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COMPARE Quick Facts

Coordinator, Frank Aarestrup

Technical University of Denmark

Co-Coordinator, Marion Koopmans

Erasmus Universitair Medisch Centrum Rotterdam

Project period	01 December 2014 – 30 November 2019
Funding	€20 million (approximately)
Contact	compare@food.dtu.dk www.compare-europe.eu @CompareEurope

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Contents

Note from Coordinators

The COMPARE project has entered its final year, but has developed into a thriving collaboration that we intend to take further. This ambition was tangible during the COMPARE General Meeting 2019, held at the campus of the Technical University of Denmark from 27 February – 1 March 2019. Despite realizing that this is the final year, additional research questions were developed and pilot studies suggested, noting that we should capitalize on what has been developed.

Among others, the following are some of the highlights of progress:

- Generic models for sampling and hot-spot surveillance
- Searchable inventories of protocols
- Working datahubs with automated analysis
- Active data sharing and joint work
- Pilot studies in different fields
- Insight into barriers and possible solutions
- An impressive list of publications, several very high impact
- COMPARE is a 'brand'
- A dynamic young COMPARE community
- First economic analysis of costs and benefits

As stated above, we have active pilot studies in different fields:

- ECDC-member states-COMPARE datahub with Salmonella
- EFSA-ECDC-COMPARE interaction
- Global tracking of influenza A H5Nx dispersal
- Machine learning of AMR resistance patterns for clinical diagnostic settings
- Global urban sewage metagenomics for surveillance
- Tracking of arbovirus outbreak using Usutu as example
- Pilot private food company – public data sharing
- Ancient DNA based virus discovery
- EFSA norovirus study

The Executive Board is supportive of the continued investigations, but is also mindful of budget and time limits. A pilot involving the food industry will be a high priority for the Consortium in the final two quarters of the project. The inclusion of MinIon/Gridion technologies are also a development that demonstrated the flexibility of the COMPARE vision and platform. Further investigations using this technology and determining the pluses and minuses will also be part of the final studies undertaken during COMPARE. New 'mapping' technology 'KMA' is a probable game changer to WGS and pathogen surveillance. KMA's mapping capabilities, speed and scalability open new possibilities for sequencing data to be explored. The addition of new and improved pipelines, workflows and software to the COMPARE platform is a testament to the flexibility and continuous evolution of the solution.

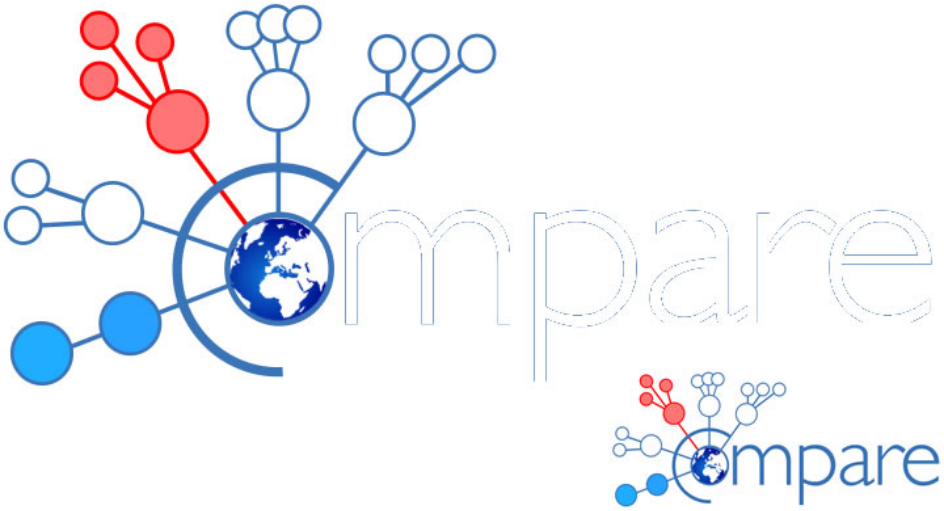
Future steps

The coordinating team and Executive Board agree that it is important to look for further opportunities to take the "COMPARE" mission forward. Scientific developments aside, the datahub concept and initial version of a

'safe space' for collaborative analysis of next generation sequencing data will be developed further. As was expected, the development of the COMPARE solution was never going to be a simple website as a finished product. Like many research-based solutions, the technology behind it, the science supporting it and the maintenance demanded by it continues after version 1.0 is released. The coordination team is exploring the opportunities for launching a COMPARE foundation, in which our joint brainwork can be further developed, while looking for additional sources of funding. For clinical research, the datahub concept will be further developed through the new H2020 projects RECODID and ECRAID, coordinated by the University of Heidelberg, and University of Antwerp, respectively. Additional applications have been submitted for parts of the infrastructure- and tool development.

To launch a COMPARE foundation, we need a critical appraisal of what the basis would be. The "COMPARE vision", leading to the development of the COMPARE approach: its datahubs, automated workflows, visualization tools, and code of conduct, have been piloted beyond the borders of the COMPARE Consortium to garner input for this appraisal. The challenge now is the sustainability of this approach, as generic solutions are difficult to recognize in a funding landscape that likes focused efforts. As was requested in the call text, the sampling and collection of materials, the sequencing protocols, the sharing of data, and the common pipeline and mapping solutions, all independent of pathogen, source, and geography must now be offered as a sustainable option to not only governmental institutions, but also independent research bodies.

The COMPARE project, and the solution established, has made a change in the landscape. However, a structure for the shared solution and its continued evolution must be developed, otherwise, energy and talent will be wasted by not focusing and using synergy to adapt the solution to the needs of all stakeholders; public health, food industry and clinical surveillance. It is clear that we are at version 1.0, and work is needed to further develop the datahubs regarding user-friendliness and flexibility. We aim to do that through the COMPARE foundation, supported by the above mentioned new funding initiatives, as well as more targeted funding.



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.

Overall, the work in the tasks is progressing to the final phases; finalizing the different pathways and tools and preparing manuscripts to disseminate the methodologies developed.

As we move towards the final phase of the project, WP1 contributors are finalizing the risk assessments, case studies, tools and pathways that have been developed across the Tasks. The main focus now is the dissemination of findings and knowledge sharing. Manuscripts are being submitted for publication, conference presentations are being given and contemporary ways of utilizing the outputs of COMPARE are being investigated such as the development of user-friendly apps.

The focus of Task 1 is to develop methodologies and tools for spatial and food chain risk assessments to support outbreak investigations. Contributors to Task 1.1 have been preparing a manuscript based on an African swine fever (ASF) case study in collaboration with Tomasz Podgorski from the Mammal Research Institute at the Polish Academy of Sciences, in addition to a second paper predicting the risk of infection of ASF across Europe by trade, boar movement and food pathways. Two manuscripts have been published during the reporting period under Task 1.2 – which examine possibilities for conducting microbial risk assessment using WGS data, machine learning and STEC. A further manuscript is being drafted based on a case study on Listeria monocytogenes exposure assessment using NGS data. Within Task 1.3, the UK livestock movement databases have been fully integrated into the framework, and work is ongoing in estimating recombination rates from previous outbreaks. Finally, a manuscript for the global sewage dataset has been accepted for publication (the statistical analysis was carried out within Task 1.3). Please see https://www.compare-europe.eu/library/scientific-publications for a listing of all COMPARE-acknowledged publications.

The goal of Task 2 is to develop risk-based sampling and data collection strategies for early detection and investigation of unusual patterns of infectious disease outbreaks. The combined package of tools developed (flowchart, database with protocols, syndrome based sampling protocol, metadata checklist) has undergone two rounds of expert review and will now be presented as a manuscript and developed into an app. The deliverable report 1.2 is at the final draft stage.

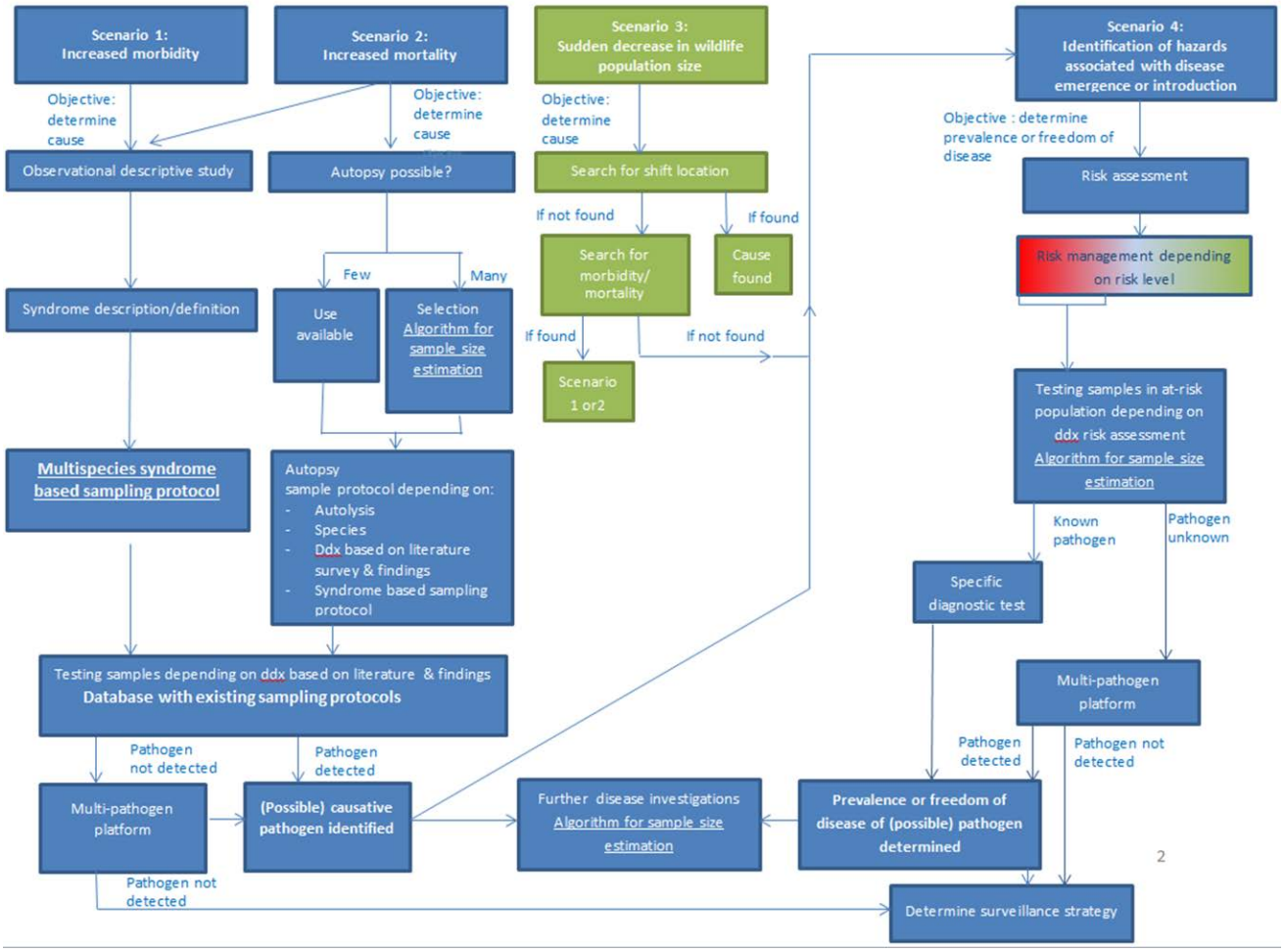


Figure 1. Sampling flowchart for harmonized sampling for the detection of emerging infectious diseases.

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.

During the recent reporting period, WP2 continued the validation of sample processing workflows using ring trials (RT).

COMPARE Ring Trial #1 - The GMI Virus Proficiency Test (see also Deliverable D2.5) with a dry and a wet lab part organized by RKI was finished in 2017. The interpretation of the results together with a fictitious case report by the participants showed that, in addition to the bioinformatics analysis, the virological evaluation of the results can be important in clinical settings (Brinkmann et al., submitted).

COMPARE Ring Trial #2 - The RT on food metagenomics was analyzed during the reporting period (see also Deliverable D2.6). In the wet lab part, a complex mock community containing bacteria, viruses, parasite and fungi was spiked in a sample of smoked salmon. Analyses of the data sets are currently being finalized.

In the dry lab part, a synthetic dataset was created simulating a sample of contaminated trout. The analysis showed that despite shortcomings in some analyses (namely usage of incomplete databases or improper data pre-processing), overall the used software appears to have matured over last years. However, for a truly beneficial effect of diagnostic metagenomics for the detection of potentially present pathogens, it is especially necessary to put more effort into the training for the assessment of the results delivered by the different software pipelines for the analysis of metagenomics data (see Figure 2).

COMPARE Ring Trial #3 - The next RT was planned during the reporting period. It will be conducted in the next reporting period to be reported as Deliverable D2.7 (due November 30, 2019). The subject of that RT is the handling and processing of difficult material like formalin-fixed parafine-embedded tissue samples with a natural virus infection.

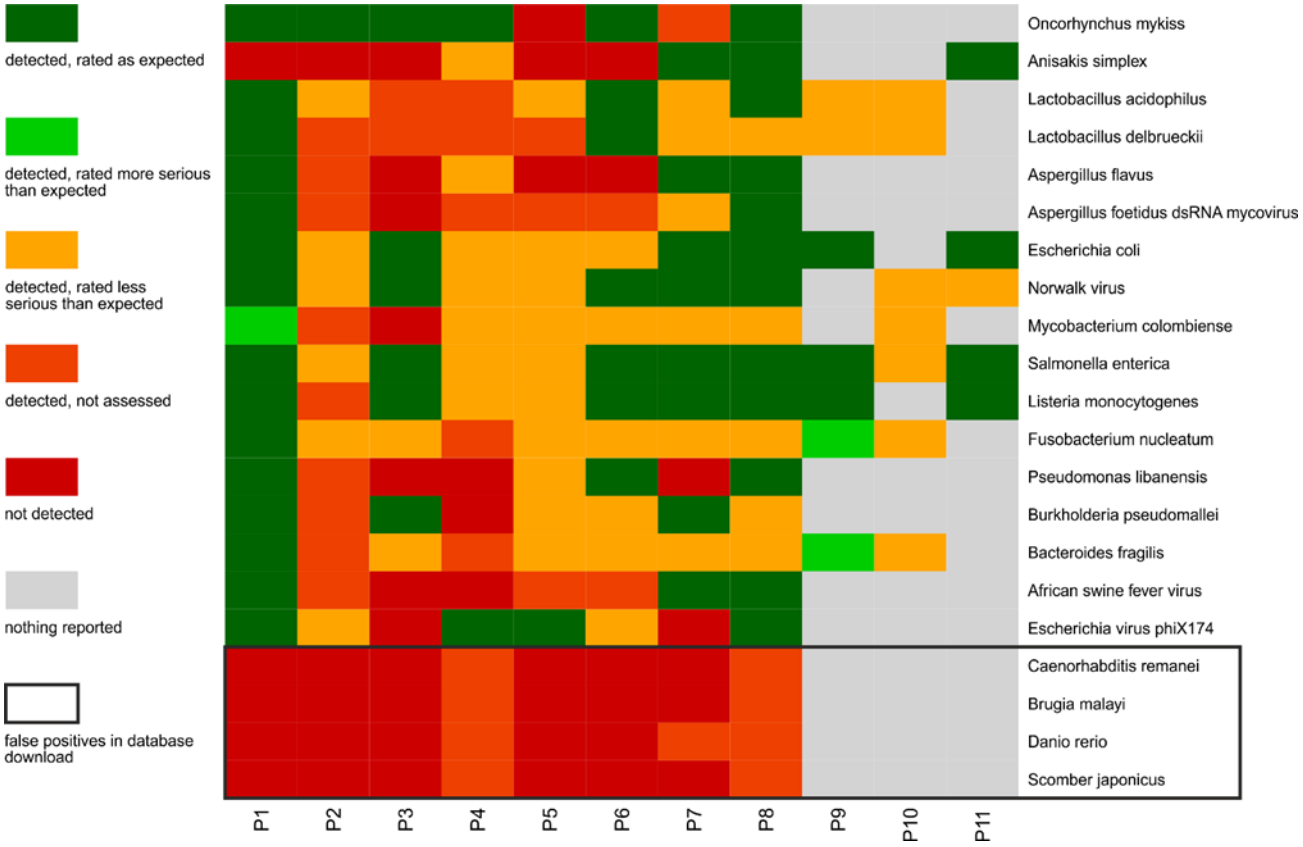


Figure 2. Heatmap summarizing assessments of the detected species by the participants of the COMPARE Ring Trial #2. The species within the black frame were erroneously comprised in the dataset as false positives when retrieving the reference sequences for the genus Anisakis from the database; this could not be reproduced, hence the reason for this downloading remains unclear.

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.

In WP3, during September 2018 to February 2019, workflow implementation and validation has been done. Especially in work bundle 1 (WB1), analytical workflows and pipelines have been updated and integrated into public datahubs at ENA (EMBL-EBI). The metagenomics workflow RIEMs has been used in the identification of bacterial and viral co-infection, and in parasite detection. Data from these studies are shared on ENA datahub ("dcc_brahms"). RIEMs is being integrated into EBI_SELECTA. The whole genome sequencing workflow BacPipe was integrated into EBI_SELECTA and validated with more than 4000 paired end sequences from different bacterial species. The two open-source applications (refRank and SNPfilter) supporting reference genome selection and alignment-based SNP-filtering in NGS analyses are being optimized and published. Performance of in-house developed database and commercial software of Seqsphere+ in predicting resistance phenotypes in *S. aureus* from WGSs have been compared. Sequence-based database for *Clostridium difficile* is being developed. Pacbio long-read sequencing on 80 reference strains representing the most prevalent ribotypes in Europe is ongoing. From this work, accurate and high resolution sequence-based ribotype schemes will be created.

In WB2, the machine-learning approach for prediction of fluoroquinolone-resistant *Escherichia coli* is progressing. The database from this study is online and available for COMPARE partners. The manuscript on the database and datahub development is submitted to BioRvix. The database for prediction of colistin resistance by Hidden Markov-Model (HMM) in Klebsiella pneumonia has been created. This database includes colistin MIC and whole genome sequences of > 800 K. pneumonia. More than >65% of K. pneumoniae in the collection are colistin resistant due to various mgrB modification. Experimental validation for mgrB modifications and MIC correlation will be confirmed.

In WB3, a number of viral and bacterial outbreaks have been studied, including the influenza outbreak in poultry, West Nile virus outbreak in Greece, outbreaks of VRE, and carbapenem-producing Enterobacter cloacae. Transmission dynamics of *S. aureus* amongst households, *Clostridioides difficile* in a tertiary-care hospital, and ESBL *E. coli* amongst patients in a single hospital have been established.

The metagenomics approach has been applied in the identification of the porcine epidemic diarrhea virus outbreak, in establishing the causal link between zoonotic Borna disease virus 1 and encephalitis in organ transplant recipients, and in detecting batai virus in CNS of a harbor seal suffering from meningoencephalitis (WB4). A pre-sequencing screening method based on DNA concentration has been developed and the threshold of 6 ng/ml DNA has been established with negative predictive value of 91% for ruling-out culture positive urine samples. The use of WGS for a nosocomial VRE outbreak characterization has been shown to be superior to AFLP and the manuscript is under review.

In WP6, NGS has been applied in the characterization of livestock-associated MRSA isolated from farmers and goats in Greece. The feasibility of NGS in clinical diagnosis is evaluated in a comparative analysis of cost, time to

result, and robustness of metagenomic and targeted sequencing of flaviviruses from clinical samples. A pilot study to assess the cost-effectiveness of shotgun metagenomics in the clinical laboratory is being conducted.

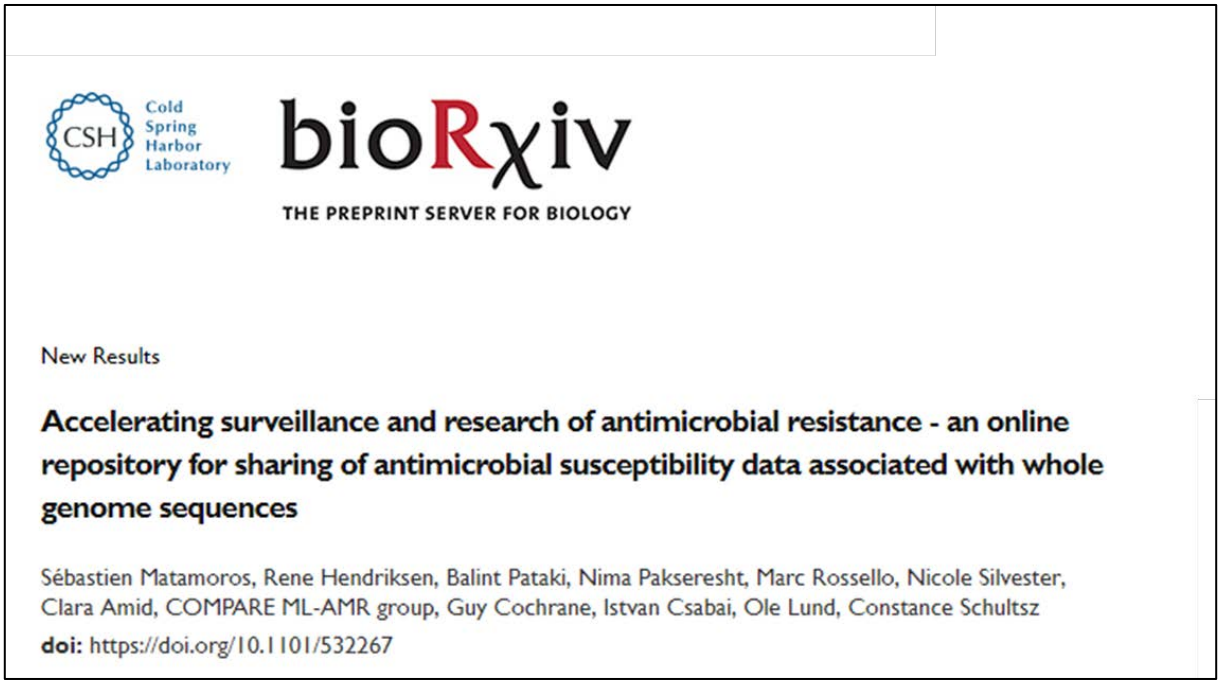


Figure 3. Manuscript on the database and datahub development from machine-learning approach for prediction of fluoroquinolone-resistant Escherichia coli *on BioRvix.*

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.

In this period, the group continued the work on source attribution modelling. This involved the developing and adjustment of a machine-learning model that was tested by the use of all four European datasets collected for the purpose (DTU). The modified Hald method (Mullner et al., 2009) was applied to UK data by APHA. The data included Salmonella typhimurium sequence data for humans and animals clustered using three different approaches: seven loci MLST; SNP distance; and cgMLST (hierarchic clustering using enterobase). Furthermore, RKI developed a source attribution model using cgMLST data and validated it using the German and the Danish data set.

Partners from UK, Denmark, France, Germany and Italy collaborated with regards to selection and inclusion of 328 Salmonella genomes for the long-term evolution study of monophasic S. Typhimurium (mST). The selected genomes were analysed to compare and describe the presence of four genomic regions of interest in the isolates from different countries. This was followed up by phylogenetic analysis of the isolates.

Regarding the *Campylobacter lari* study, a total of 128 *Campylobacter lari* strains from mainly France, Denmark and Germany were selected including 36 human stool isolates, animal strains (dogs, cattle and wild birds) and environment (mainly shellfish) isolates. Currently WGS data are available for 106 of these strains. A first comparison of the strains from France and Denmark by MLST typing and SNP analysis revealed a high diversity of investigated *C. lari* with several unknown STs. ST-21 was prevalent among human stool strains and was found in dog feces and seagull feces strains as well. Interestingly, some clinical strains from France clustered with clinical strains from Denmark by SNP analysis. Additional strains from Australia, UK and Italy could complete this collection.

RIVM routinely sequence a subset of viral gastro-enteritis samples via agnostic virus enriched metagenomics (viromics) and has generated 85 NoV full-genomes (>90% complete) and several sapovirus genomes.

A subset of HAV samples from several European countries were genotyped resulting in 32 full-genomes (>90% complete). Using viromics, we generated full genomes and were able to trace outbreaks; we differentiated a foodborne sub-cluster within an ongoing outbreak amongst men who have sex with men. This was not possible with our routine Sanger VP1/2A sequencing workflow.

We developed a SISPA protocol for Hepatitis E, which can amplify GC-rich regions more efficiently, thus, full viral genomes are generated more robustly.

We developed the Jovian pipeline, an automated web-based viromics pipeline that is used by lab technicians in a routine public health setting. It automatically analyses Illumina metagenomics data and presents results in a user-friendly, interactive web-report and it contains a succinct methodological “fingerprint” allowing results to be perfectly reproduced (audit trail).

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.

Nanopore sequencing, including on the MinIon and GridIon platforms, continued to be developed for many different agents, as the long-reads that are generated in this system can help the sequence assembly process for micro-organisms and the rapid turn-around and relatively low capacity are suitable for virology and microbiology applications. As a consequence, an entire session was dedicated to this topic at the COMPARE General Assembly meeting in Copenhagen. The first publications from the COMPARE consortium on this topic are underway, and the techniques are now being evaluated by the Dutch National Influenza Center for influenza virus sequencing, to evaluate a "sequence-first" surveillance, whereby all clinical specimens submitted by hospitals in the country are first sequenced directly, to guide the decision of which samples (dominant genetic prototypes and selected outliers) to use for virus isolation attempts and phenotypic characterization.

Our main projects (wildlife sampling, sewage investigations, genotype/phenotype) have made good progress again, and several publications were submitted or just published in this reporting period on cowpox virus, Usutu virus, West Nile virus, ancient viruses, and the microbiome of ticks. Publications from several major COMPARE multi-institute collaborative projects including on the spread of H5Nx viruses, the minor-variant sequencing pilot for H5N8, and the sewage microbiome/virome project are now being prepared or submitted by the Consortium.

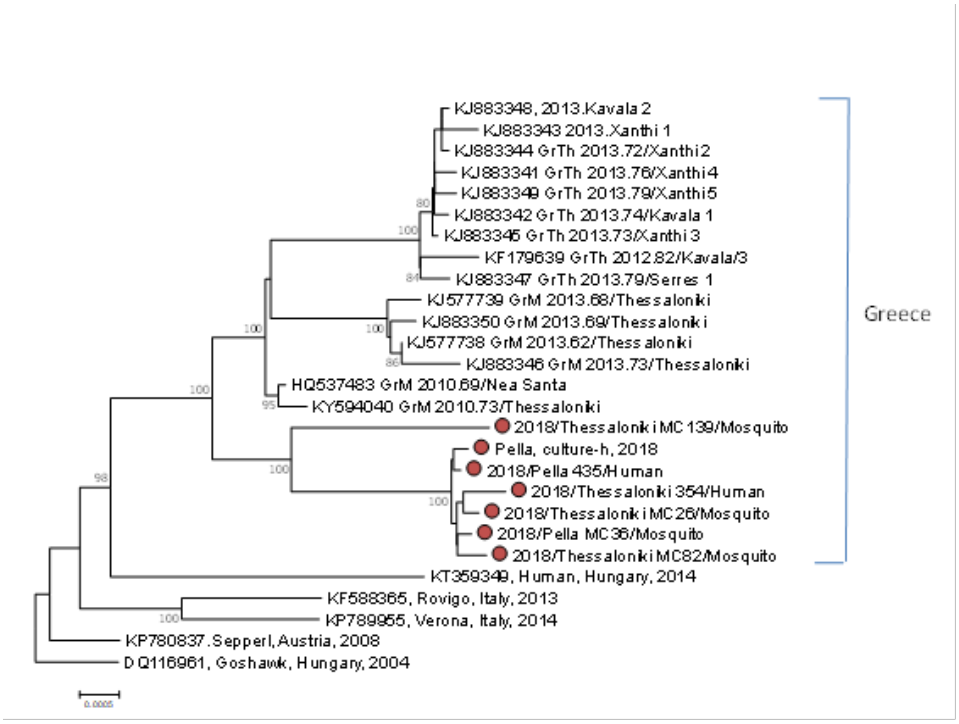


Figure 4. Phylogenetic tree based on WGS of West Nile viruses in Greece (lineage 2).

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.

We have continued to operate and support the datahub system for the sharing and analysis of pathogen sequence and related data types. Covering a number of established, and several new, we operate over 10 individual datahubs spanning broad usage, from sewage metagenomics, through pilots of public health surveillance to parasite analysis.

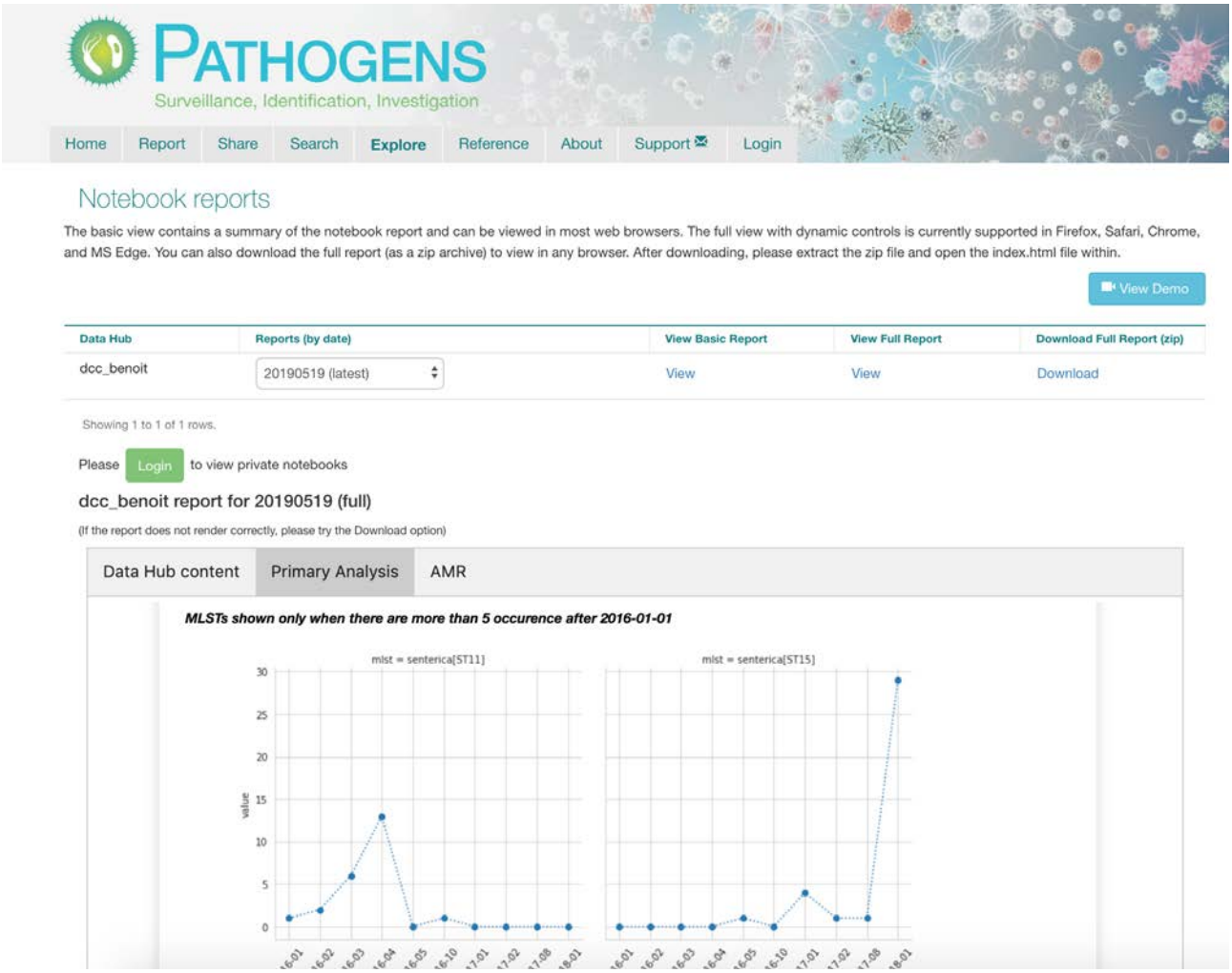
New functions added to the Pathogen Portal, the point of entry into the datahubs for most users, include improved search, better Notebook integration and a range of usability additions, including a Notebook demonstration video. The Notebook system itself grew in sophistication, provide richer code support (such as with the addition of RStudio) and greater reporting options. For proximity to datahub - and ENA-held data, a Notebook server instance has been established directly within EMBL-EBI's Embassy Cloud system.

We have continued development and improvement of the SELECTA workflow system, such as through migration to a higher performance tracking database system, a RESTful API and containerisation of the system.

With the installation of the BacPipe workflow and new releases of existing workflows, flexible analysis choices are now on offer for datahub users; work continues on the integration of several further workflows.

We have continued work on a number of software packages outside SELECTA, including published code for antibiogram validation and submission and technical design to install the Evergreen system to operate across datahubs.

Finally, we have written and submitted the datahub (pre-print at https://www.biorxiv.org/content/10.1101/555938v1) and sewage mitochondrial haplotypes papers and have participated in the writing of five further papers.



Figures 5. A demonstration datahub including Notebook has been made available for public use; this allows data exploration for those interested in establishing a datahub for their community. For access, go to https://www.ebi.ac.uk/ena/pathogens/explore and explore "dcc_benoit"

WP10 – Risk communication tools

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

In the period from September 2018 to February 2019, WP10 organized three workshops devoted to health and risk communication on vaccine and vaccination.

From 26-27 October 2018, COMPARE WP10 organized a workshop on Vaccines, Anti-vax, and Health Communication, at the Ultimo Mulino of Fiune Veneto. The workshop was organized under the sponsorship of the Italian Ministry of Health and the Medical Association of Pordenone. Speakers included Gerardo D'Amico, scientific writer and journalist, vice editor-in-chief, RaiNews24, Rome; Elena Fattori, vice-president of the Standing Committee Food and Agriculture of the Italian Senate, Rome; Alberto Garcia, UNESCO Chair on Bioethics and Human Rights, Rome; Donato Greco, past-Director of the Laboratory of Epidemiology and Biostatistics of the Italian National Institute of Health, Roma; Guido Lucchini, Chairman of the Medical Association of Pordenone, Pordenone; Alessandra Martini, European Commission. Research & Innovation DG, Unit RTD.E.3 Fighting infectious diseases and emerging epidemics; Emilio Mordini, COMPARE Risk Communication, Responsible Technology, Paris; Giorgio Mustacchi, Professor Emeritus of Medical Oncology, University of Trieste, Trieste; Andrea Rubin, Sociologist, "Observa Science in Society", University of Salerno, Salerno; Giorgio Simon, Managing Director, Local Health Authority of Pordenone, Pordenone; Fabrizio Turoldo, Professor of Moral Philosophy, University Ca' Foscari, Venice.

A larger Advisory Committee shared all workshop documents and participated in the online discussion. In total, 22 experts were involved. The workshop addressed vaccine hesitancy and refusal, which are complex phenomena, indubitably due also to disinformation, scientific illiteracy, and medical quackery. Yet – workshop participants argued - medical education, correct information, prosecution of charlatanism are not enough, although essential. Why do so many educated people, even apparently scientific literate, distrust vaccination and believe in unbelievable conspiracy theories concerning vaccines? According to workshop participants, the current crisis of trust, involving scientific expertise and health communication, demands a more in-depth analysis. The workshop was articulated in an internal session (restricted to experts) and a public session involving more than 60 GPs and health professionals.

The COMPARE workshop prompted, and paved the way for, further initiatives on vaccine communication. On November 9, COMPARE WP10 co-promoted with local authorities and the Blood Donors Association a conference on vaccinations open to the general public. Approximately 300 citizens participated. On December 4, COMPARE WP10 co-promoted with the Medical Association a course on vaccine communication, providing 1 CME credit for GPs, pediatricians and health personnel working in public health and prevention services. Approximately 200 health professionals participated in the course.

On November 19, COMPARE WP10 participated in the European Biomedical Policy Forum workshop on "Vaccination challenges and EU cooperation. What is the way forward?", which took place in Brussels and was convened by the FEAM (Federation of European Academies of Medicine). We contacted Heidi Larson, Professor of Anthropology and Director of The Vaccine Confidence Project, in order to strengthen cooperation in the field of vaccine communication.

Eventually, in the period from September 2018 to February 2019, we finalized and delivered D10.2 and progressed in the creation of new tools, including the finalization of the (1) PERIODIC TABLE OF NARRATIVES ON INFECTIOUS DISEASES AND EPIDEMICS, a table collecting narrative tropes, themes, topics, connected to epidemics and infectious diseases; and the (2) NARRATIVE MESSAGE MAP, which is the tool to be used to create narrative messages.

Figure 6. The Vaccines, Anti-vax, and Health Communication Workshop held 26-27 October 2018, near Pordenone, Italy, organized by Workpackage 10.

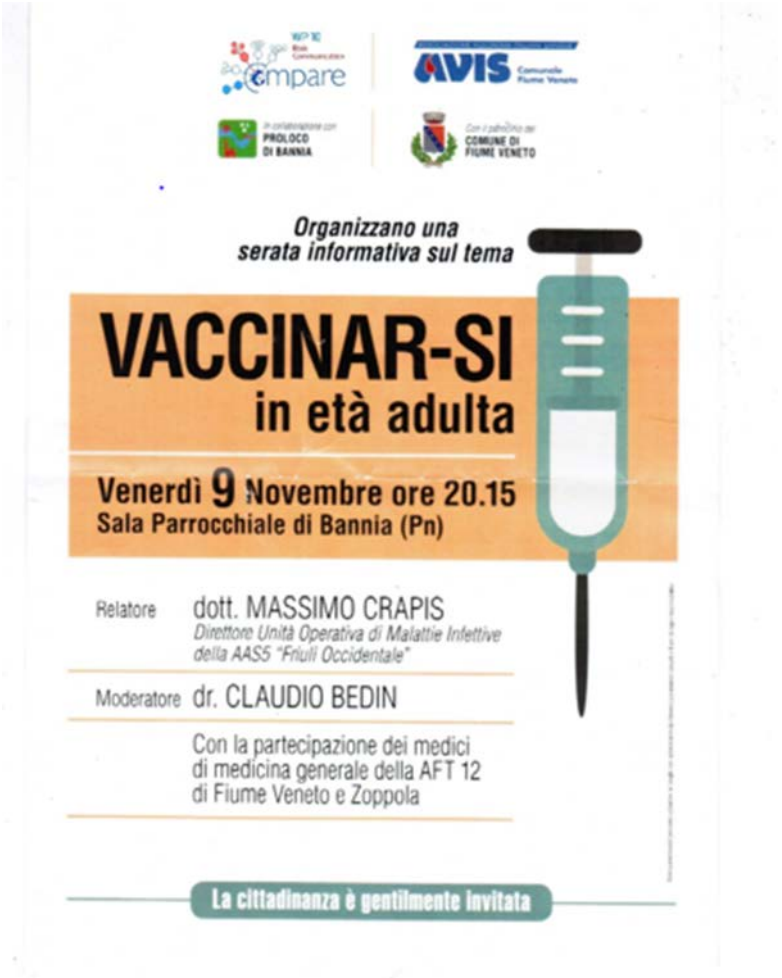


Figure 7. COMPARE WP10 co-promoted with local authorities and the Blood Donors Association a conference on vaccination open to the general public. Approx. 300 citizens participated.

Figure 8. On December 4, 2018, COMPARE WP10 co-promoted with the Medical Association a course on vaccine communication, providing 1 CME credit for GPs, pediatricians and health personnel working in public health and prevention services. Approx. 200 health professionals participated in the course.

WP11 – User consultations

The fifth round of the COMPARE Expert Advisory Panel (EAP) meetings was held during the annual COMPARE meeting at the Technical University of Denmark (DTU) in Lyngby, Denmark. The members of the EAP were invited and encouraged to attend the COMPARE meeting (February 27th - March 1st 2019). In particular, EAP members were encouraged to provide their expert advice and perspectives on the topical discussions. At the beginning of the second day of the General Meeting, a COMPARE Executive Board and EAP member meeting was held on February 28th 2019. During this meeting, the EAP members were invited to provide their feedback to the Executive Board on the progress of the project and strategic choices made by COMPARE thus far. In particular, the meeting focused on what COMPARE currently has developed (presentation by Frank Aarestrup) and further developments of COMPARE (presentation by Marion Koopmans). A particular focus was also given to the sustainability of the COMPARE platform, especially on the possibility to establish a legal entity to exploit the COMPARE platform for different purposes (industry, research and public health). In total, 16 EAP members attended this meeting: 2 from EAP Domestic Animals, 3 from EAP Barriers, 6 from EAP Food Safety, 1 from EAP Clinical Health, 2 from EAP Public Health, 2 from Databases and tools, and none from EAP Wildlife. In addition, two members of the Ethics Advisory Board (EAB) attended this meeting.

Previous to the fifth round of EAP meetings, a questionnaire was prepared and sent to the 16 attending EAP members. The aim of this questionnaire was on the one hand to guide the EAP discussion, and on the other hand to gather input from the EAP members for the sustainability plan of COMPARE. Following up on the EAP meeting, the EAP members were requested to complete the questionnaire (requested submission date for completed questionnaires is April 5th 2019).

Currently, three pilots with EAPs are ongoing:

- ECDC pilot WP4/7, 9 and 12
- EFSA pilot with WP4/7, 9 and 12
- CDC-Guangdong China with WP5/8

A pilot with the food industry is currently being discussed between the COMPARE management team (Marion Koopmans, WP11 leader and co-coordinator, and Frank Aarestrup, coordinator) and a leading food industry partner.

As reported in previous periods, the barriers work of WP12 in collaboration with the EAPs will be a continuous effort. Marion Koopmans (WP11 leader) is co-author on a paper with George Haringhuizen (WP12 leader) on the Nagoya Protocol, published last autumn in *Science*. In addition, a study into barriers and enablers to the sharing of outbreak-related data during the MERS epidemic in Arabian Peninsula, with particular focus on Qatar, as a model for the “Disease X” scenario is currently being finalized. The study is also funded by Wellcome Trust and provides insights useful for COMPARE, and involves some of the international organizations also represented in the EAPs. The COMPARE study team, as well as the methodology, is similar to the previous barriers study published in May 2018 by the WP11 and 12 teams. This study was presented as a poster presentation during the general COMPARE meeting, as well as through an oral presentation during the Young COMPARE meeting on February 26th 2019, entitled “Evaluating data sharing in the MERS-CoV epidemic: What can we learn for the next “Disease X”?”

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 reporting period, WP12 continued to work on finalizing the Deliverable 12.2: developing a charter of principles and ethical framework for the COMPARE community. In this regard, the following activities were performed: (1) field research to assess the main issues related to data sharing according to different stakeholders and possible/perceived solutions, through interactive workshops; (2) a literature review to obtain contextual insights and assess developed knowledge from relevant literature; (3) writing a draft Deliverable text to be validated in the COMPARE annual meeting of 2019; (4) presentation and discussion of the first propositions for the Deliverable in the COMPARE meeting in the form of an interactive workshop; and (5) updating the Deliverable text with the received feedback and finalizing the document.

In accordance with tasks 4, 5 and 6, WP12 developed, and was active on the negotiations with the partners of the Salmonella pilot project (ECDC and EFSA), an agreed Confidentiality Agreement and Terms of Reference for participating EU Member States and other the stakeholders involved. In addition, WP12 is involved on the same developments for another pilot project with partners from the food industry, being an important party on the establishment of agreements and a Code of Conduct for the project.

Following the WP12 field research, the working group performed two other workshops on barriers to data and possible solutions. The first of them took place in September (2018) at the PREPARE Reaching out Meeting (A meeting to advance clinical research preparedness for infectious disease outbreaks), in Brussels. The second workshop was performed in November (2018) at the COHESIVE (EJP-OH) Inventory Workshop, in Weybridge (UK). The insights from both workshops were incorporated in our analysis for the construction of Deliverable 12.2.

WP12, in collaboration with the COMPARE leadership, published on October (2018) a paper under the special issue of “Policy Forum” at the Science Magazine entitled: Threats to timely sharing of pathogen sequence data. The paper addresses the future of sharing pathogen genetic resources in relation to the most recent legal and political global developments on the field. It is an assessment of how biobanks and culture collections have been dealing so far with the sharing of pathogen isolates and sequence data under the norms of sovereignty rights of countries and the international treaty Nagoya Protocol (to the Convention of Biological Diversity). Furthermore, we reflect on if/how such models can be adapted to include genomic sequence data for existing databases, as COMPARE, and ultimately how they can be improved as an attempt to facilitate the sharing of pathogen genetic resources, so important for outbreak and epidemic control, response and research.

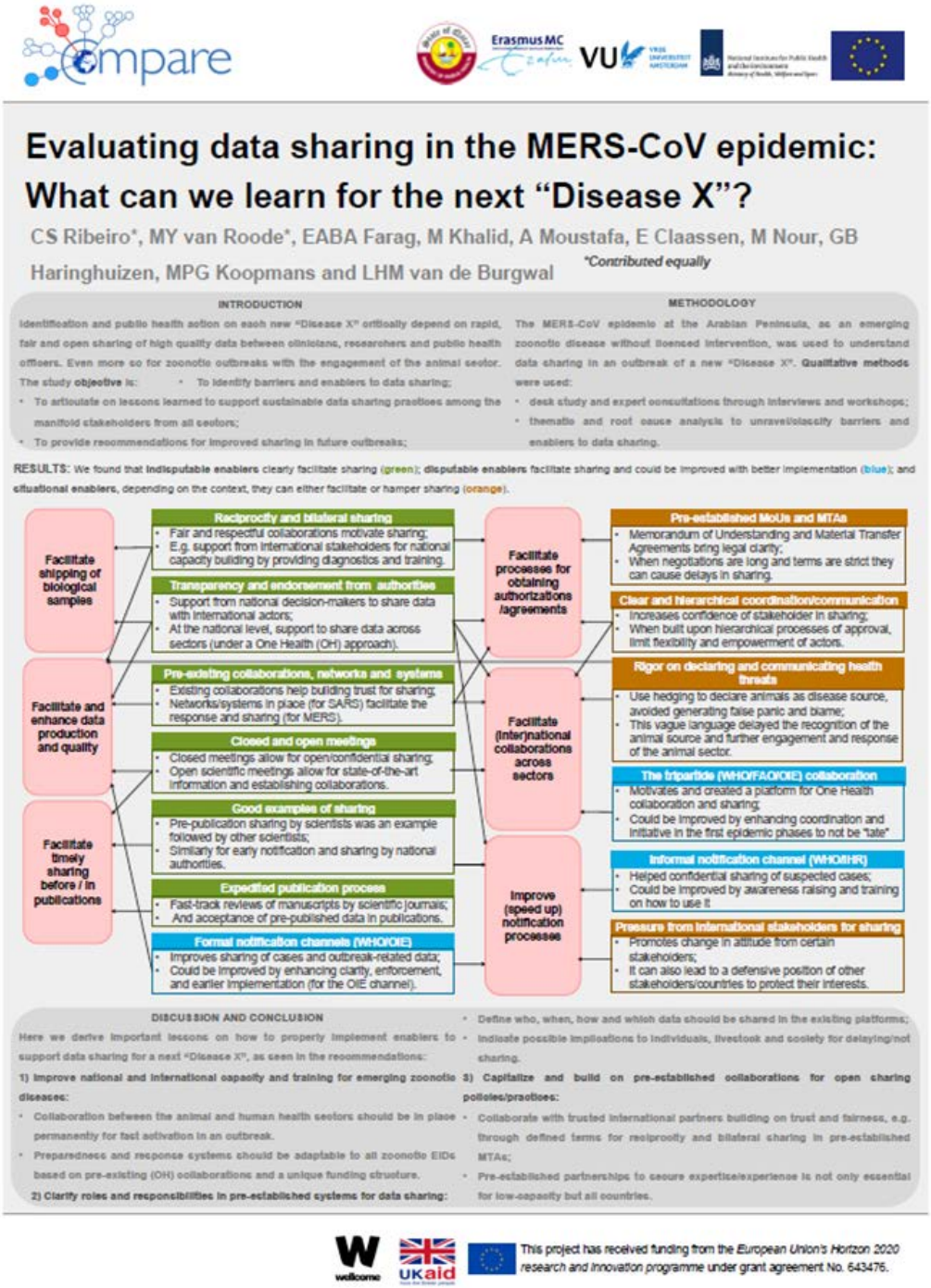


Figure 9. Scientific Poster focused on the critical evaluation of enablers that can motivate and facilitate data sharing during outbreaks and epidemics. This study was funded by the Wellcome Trust and the GloPID-R, and it is a collaboration between RIVM, EMC, Vrije Univeristeit Amsterdam, and the Qatari Ministry of Public Health.

Finally, for the Young and COMPARE annual meetings, WP12 prepared a scientific poster, oral presentation and workshop, which were presented. The scientific poster (see Figure 9) and oral presentation for the Young COMPARE meeting described an evaluation study performed as a collaboration between RIVM, EMC, VU

Amsterdam, and the Qatari Ministry of Public Health; funded by the Wellcome Trust and the GloPID-R. This study aimed to evaluate data sharing practices during the MERS-CoV epidemic in the Arabian Peninsula. In the poster and presentation, we focused on the identified enablers that can motivate and facilitate data sharing in times of epidemics and outbreaks. We critically evaluated their level of contribution to data sharing, and finally we elaborated on how such enablers can be translated in recommendations for improving data sharing in futures epidemics. In the workshop performed during the COMPARE annual meeting, on the last day (1st March 2019), firstly an overview of the activities performed under WP12 with the accomplished tasks were presented. Secondly, the overall framework for the construction of the WP12 Deliverable 12.2 was proposed to the participants. Finally, the content of the Deliverable was translated into two case studies that were presented and discussed highlighting the issues of: 1) the form of possible non-monetary benefits in collaborations within the COMPARE platform; and 2) the dilemma of trustworthiness in data and materials sharing in the eye of the world, considerations for commercial use, and the ambition of open domain/open access and their implications.

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. There are three e-learning courses available from the COMPARE website currently:

- Whole genome sequencing of bacterial genomes - tools and applications
- Metagenomics applied to surveillance of pathogens and antimicrobial resistance
- Antimicrobial resistance - theory and methods

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 180 research articles that acknowledge COMPARE support (https://www.compare-europe.eu/library/scientific-publications).

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

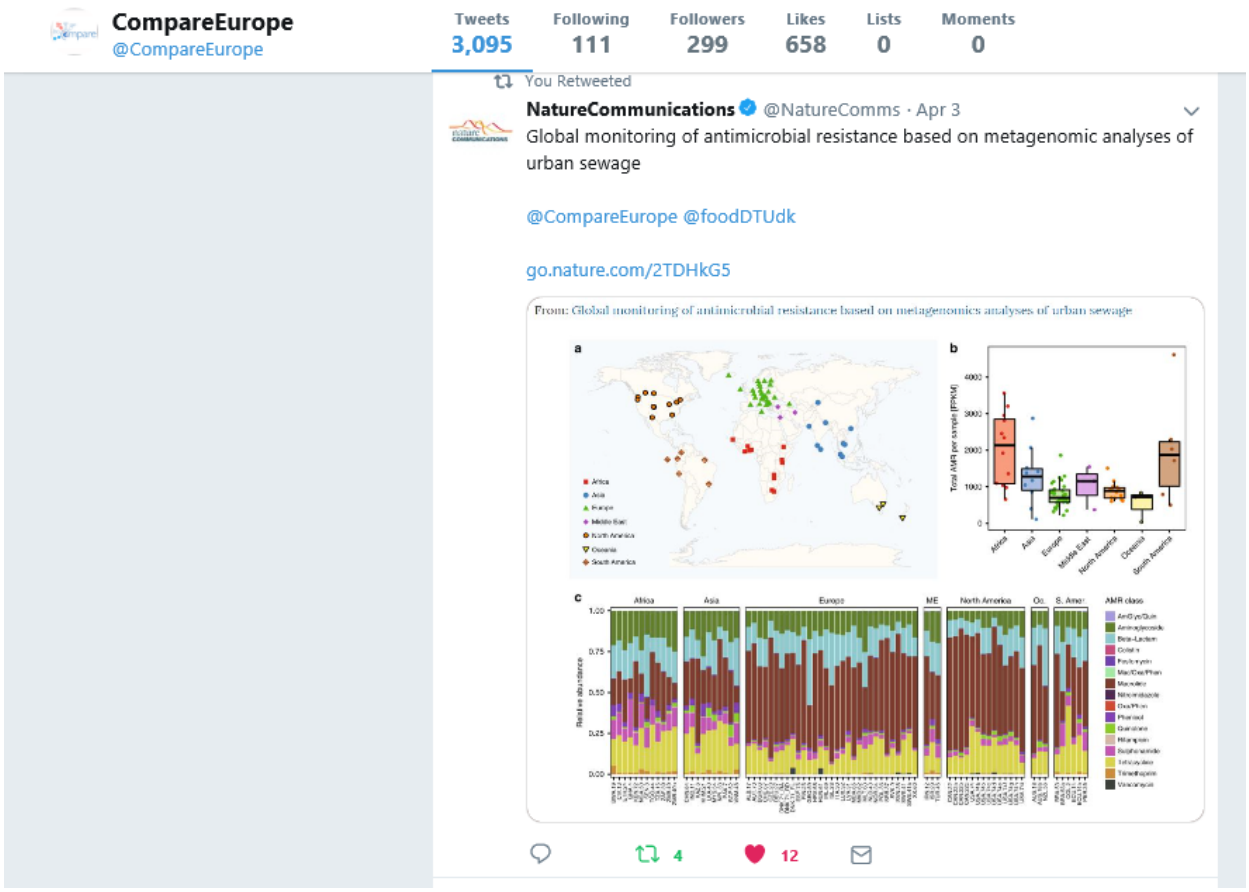


Figure 10. COMPARE Tweets. Twitter account (@CompareEurope)

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.

Between September 2018 and February 2019, WP14 has been conducting cost-effectiveness case studies in a final round of four countries (Argentina, Canada, Netherlands, USA) and analysing the results of all eight case studies conducted so far (Germany, Italy, UK (x2), and the four countries listed above). We have developed the methodology for a break-even analysis that estimates the number of cases of infection that would need to be prevented in order to 'break even' on the additional costs of WGS from a public health perspective, using the case of Salmonella. We are in the process of drafting the cross-cutting report which brings together the results of all cost-effectiveness case studies. This work is relevant for the fulfillment of Task 5 (Estimating the cost of COMPARE and related methods and tools using case studies).

WP14 has also been busy developing methods to estimate future costs that may result from increasing life expectancy due to successful prevention of disease outbreaks. Results suggests that previous studies have overestimated such costs because of neglecting economies of scales within households. Follow-up studies using case studies will explore the impact of including future costs on the cost effectiveness of interventions aimed to prevent or mitigate disease outbreaks. This work is relevant for Task 2 (Identify and where necessary develop state-of-the art costing methodologies for the different elements in the framework). We have also started working on our last deliverable in which is relevant for Task 6 (Assess options for refining selected elements of COMPARE in view of improving the overall cost-effectiveness of the system). Here, we will think more broadly on how to evaluate health system interventions such as a COMPARE like platform. Furthermore, we will elaborate on how value of information analyses can be used to prioritize investments in disease surveillance systems. Finally, in this deliverable, we will discuss how methods of financing may influence the cost-effectiveness of COMPARE.

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.

An Amendment to the Grant Agreement was accepted by the EC regarding the work from Workpackage 5/8 and the gain of function activities.

A new pilot study involving the food industry is being negotiated and will start before summer 2019.

The Consortium continues to submit deliverables. The COMPARE public website maintains a list of those Deliverables accepted by the EC and available for public dissemination.

The COMPARE General Meeting 2019 was held from 27 February – 1 March 2019. It was held at the Technical University of Denmark campus with more than 100 participants in attendance. The Young COMPARE research event was held 26 February 2019. There were 23 posters presented.

COMPARE Partners