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Meeting report

Symposium report: One Health meets sequencing

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According to the World Health Organization (WHO), One Health is an approach to design and implement programs, policies, legislations, and research in which multiple aspects of the interactions of humans, animals, food, and the environment are interconnected (https://www.who.int/features/qa/one-health/en/). These aspects have a particular relevance for food safety, control of zoonoses and antibiotic resistance [1–3]. Many microbes can infect or colonize various compartments forming a complex interplay between humans, animals and the environment [4]. Efforts focusing on a single aspect cannot prevent or eliminate the problem. Information sharing is key and multiple examples exist show-casing this e.g. drug-resistant bacteria can be transmitted through direct contact between animals and humans or through the food chain. In order to effectively detect, respond to, and prevent transmission events, zoonoses and food safety issues, epidemiological and laboratory/microbiological data have to be shared across stakeholders. Experts in the fields of microbiology, epidemiology, infectious diseases, veterinary, and public health should form local, national, regional and global networks to link the responses of these highly important public health threats.

A key element in approaching the challenges of One Health includes generating high resolution spatio-temporal data on pathogens together with genomic relatedness of pathogens [5]. Whole genome sequencing (WGS) has become the new gold standard for typing and further characterizing of pathogens. WGS enables understanding transmission chains of bacteria, exchange of mobile genetic elements, and variation in viruses with the highest resolution. In the near future national and international databases will allow tracking pathogen transmissions based on WGS data in and across complex settings such as humans, animals, food, water and other environmental sources [6–10].

1. Participants

The symposium attracted more than 90 participants and faculty members with a key interest in the fields of One Health and WGS. The one-day symposium was held on the 21st of May 2019 in Lucerne, Switzerland, and covered a broad diversity of topics in four

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sessions: (i) perspectives on WGS, (ii) ethics, data protection, and data sharing, (iii) foodborne pathogens, and (iv) transmissions from animals and the environment to humans. Finally, in a round table discussion the requirements and next important steps for "One Health and sequencing" were addressed. These topics and aspects were covered by leading experts in their field of One Health, public health, epidemiology, microbiology, infectious diseases, and ethics. The workshop was organized and hosted by the Clinical Bacteriology and Mycology of the University Hospital Basel (Dr. Adrian Egli), Clinical Bacteriology of the University Hospital Geneva (Prof. Jacques Schrenzel), and the Institute for Food Safety and -Hygiene of the University of Zurich (Prof. Roger Stephan). The symposium was sponsored by the National Research Program 72 (www.nrp72.ch/en). During breaks, there were opportunities for networking and fruitful discussions about new ideas and innovative past and future studies in the field of "One Health".

2. Session I: perspectives on whole genome sequencing

In the first session of the symposium, perspectives from regulatory federal offices (Federal Office of Public Health and Federal Food Safety and Veterinary Office) were summarized and discussed by Dr. Koch and Dr. Danuser. Key points included the mindful usage of new technologies, involvement and interactions with reference laboratories. In the keynote lecture Prof. Hendriksen addressed the global connection of animals, food, environment, and humans. He showcased the power of metagenomic approaches in sewage samples.

2.1. Federal Food Safety and Veterinary Office FSVO (Jürg Danuser)

The nucleus of One Health is an integrative collaboration of human and veterinary medicine. Today not only physicians and vets are One Health agents, but experts from agriculture, food, environment and other disciplines as well. One Health implies an agreement between sectors on super ordinated goals and on measures to be taken. Using a One Health approach, we aim to generate additional value in terms of better health of humans and animals, in terms of saving resources and in terms of a positive impact on the environment. Zoonoses, vector borne diseases, antimicrobial resistance are main One Health issues. With the Epidemic act [11] a coordinating platform was established, the so-called subsidiary body One Health. It coordinates the cooperation of the concerned sectors in the confederation and the cantons. As sequencing is a key technology to characterize public and animal health threads it suits well to the One Health approach.

In the competence of the FSVO sequencing plays or will play an important role in controlling foodborne diseases, in monitoring of antimicrobial resistance in food and healthy food producing animals, and in eradication of epizootic diseases. Introducing WGS should be coordinated among the stakeholders in different sectors and with respect to European standards.

2.2. Usage of WGS to address One Health challenges (Rene S. Hendriksen)

The dynamics of common infectious diseases are changing with the world heading towards an era of emerging and re-emerging infectious diseases where antimicrobial resistance threatens the very core of modern medicine and the sustainability of an effective, global public health response. Due to the complexity of the problems, there is a need for a harmonized and immediate action setting up surveillance.

From a surveillance point of view, sewage as well as animal wastewater are attractive matrices because it combines material from a large and mostly healthy population, which would otherwise not be feasible to monitor. Metagenomic sequencing of sewage and wastewater as well as quantification of antimicrobial resistance genes and residues combined with epidemiological data is a possible way to determine the occurrence and burden of resistance in defined healthy populations.

Recent developments in high-throughput sequencing offer the ability to rapidly identify nucleic acids from various organisms in clinical and environmental samples and provide a much broader resolution than offered by current methodologies. Thus, we launched a Global Sewage Surveillance study, collecting urban sewage from 77 cities across 63 countries including all inhabited continents. Our findings suggest that global AMR gene diversity and abundance vary by region and are caused by national circumstances. Improving sanitation and health could potentially limit the global burden of antimicrobial resistance [8].

3. Session II: ethics, data protection and data sharing

In the second session of the symposium, various aspects of data collection, data sharing, and data protection were discussed. Platforms and incentives to share sequence and epidemiological data were discussed by Dr. Egli and Prof. Neher. Basic and practical aspects of data protection and sharing were discussed by Dr. Coman Schmid. The legal and ethical framework in Switzerland was discussed by Dr. Driessen.

3.1. Overview on a Swiss pathogen surveillance platform (Adrian Egli)

Multidrug resistant (MDR) bacteria are one of the most urgent public health threats for our society. The spread of MDR bacteria can be described and analyzed using high-resolution molecular typing technologies, such as WGS. WGS data can be fused with spatiotemporal epidemiological and demographic patterns thereby allowing explain transmission events and outbreaks at different scales [12,13]. However, the data from human, animal, food, and the environment are fairly complex and often not structured. Interoperable and curated epidemiological metadata is a key requirement to fully understand the "One Health" complexity. In addition, high quality sequence data is crucial for epidemiological applications. We aim to build a Swiss wide Surveillance platform to enable the collection, storage, analysis and interpretation of "classical" epidemiological data together with molecular epidemiological data based on WGS from pathogens [5]. The development of the platform is funded by the NRP72 from 2018 to 2020 (www.nrp72.ch) and we have achieved to develop a first prototype which was introduced (www.spsp.ch). The platform has a state-of-the-art backend bioinformatics and frontend visualization tools including phylogenies, maps and various project management features. After the proof of concept with methicillin resistant *Staphylococcus aureus*, the idea is to expand the platform to a broad spectrum of pathogens and antibiotic resistant bacteria, including food- and water-born bacteria and many other pathogens.

3.2. Ethical and legal requirements for surveillance (Susanne Driessen)

The presentation focused on basic ethical concepts including deontology and teleology/utilitarianism and links them to the four bioethical principles beneficence, non-maleficence, justice, and autonomy. Social benefit, scientific validity, a favorable risk benefit ratio, as well as an informed consent are additional key ethical requirements for human research. The basis with the Human Research Act (HRA; www.swissethics.ch [14]) provides the legal

framework in Switzerland whenever research with persons or projects involving further use of health-related data or biological material is done. The purpose of the HRA is the protection of dignity, privacy and health of the individuals within research. The main focus for the One Health approach is the demarcation of surveillance and bacterial genetics within the HRA: WGS in bacterial genetics *per se* does not fall under the scope of the HRA. However, whenever there is a linkage to coded health-related data the HRA applies and consent of the individuals is foreseen. Specific consent versus general consent apply depending on the hierarchism of coding versus anonymization and the implication of genetic versus non-genetic data. Finally, ongoing efforts regarding the implementation of ethical frameworks in the One Health approach were discussed.

3.3. Data protection of medical data (Diana Coman Schmid)

Research biomedical data from patients is sensitive personal data (also referred to as confidential data) and it requires special data and computing infrastructure services that blend three major concepts: a) *security and compliance*, to protect the research subjects' privacy, b) *scalability and performance* and c) *flexibility and usability*, to foster cutting-edge biomedical research.

Leonhard Med (https://sis.id.ethz.ch/), operated by the Scientific IT Services of ETH Zurich is one of the first such infrastructures being developed in Switzerland. Built as a security by design infrastructure, Leonhard Med is a high-performance research platform to securely store, manage, compute on and share confidential research data and support data driven biomedical research at ETH and at national level, as part of the emerging national BioMedIT network supporting projects in the Swiss Personalized Health Network (SPHN; www.sphn.ch).

Using secure IT infrastructures when working with confidential data requires awareness of data privacy, respective laws, and information security. When to use such secure infrastructures? Whenever the research data is confidential. Research data may classify as confidential (based on the SPHN IT Security Policy [15] and on the Leonhard Med Acceptable Use Policy) if: (i) it is sensitive personal data (Federal Act on Data Protection, FADP Art. 3c [16]), for example health-related or medical data, (ii) it is either identifying (directly or indirectly) or pseudonymized (i.e., real name replaced by a code), or (iii) more generally, it is information that is specific to a limited, explicitly defined group of recipients. However, data classification is not always straightforward. Given the potential of re-identification [17] should the human gut microbiome data classify as confidential even though only bacterial species information is contained?

In the dynamic fields of Precision Medicine, Personalized Health and One Health, controlled and secure handling and sharing of confidential data, according to the FAIR principles (Findable Accessible Interoperable Re-usable), must be embraced for facilitating scientific advancement. For this, the pioneering work on building secure research platforms and developing security awareness training programs should continue in the collaborative academic, medical, ELSI and IT ecosystem.

3.4. Incentives for WGS data sharing (Richard Neher)

Detecting outbreaks and transmission clusters requires dense sampling and the ability to integrate data from different stakeholders. For such detection of transmission to have impact, it needs to be timely.

Universal and rapid data sharing of epidemiological and pathogen genomic data is therefore imperative. Balancing this need with privacy concerns and the particular interests of scientists and institutions has been a recurring struggle in past outbreaks of viruses like the West African Ebola virus outbreak [18,19]. Some communities such as the GenomeTrakr network [20] or the Global Influenza Response and Surveillance System [21] have successfully established data sharing mechanisms, while other communities remain fragmented. Such fragmentation hampers our ability to combat transmission. The emphasis should be on near universal open sharing of genome sequences, with meta data restricted where necessary. Tools and platforms that facilitate tracking of transmission and integrate data can provide important incentives for data sharing.

4. Session III: foodborne pathogens

In the third session various examples of foodborne pathogen transmission were discussed. Dr. Mäusezahl provided an overview on foodborne pathogens in Switzerland – highlighting the dynamic changes and the challenges in streamlining the notification process. This was followed by presentations focusing on *Campylobacter* spp. and *Salmonella* spp. – the two most common bacterial pathogens associated with gastrointestinal infections in Switzerland by Dr. Seth-Smith and Dr. Bloemberg. Finally, Prof. Tschudin reported on the spread of ESBL-producing *Enterobacteriaceae* and a NRP72 funded project aiming to understand the complex transmission dynamics.

4.1. Foodborne pathogens in Switzerland (Mirjam Mäusezahl)

The surveillance and control of foodborne pathogens is a classic One Health topic where interdisciplinary collaboration is key for success. The surveillance objectives for foodborne diseases in Switzerland are the early detection and investigation of outbreaks to identify sources of infection and prevent new infections as well as the analysis of long-term trends to assess food safety measures put in place. Notifications of foodborne diseases in humans are increasing for some pathogens such as *Listeria* spp., *Campylobacter* spp. and Shigatoxin-producing *Escherichia coli* (STEC) and stay at a long-term high level for others such as *Campylobacter* spp. However, it must be kept in mind that notified cases only represent the tip of the surveillance pyramid. In addition, the risk for large cross-border outbreaks increases due to the increasingly globalized food production and distribution chains. There is a multitude of players involved in outbreak investigation and management at the national as well as cantonal level and three different legislative acts (Federal Act on Epidemics, Foodstuffs and Utility, and Animal epidemics [11,22,23]) build the basis of all activities. While classical outbreak investigation involves patient interviewing paired with pathogen identification and comparison of human and food samples at the reference laboratory level, WGS enhances microbiological resolution and the level of “evidence” in case of a match. The main challenges remain to streamline notification processes and the matching of isolates between the human and foodstuff sector including creating the legal framework and to use WGS wisely, as costs are still relatively high.

4.2. Campylobacter *spp. always from chicken to men? (Helena MB Seth-Smith)*

Campylobacter causes a high burden of disease and cost in Switzerland, and globally [24,25]. The species *Campylobacter jejuni* and *Campylobacter coli* are responsible for the majority of cases. Cross contamination on kitchen level is thought to be the main reason for infection, with Multi-Locus Sequence Typing (MLST) attributing raw chicken as a source in 57–78% of cases [26–30]. Our study has collected isolates from patients in Basel over four years,

analyzing whole genome sequences and comparing them to those from potential infection sources: local shop-bought raw chicken, frozen meat for "fondue chinoise" (broth fondue), river water, pets, raw milk, and livestock. Our preliminary analysis of 685 genomes, from patients and chicken meat from 2015–2018, shows a large diversity of isolates across 24 clonal complexes. We are most interested in transmission clusters, i.e. patient isolates, which are closely related to those from chicken meat. To identify these, we used a hierarchical approach, first clustering isolates using core genome MLST ([31]; https://pubmlst.org/campylobacter/), then looking within these clusters using a whole genome single nucleotide polymorphism (SNP) approach. Using a SNP cutoff of 12, which was determined as encompassing the vast majority of cases and representing a plausible mutation rate across three years, we can identify 20 transmission clusters including only 14% of cases. This preliminary work indicates that whole genome studies provide a much higher resolution than those using MLST, and that there remain alternative, as yet unidentified infection sources, potentially responsible for up to 86% of campylobacter cases.

4.3. Outbreak investigation of Salmonella *spp. in Switzerland (Guido Bloemberg)*

In Switzerland, approximately 1500 human cases of salmonellosis are annually reported to the Federal Office of Human Health [32]. *Salmonella* is usually transmitted to humans through contaminated food or water. Recognition of outbreaks is highly relevant for source identification and effective containment (incl. product recalls). Up to 2018, *Salmonella* outbreaks were monitored using PFGE analysis of suspicious outbreak isolates. During 2018, WGS, as most discriminative typing tool, was implemented for *Salmonella* outbreak analyses. Meanwhile, several *Salmonella* outbreaks have been discovered, are being monitored or/and were solved by WGS analysis. In the presentation five examples of *Salmonella* outbreak analyses were presented. Two small outbreaks of *S.* Typhi (family outbreak after visiting Bangladesh) and *S.* Paratyphi B var. Java (4 patients) were identified in 2018 and 2019, respectively. Furthermore, *S.* Enteritidis cases identified during July–September 2018 were systematically analyzed by WGS in order to analyze the clonality of the isolates. The results showed a large diversity of *S.* Enteritidis strains with only a few small outbreaks and travel as main risk factor. Lastly, we are monitoring two ongoing outbreaks of *S.* München (38 patients) and *S.* Derby (20 patients) occurring since December 2018 and January 2019, respectively.

4.4. Transmission of ESBL-producing E. coli *in Basel (Sarah Tschudin-Sutter)*

Community reservoirs have been suggested as being an important driver for the rapid emergence and spread of ESBL-producing *E. coli*. The food chain may represent a potential community-source with over 90% of chicken meat being contaminated with ESBL-producing *E. coli* [33,34] and almost 20% of healthy Swiss fattening pigs are shedding ESBL-producing *E. coli* [35]. 39% of ESBL-producing isolates detected in retail meat samples belonged to *E. coli* genotypes also present in human samples suggesting transmission [34]. ESBL-producing *E. coli* has been identified on 12% of cutting boards and 50% of gloves after poultry preparation, pointing to a potential transmission-pathway [36]. Both human and animal intestinal carriage of ESBL-producing *Enterobacteriaceae* result in their release into the wastewater system. ESBL-producing *E. coli* have been recently identified in almost all environmental samples collected throughout a wastewater network in France, with treatment at the wastewater plant resulting in a relative enrichment of ESBL-producing *E. coli* in the sludge, which is consecutively used as fertilizer [37] thereby accelerating further dissemination. In Basel, we are currently determining migration of ESBL-producing *Enterobacteriaceae* between humans and their environment (i.e. foodstuffs and wastewater samples) by comparing genetic relatedness of strains recovered from patients and the environment as part of a NRP72 research project (http://www.nfp72.ch/) [38].

5. Session IV: transmissions from the environmental and animals to humans

In the fourth session various examples of environmental and zoonotic pathogen transmission were discussed. First, Prof. Endimiani reported on the current situation of Carbapenem resistant *Enterobacteriaceae* and a NRP72 project, which aims to understand the transmission dynamics of Carbapenemase-producing *Enterobacteriaceae*. Then, Prof. Perreten reported on increasing cases of Carbapenemase-producing *Enterobacteriaceae* found in pets. Next, Prof. Schrenzel focused on new technologies – using metagenomic approaches – and showcased the impact of this technology in three cases from clinics. Finally, Prof. Greub reported on the genomics of *Chlamydia*-related bacteria.

5.1. Carbapenemase-producing Enterobacteriaceae *in humans (Andrea Endimiani)*

The prevalence of carbapenem-resistant *Klebsiella pneumoniae* and *E. coli* strains in Europe reached 7.2% and 0.1%, respectively; however, only 50–60% of them produce carbapenemases (CPE). Most of the CPE responsible for community-onset infection are actually health-care associated. This phenomenon may contribute to the expansion of CPE in the community. In Switzerland, 1.8% of the human *K. pneumoniae* isolates are carbapenem resistant. Until 2018, CPE were not reported in pets, wild/food animals, and retailed meat. Moreover, CPE were not isolated in healthy people, but sporadic strains were reported in returning travelers, rivers/lakes, and imported vegetables.

During the first year of our NRP72 project, we analyzed 29 carbapenem-resistant *Enterobacteriaceae* of human origin using WGS. Strains were from hospital and community settings and causing infection or colonization. Of particular interest is the finding that veterinary clinic employees can be colonized at gut level with the same CPE (OXA-181-producing *E. coli* ST410) responsible for an outbreak among hospitalized pets. Moreover, at national level OXA-181 producers are increasing; therefore, an accurate WGS analysis is ongoing for different species carrying such resistance gene. The final aim of our work is to analyze the exchange of MDR organisms and/or plasmids among the different human and non-human settings.

5.2. Carbapenemase-producing Enterobacteriaceae *in animals (Vincent Perreten)*

Carbapenems are not used in food-producing animals in Switzerland. However, these last-line antibiotics of human medicine may be used in companion animals for the treatment of infections refractory to any other antibiotics used in veterinary medicine (Ordinance on Veterinary Medicinal Products, SR 812.212.27, Art. 6, [39]). NGS used during a surveillance project financed by the Swiss Federal Food Safety and Veterinary Office [FSVO Grant no. 1.18.10][a] revealed the presence of a nosocomial clone of *E. coli* containing a plasmid-mediated carbapenemase. Additionally, cases of infections caused by carbapenemase-producing *K. pneumoniae* have also emerged in our country in

companion animals. Although NGS allowed the identification of specific carbapenemase-producing clones, further additional molecular epidemiology studies are now necessary to determine the link between the carbapenemase-producing *Enterobacteriaceae* from companion animals and those from humans. Nevertheless, infection control and monitoring of carbapenemase-producing *Enterobacteriaceae* should be introduced in veterinary settings.

[a]FSVO project no. 1.18.10 (Simone Schuller, Department of Clinical Veterinary Medicine, University of Bern, Bern, Switzerland; Barbara Willi, Clinic for Small Animal Internal Medicine, University of Zurich, Zurich, Switzerland; Stefan Kuster, Division of Infectious Diseases and Hospital Epidemiology, University and University Hospital of Zurich, Faculty of Medicine, Zurich, Switzerland; Andrea Endimiani, Institute for Infectious Diseases, University of Bern, Bern, Switzerland; Stefanie Gobeli and Vincent Perreten, Institute of Veterinary Bacteriology, University of Bern, Bern, Switzerland).

5.3. Unusual zoonoses: the contribution of NGS (Jacques Schrenzel)

In some instances, the infectious source of severely infected patients remains unknown, prompting the physician to perform numerous tests, including radiological investigations. We report two such cases: the first one was a bacteremia due to an unusual *Capnocytophaga canis*, most likely transmitted from the patient's cat. Genomics revealed that this bacterium was distantly related to *Capnocytophaga canimorsus*, and hence could not be detected by MALDI-TOF MS. The second case was a septic shock with multiple organ failure due to *Streptococcus suis*. Genomic analysis revealed that the strain was markedly different from those recovered from Swiss pigs. The history of the patient ultimately revealed that she had eaten raw pork imported from Moldavia, two days before admission. The last case, analyzed by our metagenomic platform showed a prosthetic aortic infection due to *Mycobacterium chelonae*, an organism that could not be detected by conventional cultures nor by broad-range 16S rDNA PCR. The origin of the infectious organism and its relationship with the bovine aortic prosthesis are currently under investigation. Overall, these three cases illustrate various usages of genomics and clinical metagenomics to uncover bacterial causes of some infections and provide molecular hints to explain their acquisition.

5.4. Genomics of chlamydia-related bacteria (Gilbert Greub)

In the last talk of the day, Prof Greub (Lausanne) presented the lessons gathered from 20 years of genomics of chlamydia and chlamydia-related bacteria. Chlamydia are important zoonotic and veterinary pathogens. Indeed, although *Chlamydia trachomatis* – the most studied member of the Chlamydiales order – is sexually transmitted from human to human, *Chlamydia psittaci* is a well-established pathogen transmitted from birds to humans, which has recently been identified in horses as well [40]. *Chlamydia abortus*, a major cause of abortion in sheep and goats – has been shown to cause miscarriage in humans exposed to infected cattles. Thus, genomics may be pivotal to track outbreaks and to define the virulome and resistome of chlamydiae. The Greub's talk however showed that genomics may go behind typing, virulome and resistome analyses, providing insight on the evolution, biology and biodiversity of chlamydia-related bacteria. The metagenomics data that have been recently released demonstrates the huge biodiversity of Chlamydiales bacteria [41]. This biodiversity reflects the variety of ecological niches, which include amoebae (e.g. *Parachlamydia, Criblamydia, Estrella*), mammals (e.g. *Chlamydia felis, Chlamydia abortus*, *Waddlia*), fish (e.g. *Clavochlamydiaceae, Piscichlamydiaceae*), birds (e.g. *C. psitacci, C. ibidis*), reptiles (e.g. Parachlamydia), and arthropods (e.g. *Rhabdochlamydiaceae*). The latter family infects ticks with very high burden, suggesting a high transmission risk. Genomics of all these new clades led to identify interesting features, not present in *C. trachomatis*, including a CRISPR system (in *Protochlamydia neagleriophila*), large number of transposases (especially in *Waddlia*) and a DNA conjugative transfer system (in various chlamydia-related bacteria) demonstrating the high genetic plasticity of chlamydial genomes. Genomics of chlamydia-related bacteria also highlighted the conservation among all Chlamydiales of some virulence factors, involved in cell host corruption (e.g. T3SS system, CPAF) and the presence of specific virulence factors such as catalases in some species, likely implicated in the survival of these strict intracellular bacteria to the superoxydes produced by amoebae and macrophages.

6. Discussions and conclusions

The symposium brought together “One Health” leaders from Switzerland representing various backgrounds including federal offices with public health experts, legal and ethical experts, microbiologists, infectious disease specialists, and epidemiologists. Next generation sequencing technologies were broadly discussed along with concrete cases from clinics and applied and basic research showing the potential to gain a more profound understanding of transmission routes between humans, animals, food, and the environment.

Although new sequencing technologies and applications such as metagenomics rapidly move forward in research, the usage of these technologies for public health aspects was still somewhat controversial discussed in the presence of all stakeholders. Without doubt, today WGS provides the highest possible resolution for typing pathogens for either surveillance or single outbreak investigations. However, the usage of the technology in public health and routine diagnostics is still associated with high costs and requires specific trained experts such as bioinformaticians, for proper data interpretation. In addition, the full potential of the technology is not yet used: while comparison of pathogens is standard, information on resistance genes and virulence factors is often not generated due to lack of curated and standardized databases. Finally, the gain of resolution using WGS can provide “unexpected” results, where certain isolates may appear connected (or unconnected) supporting or refuting classical epidemiological typing. This raises the question of how to best combine whole genome sequencing data with data on epidemiological observations to draw meaningful conclusions regarding the dissemination and spread of target pathogens – maybe even allowing to establish causal inference. These discussions underline our recent exposure to these new technologies, while our background remains tightly linked to classical epidemiological tools. The expectation on what sequencing should deliver in the near future and how such results might impact public health actions somewhat vary between federal institutions and the diagnostic community. The discussions highlighted two possible scenarios for epidemiological analysis:

(i) Use of WGS to confirm an outbreak. A (pre-)selected group of isolates with available classical epidemiological data e.g. symptoms, exposure, time and space association of isolates etc. are analyzed retrospectively using a high-resolution method. Such very targeted usage and potential batch-wise sequencing analyses provide a high cost-efficiency. However, non-outbreak associated controls are also important in outbreak investigations, allowing to make comparison to groups and allow to calculate odds ratios, which remain the main factor of causal inference. The obvious disadvantage is the introduction of a clear bias due to the selection of cases, which may hinder broader conclusion on the “big picture”.

Whereas in a potential nosocomial cluster investigation e.g. based on similar antibiotic resistance profiles, WGS typing can be rapidly introduced, in other public health settings a delay in producing sequencing may results may be introduced due to a more complex reporting between various institutions.

(ii) Use of WGS as a real-time surveillance tool. Isolates are sequenced immediately, in a less biased way, and directly grouped based on genomic similarities. Based on molecular evidence, a detailed classical epidemiological investigation may be triggered. This approach may be particular useful when unsuspected molecular epidemiological links are discovered and are then followed up using classical epidemiological approaches. This strategy may result in significant faster responses for the identification of connected cases. However, at least for the coming years, this approach incurs higher costs as many more isolates would need to be sequenced.

Both approaches have obvious advantages and disadvantages, which need to be further explored with investigations on specific scenarios and pathogens. For our community, it is therefore crucial to learn from these new technologies, not only in tightly controlled experimental research conditions, but also in the real-world of public health. Both approaches need to be explored and tested in different scenarios and order to define the specific advantages. Independently of which approach is preferred, the distribution of molecular and epidemiological information to laboratories, policy makers, and public health experts is essential.

Data access and sharing, especially of demographic and epidemiological data, is often critical in order to use the synergistic potential of classical and molecular epidemiology. In this regard, regulations, legal and ethical considerations were discussed. The experts agreed that public health questions may be complex and sometimes there are overlaps between public health and research objectives. In order to understand the impact of a new technology, data has to be analyzed using state-of-the-art research methodologies. Public health investigations benefit from timely reporting and dissemination of results – classically this is performed on data from mandatory notification (high sensitivity, but low specificity for an outbreak) – however given current technological advances sequencing information is now expected to provide highly specific data. Molecular surveillance also provides a high sensitivity in contrast to targeted outbreak investigation. Pragmatic solutions should be developed for the sharing of classical and molecular epidemiology information by carefully addressing the special needs of the different stakeholders. The legal framework provides the basis for what information can be shared in which situation. The epidemic act provides the legal basis to share information at the governmental level (federal and cantonal) but not with the private sector, which induces a series of practical challenges for management of transmission events. In the case of an immediate public health threat e.g. a new pandemic influenza virus, the epidemiological act provides a more clear legal basis. Although also research can be performed under the epidemic act, the separation to the human research act has to be further discussed with legal and public health experts. Whereas in the case of a research related question, the Human Research Act constitutes the legal basis.

In summary, it became clear, that the various experts attending symposium are keen and highly motivated to further develop the concepts and knowledge on sequencing for public health and One Health. In a small country like Switzerland, the development of a molecular surveillance platform integrating the different needs and aspects of the identified stakeholders can be developed in as a research project and later scaled up to fit various needs with increasing complexity such as specific public health needs. The symposium clearly showed that the state-of-the-art infrastructure e.g. sequencing machines, computational clusters, the bioinformatic, legal and ethical expertise for a responsible usage of the technologies is in place. Several research projects showcased the feasibility and the potential impact, as well as the benefits for humans, animals and the environment. What is now needed is the willingness and the political support to fill the gaps and scale up.

Conflict of interest

None of the authors have a conflict of interest.

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