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Molecular surveillance of pathogens in Switzerland – Focus: SARS-CoV-2 and its variants

Currently, the BA.2 variant of SARS-CoV-2 dominates in Switzerland as it does in places around the globe. In recent months, circulating virus lineages have been widely monitored by sequencing the genomes of thousands of SARS-CoV-2 isolates. These efforts were coordinated by the National Reference Centre for Emerging Viral Infections (CRIVE) in Geneva. A total of 15 laboratories from diagnostics and research supported this and thus contributed significantly to the surveillance and risk assessment of viral evolution in Switzerland. The large quantities of sequencing data and associated metadata were centralized at the «Swiss Pathogen Surveillance Platform» (SPSP), where quality was checked, the sequences annotated, and finally transmitted to other databases. Data was visualized for example in the dashboard of the Federal Office of Public Health (FOPH) or using international comparisons via GISAID on platforms such as nextstrain.org. SPSP was developed together with the SIB Swiss Institute of Bioinformatics as a «One Health» focused platform to share genomes and associated metadata between institutions for surveillance and research. The project was initially funded by the National Research Programme (NRP72) of the Swiss National Science Foundation and has since been further developed.

Today, SPSP represents a key platform for the molecular monitoring of human, animal, and environmental pathogens (viruses, bacteria, fungi) in Switzerland and clearly passed the maturity test during the COVID19 pandemic. A key challenge now is to secure sustainable funding for SPSP and to motivate diagnostic and research laboratories to share sequence data via SPSP as an essential step in comprehensive «One Health» surveillance and outbreak monitoring of infectious diseases.

Monitoring of SARS-CoV-2 variants at national level

Yesterday Alpha and Delta, today Omicron, and tomorrow maybe Pi: SARS-CoV-2 rapidly evolves and adapts to selection pressures. Within the past two years, the surveillance of SARS-CoV-2 using whole genome sequencing of viral isolates has resulted in an unprecedented global program to tightly monitor the evolutionary steps. Also Swiss laboratories are on a daily lookout for new SARS-CoV-2 variants and their transmission chains. Sequencing of the viral genome makes it possible to identify the variant in question and its complete genetic profile with detection of single nucleotide polymorphisms at high spatiotemporal resolution. Indeed, early detection of new viral variants that are more contagious or lead to vaccine failure (immune escape) are critical for public health decisions and information of the general public. In addition, outbreaks and transmission patterns can also be studied in detail in order to adapt protective measures and to guide decisions regarding vaccine adaptation. Knowledge about variants also matters for the timely and targeted treatment of individual infected patients when using monoclonal antibodies or newly developed antivirals for therapy. In 2021, more than 100’000 SARS-CoV-2 viruses were sequenced and analyzed by 15 academic or private laboratories throughout Switzerland (Figure 1). However, sequencing data is only useful if it is linked and shared as quickly as possible – hence the essential need for coordination and standardization of sequencing programs. The sequencing effort in Switzerland was coordinated by the National Reference Centre for Emerging Viral Infections (CRIVE, Geneva) and funding was provided by the Federal Office of Public Health (FOPH). By April 2022, more than 135,000 genomes have been examined. Due to federal cost restrictions, the sequencing efforts were centralized in April 2022 over two scientific core facilities (H2030 in Geneva and ETH Zurich in Basel). Nevertheless, «diagnostic» sequencing, as an alternative to «surveillance» sequencing, may still be applied in certain cases by diagnostic laboratories to keep research expertise in place.

For harmonized, standardized analysis and rapid sharing of sequencing data, the «Swiss Pathogen Surveillance Platform» (www.spsp.ch) was established. This collaborative and secure infrastructure was originally developed by the SIB Swiss Institute of Bioinformatics together with the University Hospitals Basel, Geneva and Lausanne (CHUV) and the Universities of Basel, Bern and Zurich as a "One Health"-related platform between 2018 and 2020. The platform core development was funded by the National Research Programme 72 with a focus on antibiotic-resistant bacteria with methicillin-resistant Staphylococcus aureus (MRSA) as a proof of concept. However, during the SARS-CoV-2 pandemic, we rapidly adapted and optimized the data- and workflows of the platform for viral genomes including specific bioinformatic

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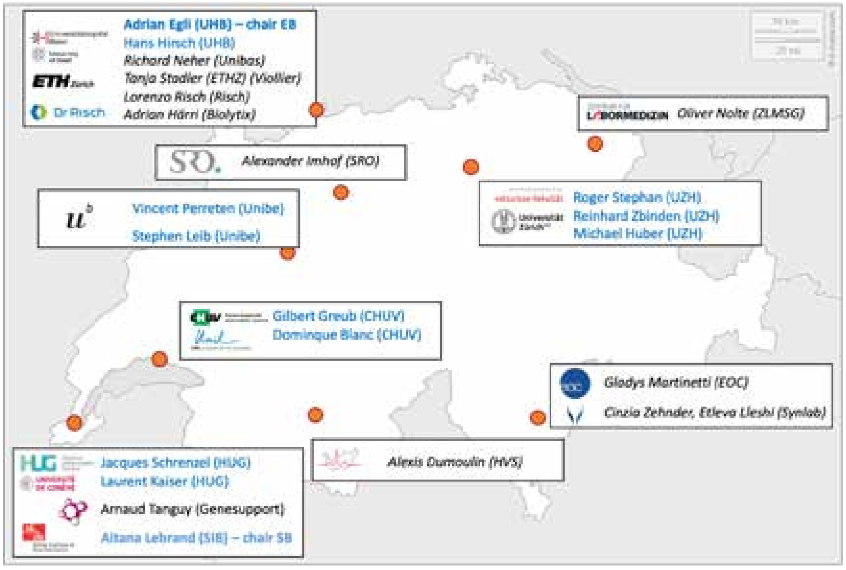

Figure 1: SARS-CoV-2 sequencing centers (until March 2022). Names in blue are members of the SPSP Executive Board.

tools. The SARS-CoV-2 genome sequences and the associated metadata such as laboratory and sample identifiers, date of PCR test, type of sample collection, reason for sequencing, sequencing machine used, sex and age of the patient are loaded onto SPSP in a secured and centralised way, harmonised, annotated and shared with the FOPH.

Accelerated surveillance of the epidemic in Switzerland

SPSP was adapted for SARS-CoV-2 surveillance at the beginning of 2021 and has been sending uniform reports on SARS-CoV-2 variants circulating in Switzerland to the FOPH since May 2021 as part of the national surveillance programme. Since the end of July 2021, all Swiss laboratories participating in the surveillance programme have been obliged to submit their SARS-CoV-2 sequences to SPSP (Figure 2). Thus, the data collected on SPSP today allow a comprehensive and representative overview of the circulating variants in Switzerland. Three times a week, the platform sends its genomic surveillance report to the FOPH. This notably allows the FOPH to have a precise picture of the variants circulating in Switzerland. The FOPH then integrates these data into statistics (https://www.covid19.admin.ch/en/overview) . The sequencing data can also be used by FOPH to match sequence data with available patient data on hospitalisations, vaccinations, symptoms at the time of the test, etc. In this way, FOPH could determine whether a variant or specific mutation is associated with higher pathogenicity or vaccine resistance among all observed mutations.

Thanks to this monitoring platform, the FOPH can access a centralized and standardized database via a single access point instead of receiving reports in different formats from each laboratory. This results in significant time and cost savings, as well as greater granularity in the analysis of sequencing data. We hope that the value and important advantages of SPSP is recognized and will be applied to other pathogens in the future, thereby better understanding the complex transmission routes of pathogens in humans, animals, the environment and the foodchain.

Boost international surveillance and research by facilitating Open Data

SPSP enables the central storage of virus sequences in Switzerland with rich and structured metadata that is very useful for research. As this is potentially sensitive data, SPSP is hosted on a highly secure infrastructure of a BioMedIT node, making this data available for research in an ethically and legally controlled framework. In addition, the SPSP platform also transfers anonymised viral data to the open data platform European COVID-19 portal (https://www.covid19dataportal.org/) and to GISAID to support global surveillance and research. Thanks to these

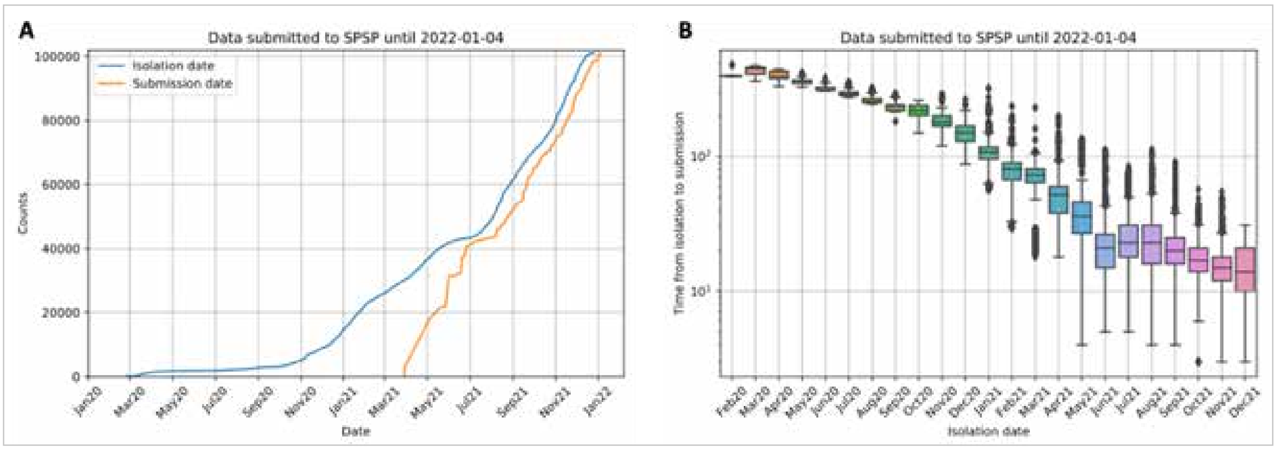

Figure 2: Data on SPSP in 2021. A. Available sequences. Blue, data depending on date of sampling; Orange, data depending on date of submission to SPSP (start-up in March 2021 for SARS-CoV-2). B. Turn-around times from acceptance to publication of sequence data.

efforts, Switzerland currently ranks fourth after the UK, the USA and Germany in terms of the absolute number of openly shared SARS-CoV-2 sequences (Table 1 and Figure 3). These public databases are essential for studying and understanding the role of observed variations on the pathogenicity of the virus, its interaction with host cells at the time of infection, or even for the development of vaccines and treatments.

Country	Sequences submitted	Raw sequences submitted
USA	2,077,366	1,396,278
United Kingdom	1,811,616	2,462,155
Germany	304,074	7,510
Switzerland	129,060	38,107
Denmark	41,834	753
Australia	26,589	15,889

Table 3. Statistics from the EU Covid-19 Data Portal – ranking by country. Reproduced from https://www.covid19dataportal.org/statistics

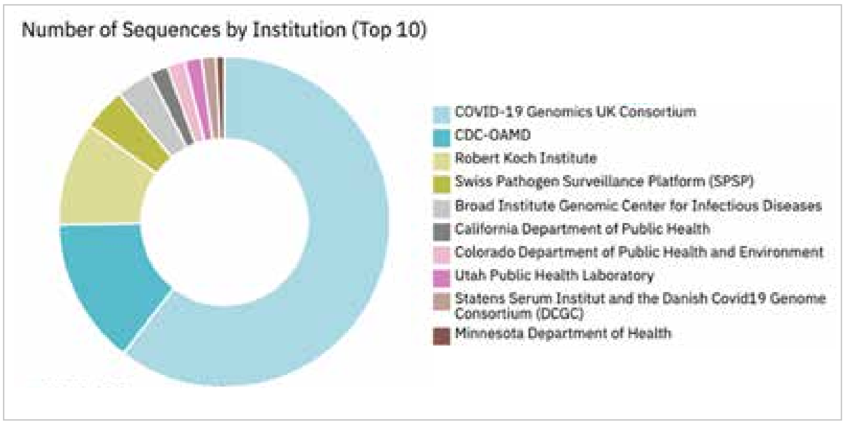

Figure 3. statistics from the EU Covid-19 Data Portal - ranking by institution. https://www.covid19dataportal.org/statistics

A secure platform and effective governance for future surveillance.

SPSP is a collaborative platform that follows the «One Health» approach, i.e. is multidisciplinary and aims, among other things, to explore and optimize human and animal health outcomes, but still meets the data security standards of the Swiss Personalized Health Network (SPHN). The Executive Executive Board of SPSP includes representatives from five universities and university hospitals as well as from SIB, and decides on important strategic decisions. There is also an Advisory and a Scientific Board with various stakeholders, including regulatory and scientific representatives, which allows rapid integration of new tools into the platform e.g. an automated cluster detector. SPSP can count on an efficient governance and clearly defined ethical and legal framework to quickly integrate new laboratories wishing to contribute to SPSP. Contracts for data exchange and sharing as open data were concluded with all centers. The FAIR principles of data including findability, accessibility, interoperability, and reusability are central values for SPSP.

After successfully testing the platform during the SARS-CoV-2 pandemic, we now look to expand surveillance with new pathogens and hope for sustained funding from federal agencies to optimize infectious disease surveillance between humans, animals,the environment and the foodchain and generate reliable data with regularity. More recent outbreaks like the Hepatitis E outbreak in 2021, the Salmonella outbreak of chocolate eggs before Eastern, or Listeria monocytogenes outbreaks are covered in the media and have an important impact on food safety and reputation of the food industry. Similar monitoring of Legionella pneumophila can be very important to link an environmental source with a severe pneumonia of a patient. Often sequencing data is lacking or not exchanged, which hinders clear conclusions. SPSP can close this important gap between different stakeholders involved in an outbreak investigation.

Our vision is that SPSP can be used by different specialists with highly customized analytical and visualization tools to quickly detect the emergence and spread of pathogens and take early action to contain transmission by tracking them in near real time. The data will also be made available to researchers to monitor the dynamics of diseases and measures such as vaccinations and antibiotics. The possibility of using SPSP in the long term to link genomic data of bacteria or viruses emerging in Switzerland with epidemiological data is promising for ensuring Switzerland's exemplary public health response capacity and providing patients with the most appropriate treatment.

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