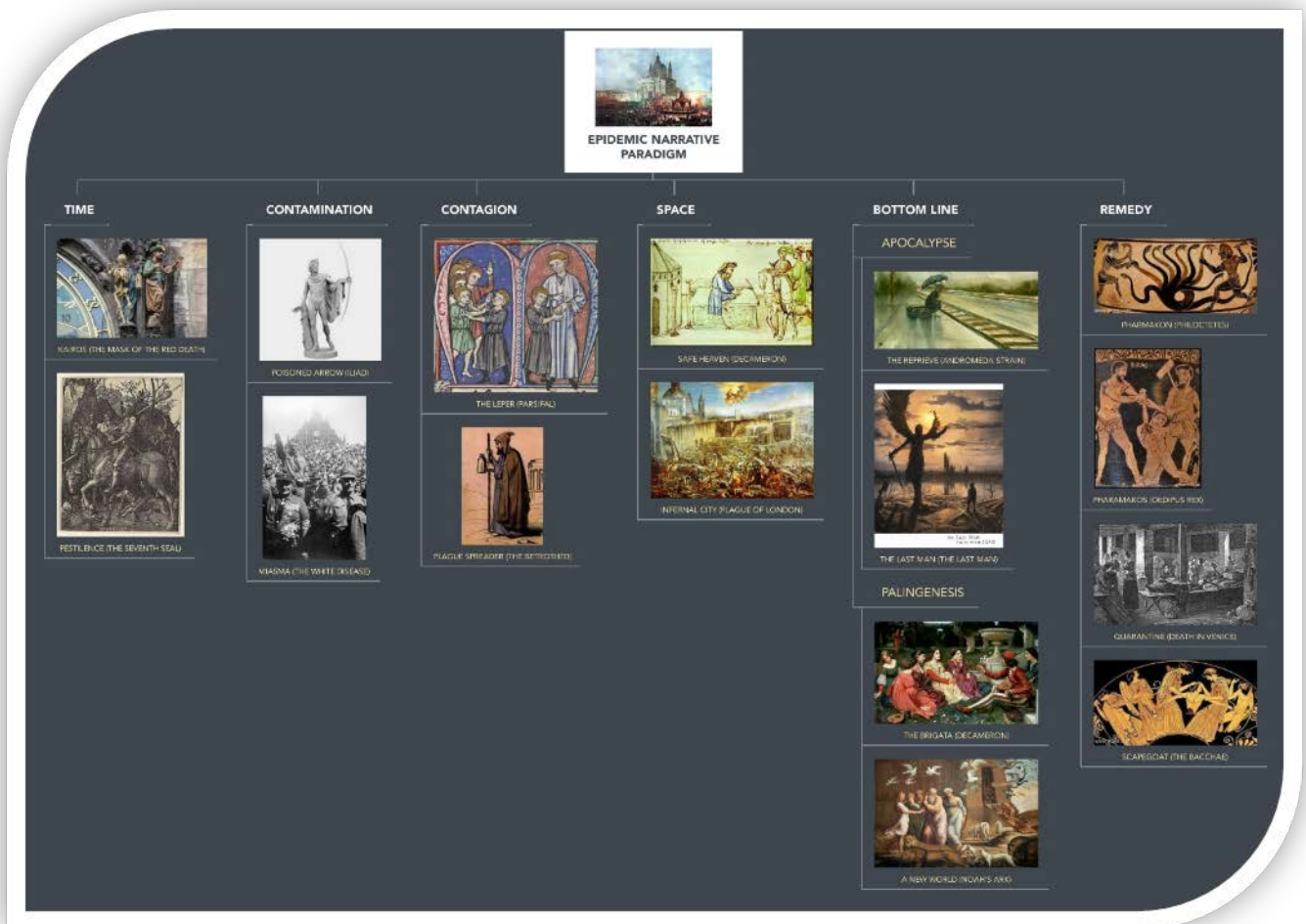


Figure 7. Epidemic Narrative Paradigm

The second direction has concerned the design of the architecture of the COMPARE Risk Communication Tool Box macroscopic system structure (overall architecture), which is the high level representation (main elements and connectors) of the COMPARE Risk Communication Tool Box, describing structure, behavior, and more views of the tool box (Figure 8).

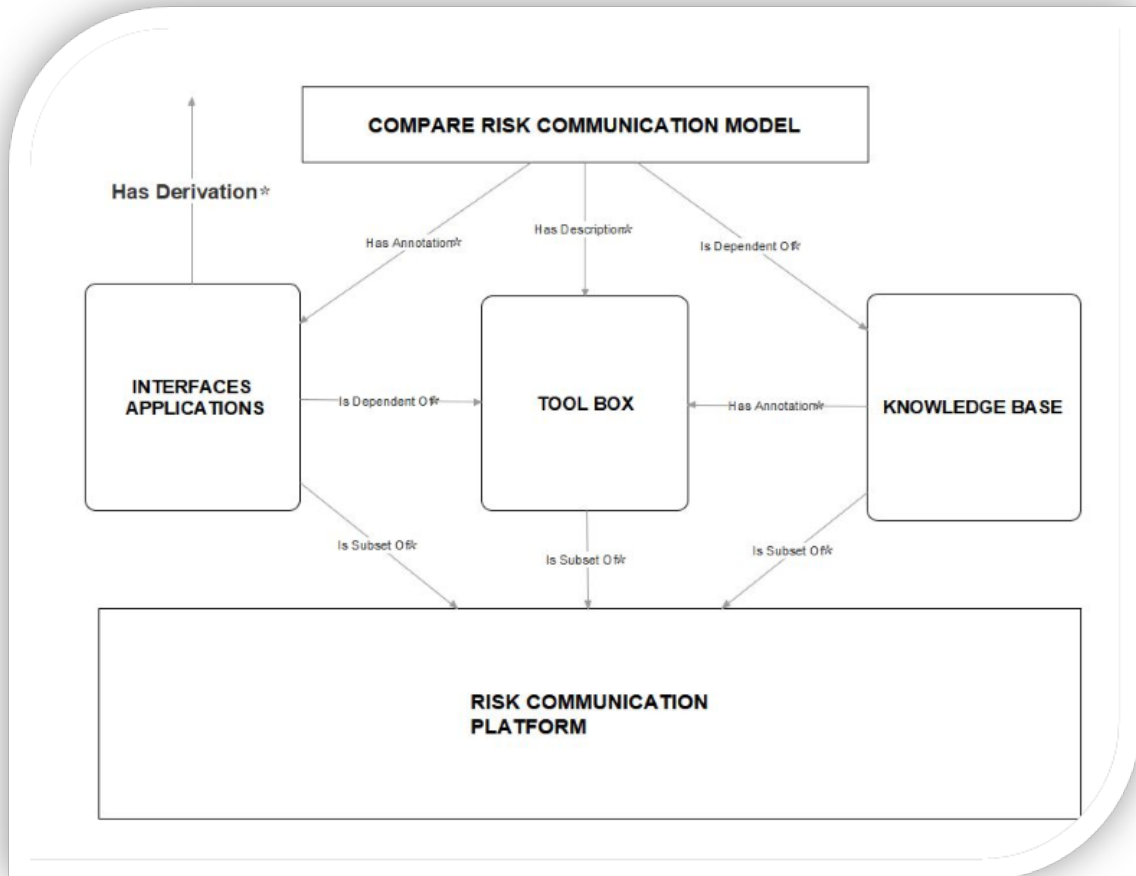


Figure 8. Risk Communication Tool Box Architecture

The third direction has concerned the development of the main set of tools (Figure 9) to be incorporated in the tool box, including 1) Stakeholder dynamic list; 2) Narrative Paradigm Generator; 3) Risk Communication Ecosystem; 4) Message Map; 5) Message Templates, 6) Additional Templates; 7) Digital Trust Model, 8) Persuasion Matrix. Further tools (e.g. e-learning, training, self-assessment) are in the pipeline.

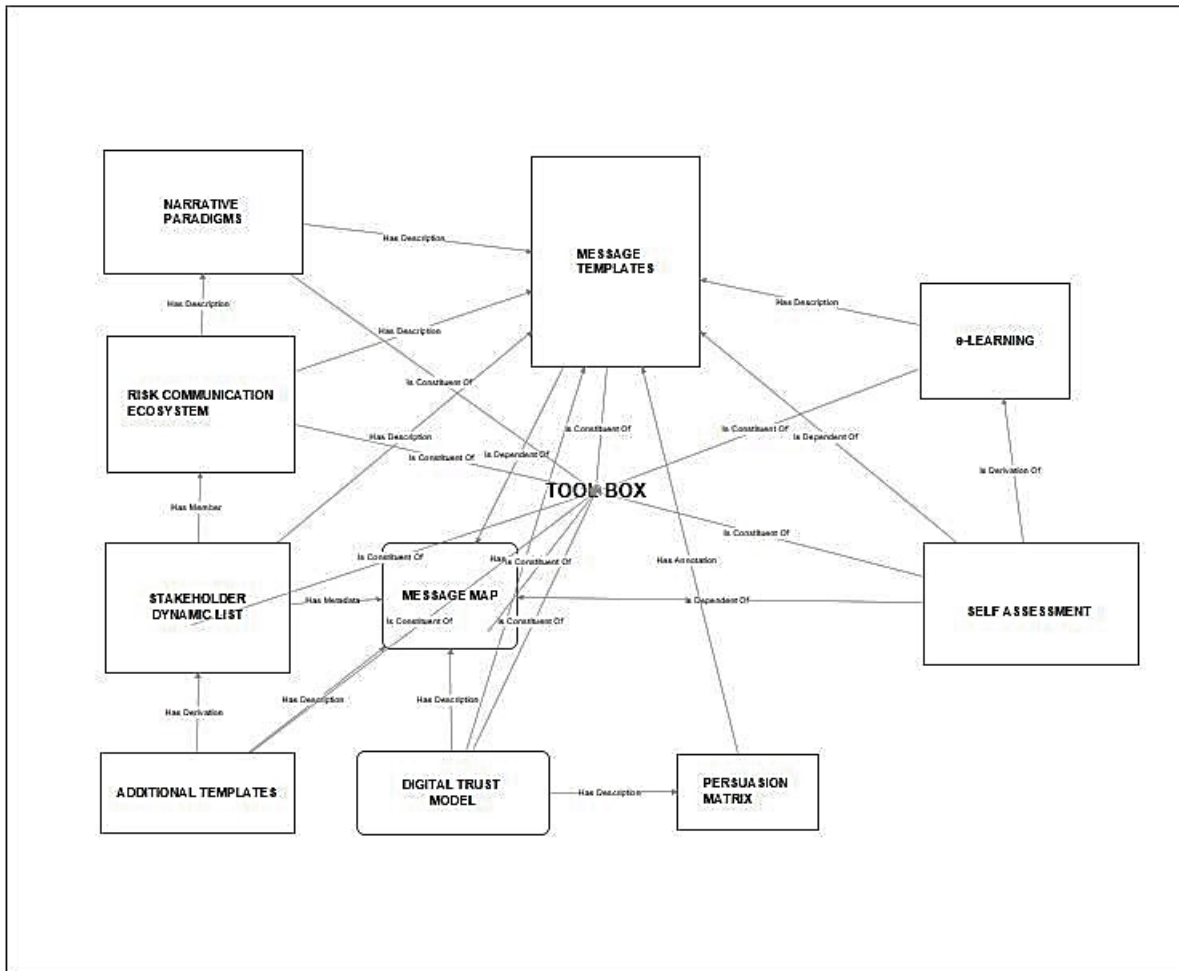


Figure 9. Risk communication, main set of tools.

WP11 – User consultations

The fourth Expert Advisory panel (EAP) round was planned for month 36 (November 2017). However, as the EAP meetings are held face-to-face and in accordance with the COMPARE annual meetings, the fourth round of EAP meetings took place in March 2018. Furthermore, a separate meeting was held by WP12 with 9 EAP members on data sharing during the COMPARE annual meeting on March 2, 2018. During the reporting period, preparations took place to plan for and organize the below-described EAP meetings.

The fourth round of the COMPARE EAP meetings will be held during the annual COMPARE meeting at the Technical University of Denmark (DTU) in Lyngby, Denmark. The members of the EAP are invited and encouraged to attend the COMPARE meeting (28 February, 1 and 2 March 2018). In particular, EAP members are encouraged to participate in the WP meetings and cross-WP meeting on Barriers providing their expert advice and perspectives on the topical discussions. At the end of the second day of the General Meeting, a COMPARE Executive Board and EAP member meeting will be held on March 1, 2018.

During the fourth round meeting, the EAP members will be invited to provide their feedback to the Executive Board on the progress of the project and strategic choices made by COMPARE thus far. In addition, the plan for the development of the COMPARE sustainability plan will be presented and EAP members will be invited to give feedback on this plan. In total, 18 EAP members will attend this meeting: 2 from EAP Domestic Animals, 4 from EAP Barriers, 7 from EAP Food Safety, 1 from EAP Wildlife, 1 from EAP Clinical Health, and 3 from EAP Public Health. In addition, two members of the Ethics Advisory Board (EAB) will attend this meeting.

During the COMPARE meeting, a working group session on data sharing will be held by the WP12 team and EAP members. In total, 9 EAP members will attend this session, the majority representing the EAP Barriers (4 members), 3 from EAP Food Safety, 1 from EAP Domestic Animals, and 1 from Public Health.

WP12 – Barriers to open data sharing

The focus is on understanding barriers to the development of COMPARE, in terms of legal, ethical, administrative and other considerations that may play a role.

During the reported period, the WP12 working group initiated the activities for the performance of Deliverable 12.2: developing a charter of principles and ethical framework for the COMPARE community. Two main activities were performed as (1) planning the execution and content of the deliverable, and (2) performing a literature review to obtain contextual insights from relevant literature. An oral presentation about the work performed on WP12 so far and the planning of Deliverable 12.2 was given at the COMPARE past, present and future meeting on October 2017, at the EMC in Rotterdam.

Following from the previous activities of WP12 (WP12 Workshop I), another workshop elaborated on the development of case studies (real-life situations) that illustrate how barriers to data sharing occur in practice was performed, this time at the EVD-LabNet meeting, on October 2017, in Rotterdam.

In accordance to Tasks 4, 5 and 6, WP12 developed in collaboration with the governance group of the COMPARE-ECDC pilot project, a confidentiality agreement for participating EU Member States and the other stakeholders involved. The draft documents are currently being assessed by ECDC, EFSA and the other members of the group.

As case studies and for real time information gathering, several internationally relevant meetings have been attended on the topic of data sharing and public health. In October 2017, the WHO consultation on biobanking meeting; In November 2017, the WHO PIP Framework consultation meeting, related to the inclusion of genetic sequence data on the international treaty Nagoya Protocol.

During the month of February 2018, the WP12 team has also worked on preparing for the 2018's General COMPARE meeting and Young COMPARE meeting. For the Young COMPARE meeting, a poster and oral presentation were prepared, under the title of "Data sharing under the NP: what if genetic sequence databases have to function as culture collections?" These products were a result from our previous research on the impact of the Protocol on the sharing of genetic resources through biobanks/culture collections for public health purposes. For the General Meeting, a workshop (WP12 Workshop II) was prepared under the title: "Responsibility for Data and Sharing: An interactive session of case studies". This workshop was based on case studies developed from the knowledge accumulate from the researches performed under WP12.

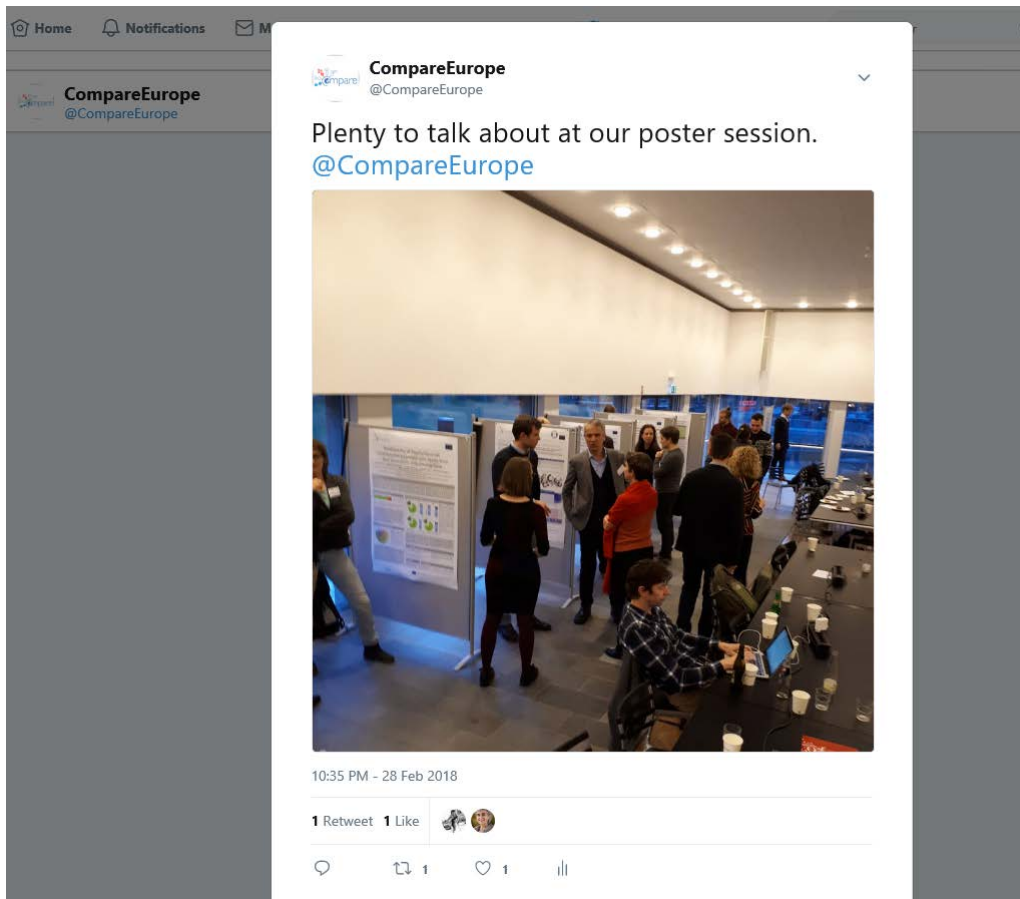
WP13 – Dissemination and Training

Members of the COMPARE Consortium share their experiences and results from COMPARE at conferences and workshops all over the world.

Regarding Training, COMPARE is providing e-learning options that can be accessed online via the COMPARE portal. An introduction to Metagenomics is being evaluated and will be available in early summer 2018.

Members of the COMPARE Consortium continue to publish manuscripts in peer-reviewed scientific journals. These are reported via the public website. There are more than 100 research articles that acknowledge COMPARE support.

The COMPARE Twitter account (@CompareEurope) shares related news about COMPARE and from the project partners.



*Figure 10. COMPARE Tweets.
Twitter account (@CompareEurope)*



WP14 – Cost-effectiveness framework

COMPARE can potentially bring about huge benefits through a variety of mechanisms such as earlier detection of disease outbreaks but also through increased research output. However, quantifying and valuing the benefits is often more challenging than quantifying the costs. Workpackage 14 has the aim to quantify costs and benefits of the COMPARE system and will develop methods to value the benefits of COMPARE.

WP14 has finished developing the questionnaire to estimate the value of safety after conducting several pilot studies. Results from the questionnaire for the United Kingdom have already been collected and currently the questionnaire is being translated to other languages so that the questionnaire can be rolled out to other countries. This work is relevant for Task 4 (Develop and apply a methodology to value safety in several countries). Furthermore, EUR has started on a review on economic evaluations of pandemic outbreaks which is relevant for Task 2 (Identify and where necessary develop state-of-the art costing methodologies for the different elements in the framework) and Task 6 (To assess options for refining selected elements of COMPARE in view of improving the overall cost effectiveness of the system.)

Civic Consulting defined the scope and focus of the cost-effectiveness case studies to measure and value elements of the system, i.e. the system subject to the cost-effectiveness estimation, the scope of activities to be assessed, the perspective of the analysis and the time period and geographical scope. We have refined the methodological approach and determined the baseline scenario, based on the previous identification of cost and benefit types, existing methodologies and empirical studies, as well as developed a draft case study approach accordingly. The case study methodology has been finalised, taking into account the in-depth review of the pilot case study that we conducted at the Friedrich-Loeffler-Institut (Compare WP2 leader) in October 2017.

We have selected candidate case studies on the basis of criteria related to the type of surveillance system, the sector of application and the geographical region. Finally, we have launched the data collection process for case studies. Data collection is ongoing with three institutions and expected to be launched with two more shortly, and initial results were presented at the Compare General Meeting in February 2018.

WP15 – Management

The appropriate organizational structures and processes have been put in place to respond to the EC's as well as partners' needs and to ensure COMPARE's compliance with the EC Grant Agreement and the COMPARE Consortium Agreement.

COMPARE partners submitted the Scientific and Financial reports for the 2nd Reporting Period. The reports were approved by the EC and the distribution of payment was made to Consortium members.

The COMPARE General Meeting 2018 was held 28 February – 2 March 2018 at the Technical University of Denmark. More than 125 participants came together to review the progress of the project as well as interact with the Expert Advisory Panel members as well as the newly installed Ethics Advisory Board members.



Figure 11. Welcome to the COMPARE General Meeting 2018 – Marion Koopmans.



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

COMPARE Partners

