UNIVERSITÄT
BERN

Graduate School for Cellular and Biomedical Sciences
University of Bern

Modeling transmission dynamics and human behavior during the SARS-CoV-2 epidemic in Switzerland

Doctoral thesis submitted by

Martina L Reichmuth

for the degree of

PhD in Biomedical Sciences

Supervisor
PD Christian L Althaus, PhD
Institute of Social and Preventive Medicine (ISPM)
Faculty of Medicine of the University of Bern

Co-advisor
Prof. Niel Hens, PhD
Interuniversity Institute for Biostatistics and statistical Bioinformatics, Data Science Institute
Faculty of Sciences, Hasselt University
Centre for Health Economics Research and Modelling Infectious Diseases, Vaccine and Infectious Disease Institute
Faculty of Medicine and Health Sciences, University of Antwerp

source: https://doi.org/10.48549/5351 | downloaded: 7.11.2024

This work is licensed under the Creative Commons Attribution 4.0 International license

Accepted by the Faculty of Medicine, the Faculty of Science and the Vetsuisse Faculty of the University of Bern at the request of the Graduate School for Cellular and Biomedical Sciences

Bern, Dean of the Faculty of Medicine

Bern, Dean of the Faculty of Science

Bern, Dean of the Vetsuisse Faculty Bern

"*A jack of all trades is a master of none, but oftentimes better than a master of one.*"

University of Bern - Faculty of Medicine - Institute of Social and Preventive Medicine (ISPM)

Abstract

Modeling transmission dynamics and human behavior during the SARS-CoV-2 epidemic in Switzerland

by Martina L Reichmuth

The coronavirus disease (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has posed an unprecedented threat to public health, the economy, and society at large. In response to mitigate the impact of SARS-CoV-2, Switzerland, in line with many other countries, implemented non-pharmaceutical interventions (NPIs) such as face masks and bans on gatherings. Later, vaccine and natural infection induced immunity in the population protect from COVID-19. Nevertheless, the spread of SARS-CoV-2 enabled evolution and the emergence of variants of concern (VoCs). The complexity of transmission, human behavior, control measures, and their interaction led to many unanswered questions about the spread and consequences of COVID-19 in Switzerland.

Understanding the dynamics of SARS-CoV-2 is critical for mitigating transmission and ultimately preventing severe cases and deaths. Modeling in infectious diseases can support collected data such as surveillance data and offer the possibility to study gaps in observations. The aim of this doctoral thesis was to gain insights into the SARS-CoV-2 epidemic in Switzerland, in particular, the local impact of imported cases, the impact of control measures on the spread of VoCs, changes in social contact patterns, and associations with vaccination uptake. To this end, I explored a variety of data such as (genomic) surveillance and survey data, and different methods including transmission and regression models.

Overall, the cross-disciplinary approach employed in this thesis provided evidence that imported cases significantly impacted the local SARS-CoV-2 epidemic during a period of low incidence (in chapter 2). Implementing border closures following the announcement of VoCs would have had limited impact on delaying their spread (in chapter 3). During the SARS-CoV-2 pandemic the number of social contacts was substantially reduced compared to pre-pandemic times (in chapter 4). Sociodemographic factors as well as individual behaviors and attitudes played an important role in COVID-19 vaccination uptake (in chapter 5). Finally, modeling provides evidence that can in collaboration with authorities improve public health.

Keywords SARS-CoV-2; epidemiology; transmission; control measures; behavior; vaccination; importation; variants of concern; Switzerland.

Contents

List of figures

List of tables

List of abbreviations

ABC	Approximate Bayesian Computation
ACE2	Angiotensin-converting enzyme 2
AIDS	Acquired immunodeficiency syndrome
aRR	Adjusted rate ratio
CDC	Centers for Disease Control and Prevention
CHF	Swiss Francs
CI	Confidence interval
COVID-19	Coronavirus disease that emerged in 2019
CrI	Credible interval
D	Infectious duration
ECDC	European Centre for Disease Prevention and Control
EU	European Union
FOPH	Federal Office of Public Health
FSO	Federal Statistical Office
GISAID	The Global Initiative on Sharing All Influenza Data
HIV	Human immunodeficiency virus
HCoV	Human coronavirus
HPC	High-Performance Computing
HPV	Human papillomavirus
HR	Hazard ratios
ICU	Intensive care unit
IPWC	Inverse probability weighting cumulatively
INFORM Africa	Role of Data Streams in Informing Infection Dynamics in Africa
IQR	Interquartile range
k	Overdispersion parameter
KOF	Konjunktur-Forschungsstelle
MCID	Multidisciplinary Center for Infectious Diseases
mRNA	Messager ribonucleic acid
Mtb	Mycobacterium tuberculosis
NGS	Next-generation sequencing
NPI	Non-pharmaceutical interventions
NUTS	Nomenclature of territorial units for statistics
ODEs	Ordinary differential equations
OECD	Organisation for Economic Co-operation and Development
OHHLEP	One Health High-Level Expert Panel
OR	Odds ratio
R_0	Basic reproduction number
PCR	Polymerase Chain Reaction
PISA	Program for International Student Assessment
RBD	Receptor binding domain
R_e	Effective reproduction number

RMSE	Root-mean-square error
RNA	Ribonucleic acid
RR	Rate ratio (or risk ratio)
Sentinella	Swiss Sentinel Surveillance Network
SGTF	S gene target failure
SMIDDY	Swiss Meeting for Infectious Disease Dynamics
S protein	Spike protein
SSR	Sum of squared residuals
STI	Sexual transmitted infectious
STROB	Strengthening the reporting of observational studies in epidemiology
TB	Tuberculosis
TMRCA	The most recent common ancestor
UK	United Kingdom
VE	Vaccine efficacy
VoCs	Variants of Concern
WHO	World Health Organization

Introduction

1.1 Public health during the SARS-CoV-2 pandemic

The emergence of severe acute respiratory syndrome coronavirus (SARS-CoV-2) in 2019 and its rapid global spread spotlighted the medical, social, and economic impact of infectious diseases worldwide. Suddenly, countries around the globe faced a new pandemic starting in 2020. Coronavirus disease (COVID-19) led to a staggering 1.9, 3.5, and 1.2 million deaths globally in 2020, 2021, and 2022, respectively (WHO, 2023c).

Infectious diseases, also known as communicable diseases, are responsible for high morbidity and mortality worldwide. Infectious diseases disproportionately affect lower-income countries and highlight socioeconomic inequalities. For example, tuberculosis (TB) caused by *Mycobacterium tuberculosis* (*Mtb*) accounts for 1.5 million deaths every year and the acquired immunodeficiency syndrome (AIDS) caused by the human immunodeficiency virus (HIV) accounts for 0.6 million deaths in 2022 (UNAIDS, 2022).

Prevention is an action taken prior to threats to mitigate the risk of diseases and promote well-being.

Infectious diseases increase social and economic inequality and cause medical suffering. Public health interventions focus on preserving and promoting health, preventing diseases, and offering preemptive, curative, and rehabilitative measures (*Public health kompakt* 2021). Such measures often prove insufficient in low- and middle-income countries where infectious diseases still pose a major public health concern.

Although Switzerland has social and economic resources to mitigate infectious diseases, the incidence of SARS-CoV-2 rose sharply immediately after its introduction. The lack of previous exposure was key to the spread of the newly emerged SARS-CoV-2, which is well adapted to human-to-human transmission via the respiratory tract. The first SARS-CoV-2 case in Switzerland was reported on the 25th of February 2020 (Federal Council, 2020b). During the first year, SARS-COV-2 caused an excess mortality of over 10% (Weitkunat et al., 2021). This might be even higher as Riou et al. (2023) highlighted that from February 2020 to April 2022 only about 72% of COVID-19-related deaths were confirmed in Switzerland.

A disease that occurs (in unexpected numbers) in a closed community at a given time results in an epidemic. An epidemic that impacts multiple countries is referred as a pandemic.

Overall, the SARS-CoV-2 pandemic including the Swiss SARS-CoV-2 epidemic was highly dynamic (fig. 1.1); During the first year, various non-pharmaceutical interventions (NPIs) were implemented (further detail in section 1.5.1). Nevertheless, two epidemic waves occurred. In early 2021, the epidemic remarkably changed with the introduction of vaccines against COVID-19 (further detail in section 1.5.2; Federal Council, 2020a). In parallel, there was a rise of variants of concern (VoCs) (further detail in section 1.2.4) (Carabelli et al., 2023; WHO, 2023b). To mitigate the transmission of SARS-CoV-2 and prevent severe illness and deaths it became increasingly crucial to study the dynamics of SARS-CoV-2, on a global scale as well as within regional contexts.

Epidemiology is derived from Greek epi 'among', demos 'people, district', and logos 'study'.

The scientific basis for analyses in public health is the field of epidemiology. Epidemiology is the study of health and disease in a given population (*Public health kompakt* 2021). Epidemiological research can be divided into four steps I) identifying study questions (see section 1.6 about the objectives of this thesis), II) study design and data collection (see section 1.3), III) data analysis (see section 1.4 about modeling in infectious diseases),

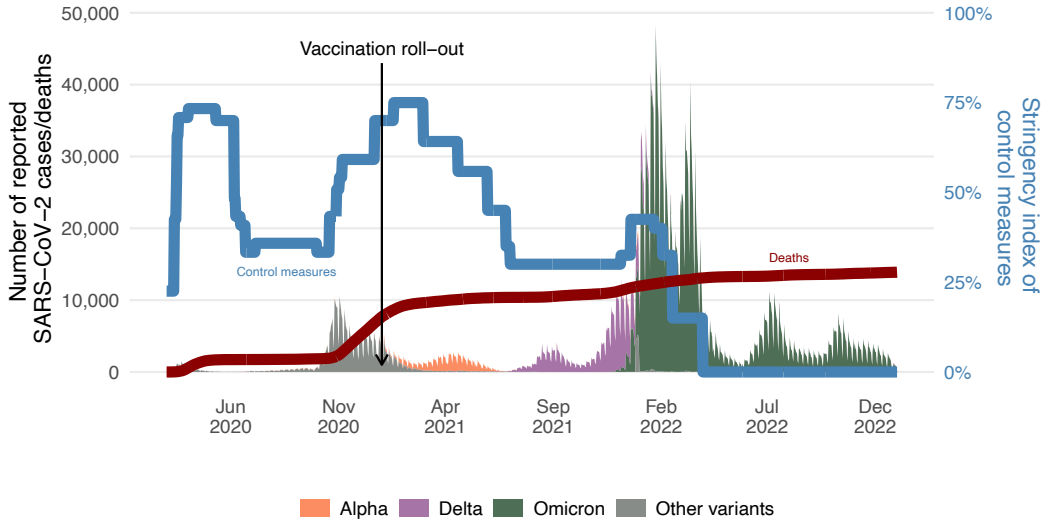

FIGURE 1.1: SARS-CoV-2 epidemic in Switzerland: Reported number of SARS-CoV-2 cases per day by the FOPH (2023a) and colored by frequency of SARS-CoV-2 variants, the cumulative number of deaths colored in red, the arrow indicates the start of the vaccine roll-out in Switzerland, and the KOF stringency index colored in blue. The KOF stringency index values range from 0 (no measures) to 100 (full lockdown) (Pleninger et al., 2021). Abbreviations: FOPH, Federal Office of Public Health; KOF, 'Konjunktur-Forschungsstelle', meaning economic research center in English.

and IV) finally applying research findings to improve public health (see section 1.5). Particularly, infectious disease epidemiologists are interested in the spread of diseases and their determinants such as causes and risk factors.

1.2 SARS-CoV-2 as an emerging infectious pathogen

Emerging infectious diseases are caused by new, previously unknown pathogens, new variants of known pathogens, and re-emerging pathogens with high potential to spread.

When SARS-CoV-2 emerged in 2019, little was initially known about its origin and transmission dynamics. In general, pathogens persist in reservoirs and infect hosts through various modes of transmission, i.e., through direct contact such as body fluids, indirect contact such as airborne transmission, or vectors such as mosquitoes (Van Seventer and Hochberg, 2017). Reservoirs are one or more epidemiological connected populations or environments in which the pathogen can persist and replicate (Haydon et al., 2002). This can include people, animals, and the environment. Understanding these reservoirs, modes of transmission, and their impact on the host is crucial for effectively developing strategies to mitigate the negative impact caused by pathogens such as SARS-CoV-2.
For instance, bats are considered a natural reservoir of SARS-CoV-2 (Liu et al., 2020b). The spillover of SARS-CoV-2 from animals to humans likely occurred via an intermediate host at the 'Seafood and Wildlife Market' in Wuhan (Liu et al., 2020b). Eventually, SARS-CoV-2 acquired the ability to transmit from human to human. The spillover from animals to humans is referred to as zoonosis. Zoonosis is a main cause of emerging infectious diseases (Grubaugh et al., 2018).

Zoonosis is an infectious disease that is transmitted between species (from animals to humans or vice-versa).

Emerging infectious diseases pose public health challenges in the 21st century (Grubaugh et al., 2018). SARS-CoV-2 clearly demonstrated human's vulnerability to infectious diseases. The emergence of infectious diseases can be exacerbated by population growth, increasing frequency and range of travel, changing land use patterns, changing dietary habits, wars, social, and climatic changes (Cohen, 2000; Grubaugh et al., 2018). For

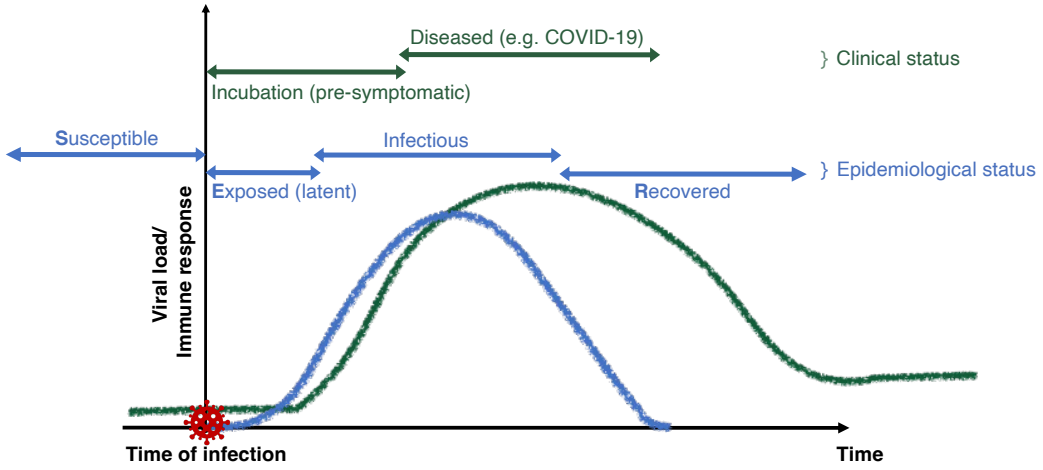

FIGURE 1.2: Typical clinical and epidemiological course of infectious diseases adapted from Keeling and Rohani (2008). The scheme also reflects the course of SARS-CoV-2. Original figure available at https://homepages.warwick.ac.uk/~masfz/ModelingInfectiousDiseases/Figures/index.html.

instance, Mora et al. (2022) estimated that climate change has worsened more than half of known infectious diseases in humans.
Moreover, infectious pathogens can spread rapidly in the modern world. Globalization and high population density favor spread of pathogens. SARS-CoV-2 and especially VoCs could therefore spread rapidly across continents. This underlines the importance of global collaboration and data sharing for the development of evidence-based decision-making.

1.2.1 Clinical course of COVID-19

The clinical course of SARS-CoV-2 infection is heterogeneous. The onset of symptoms may not start with infection (fig. 1.2). The pre-symptomatic period is called the incubation period. The incubation period from exposure to SARS-CoV-2 to COVID-19 symptoms was estimated to be around 4.8 ± 2.6 days (Liu et al., 2020a). The onset of COVID-19 symptoms co-occurs with the most virions (shedding) in humans which is 2 to 5 days post-infection (Markov et al., 2023). However, not all infections cause symptoms. At the beginning of the SARS-CoV-2 pandemic, about 20% of infections were asymptomatic (Buitrago-Garcia et al., 2020). SARS-CoV-2, similar to SARS-CoV and MERS-CoV, can cause severe acute respiratory syndrome, which is a life-threatening condition (Liu et al., 2020b). In contrast, infections with other hCoVs often present with upper respiratory symptoms such as a cold (Liu et al., 2020b). In general, ten to fifteen days after symptom onset, SARS-CoV-2 virions are cleared in the host (Markov et al., 2023). In cases where virions are not cleared, severe disease or death occurs around the third week post-infection (Markov et al., 2023; Ward and Johnsen, 2021).

The secondary attack rate is the probability that an infection occurs among susceptible people within a specific group like within a household.

The epidemiological status of SARS-CoV-2 differs from the clinical status. The time between infection, i.e. exposure, and infectiousness is called latent period. By definition, an infected individual can not transmit during the latent period (fig. 1.2). Infectiousness is highly heterogeneous for SARS-CoV-2 (Jones et al., 2021). Overall the secondary attack rate was around 19%, which increased for VoCs (Madewell et al., 2022). Buitrago-Garcia et al. (2020) estimated that asymptomatic individuals had a reduced secondary attack rate of 35% during the first months of the pandemic.

The course of SARS-CoV-2 infection depends on the host's immune system. When infected with SARS-CoV-2, the immune system is activated to clear the virus. SARS-CoV-2 enters human cells by binding to angiotensin-converting enzyme 2 (ACE2) receptor in humans (Jackson et al., 2022). More specifically, the receptor binding domain (RBD) of the spike protein docks to the ACE2 receptor. The immune response is activated with the presented epitope of SARS-CoV-2. In general, the immune response can be categorized into the cellular and humoral immune responses (Marshall et al., 2018). The cellular system involves the activation of cytotoxic T cells and cytokines. The humoral immune response is the activation of B cells and helper T cells. The activated cells secrete specific antibodies. The antibodies are specialized in recognizing an antigen. On first contact with the pathogen, this specialization begins to develop. After that, memory cells are ready to secrete antibodies to quickly protect against disease, which is known as adaptive immunity. The adaptive immune system exerts selection pressure on the pathogen. The selection pressure plays a crucial role in the evolution, i.e. genetic variation, of pathogens (Carabelli et al., 2023; Markov et al., 2023).

Immunity to a disease is the opposite of susceptibility and means being protected from a disease.

1.2.2 Phylogeny of SARS-CoV-2

SARS-CoV-2 belongs to the family of coronaviridae (Baker et al., 2020). The coronaviridae genome consists of a single strand of positive RNA and is approximately 30 kilobases in length for SARS-CoV-2 encoding for viral and structural proteins (Liu et al., 2020b). The genome includes four major structural proteins, namely the spike glycoprotein, membrane, envelope, and nucleocapsid protein (Liu et al., 2020b). The coronaviridae are divided in coronavirinae which are further divided into genera such as alphacoronaviruses and betacoronaviruses (Liu et al., 2020b). These two genera include the seven coronaviruses that infect humans (human coronaviruses, hCoV), whereby four infect humans seasonally, namely HCoV-NL63, HCoV-229E, HCoV-OC43, and HCoV-HKU1 (Liu et al., 2020b). In 2003 and 2005, the SARS-CoV and the Middle East Respiratory Syndrome coronavirus (MERS-CoV) emerged, respectively. More recently and mentioned previously, in 2019, SARS-CoV-2 emerged, sharing a genetic similarity of 80% with SARS-CoV (Liu et al., 2020b).

'Phyle' in Greek means 'tribe' and 'genetikos', means relative to birth.

Seven human coronaviruses (HCoV) are known.

1.2.3 Genetic variation of SARS-CoV-2

The genetic variation of SARS-CoV-2 depends on within-host and population-level processes (Markov et al., 2023). Mutation rates, substitution rates, and recombination can explain the viral evolutionary variation. The mutation is the change in the viral genome of the offspring compared to its parent. For SARS-CoV-2, the mutation rate was estimated to be 1×10^{-6} to 2×10^{-6} mutations per nucleotide per replication cycle (Amicone et al., 2022). This mutation rate is similar to other betacoronaviruses and lower than for other RNA viruses such as HIV (Markov et al., 2023; Sanjuán et al., 2010). In general, most mutations are deleterious which prevents viral replication. Therefore mutations often have no further impact. The substitution process, on the other hand, is the fixation of a viral change over time for an established group such as a SARS-CoV-2 variant (Belshaw et al., 2011; Markov et al., 2023). A variant is antigenically distinguishable from other groups of SARS-CoV-2 and shares mutation within its group. Further genetic variability can be generated through recombination which is the exchange of genetic material between (distinguishable) parental genomes. The resulting offspring combines viral properties from another genome and differs from their parents. Such recombination may occur during coinfection.

Mutation refers to a single change in the genome. If mutations change the properties of the virus, which are non-synonymous mutations.

TABLE 1.1: List of VoCs: Emergence and viral properties of SARS-CoV-2 variants that have been of concern during the SARS-CoV-2 pandemic and were dominant in Switzerland (FOPH, 2023a; WHO, 2023b).

Variants	Alpha	Delta	Omicron
Country first detected	United Kingdom	India	South Africa and Botswana
Time retrospectively detected in Switzerland	November 2020	January 2021	November 2022
Impact on transmissibility	Increased	Increased	Increased
Impact on immunity	-	Increased	Increased
Impact on severity	Increased	Increased	Decreased

Transmission also contributes to the evolution of SARS-CoV-2. It defines which virus particles 'virions', are transmitted to the recipient. The donor-host has a large number of virions. However, due to a bottleneck during transmission, only a small diversity will seed in the recipient (Bendall et al., 2023). The virion that establishes itself in the host-recipient is random. This stochastic process leads to an increase in the frequency of certain mutations, which is called genetic drift (Markov et al., 2023).
Furthermore, superspreading contributes to the stochasticity in the evolution of SARS-CoV-2. In superspreading, a host infects above-average number of recipients (fig. 1.4) (Lloyd-Smith et al., 2005). This variability in transmission is also called overdispersion and generates heterogeneity in the number of secondary cases. superspreading reduces the genetic variability of the virus within the population. Gómez-Carballa et al. (2020) suggested that the early genetic variation of SARS-CoV-2 worldwide can be explained by superspreading in combination with the founder effect. The founder effect refers to the phenomenon that only a small number of virions from certain infected individuals, such as travelers and super-spreaders, introduce genetic variation into the population (Markov et al., 2023). In contrast, the fixation of genetic variation due to fitness advantages is non-stochastic and referred to as natural selection.

1.2.4 Characteristics of SARS-CoV-2

A viral fitness advantage allows a variant to dominate. Viral advantages include an increase in intrinsic transmissibility, immune escape, and prolonged infectiousness (Carabelli et al., 2023; Markov et al., 2023). Increased intrinsic transmissibility depends on the capacity of shedding within the host, and transmission in the environment including the number of contacts (Markov et al., 2023). This defines the potential to spread from a donor to a susceptible recipient. In a population with a high level of (vaccine-induced or natural) immunity, immune escape also increases the potential for spread. Immune-escape mutations are changes in antigens that mean the adaptive immune system no longer recognizes the virus. This allows variants to maintain high transmissibility in previously immune populations. The selection pressure for immune escape mutations is reduced with waning immunity (Markov et al., 2023). Waning immunity is the decline of immune protection over time. This leads to a population with partial immunity and increased susceptibility. I.e., variants can maintain high frequency with only an intrinsic transmissibility advantage (and no immune escape) (Markov et al., 2023). Genetic alterations can also impact the clinical outcome, i.e., the severity of COVID-19. The severity of the disease is also influenced by the patient's immunity and genetics. Variants with viral properties including improved intrinsic transmissibility, immune escape, and more severe COVID-19 are referred to as VoCs. For example, antigenic evolution in SARS-CoV-2 was identified in late 2020 for VoCs such as Beta and Gamma variants, and later for Delta and Omicron variants (table 1.1; WHO, 2023b). These, as well as the Alpha variant, had increased intrinsic transmissibility to earlier circulating variants.

1.3 Data collection related to public health

Epidemiology is data-driven. Epidemiological studies use data from observational studies such as cross-sectional, case-control, and cohort studies, but also from surveillance systems (*Public health kompakt* 2021). Data sources can be, for example, government statistics, routinely collected data such as from hospital information systems, and individual surveys. For example, Mossong et al. (2008) conducted surveys in several countries that were nationally representative for quotas on age, gender, and region of residence to gain insights into patterns of social contact. Data collection - as well as analysis and interpretation - should be systematic and unbiased. Common types of systematic errors are selection and information bias and confounding (*Public health kompakt* 2021). Selection bias occurs when the study population is not representative of the population of interest. Information bias occurs when participants are misclassified. For example, a participant misreports a behavior. In analyses, confounding can explain the observed association between the factor of interest and an outcome. A confounder correlates with the actual risk factor. Systematic data collection must also guarantee the protection of participants. Protection includes informed consent, risk minimization, and adherence to an approved research protocol, which is confirmed with ethical approval (Martani et al., 2020; *Public health kompakt* 2021).

1.3.1 Surveillance of pathogens

Surveillance of diseases is the ongoing systematic collection, identification, and subsequent analysis and interpretation of their occurrence (WHO, 2023a). Ultimately, surveillance aims to provide insights into the dynamics of diseases. With the start of an outbreak, the most critical task is to identify a causal pathogen (Grubaugh et al., 2018). In the case of SARS-CoV-2, the first reported cases of severe pneumonia occurred in Wuhan, China, in December 2019 (Wu et al., 2020). The collection of symptomatic cases information showed a clustering of cases with symptoms similar to SARS-CoV. Later, SARS-CoV-2 was identified through sequencing of its genome. Information on cases and the SARS-CoV-2 genome was collected and reported throughout the pandemic. The information collected generally includes date of symptom onset and the location where cases occurred. Additional information might include demographics as well as symptoms of cases.

'Our World in Data' focuses on collecting, visualizing and analyzing data on major global issues such as disease, poverty, hunger, war and climate change.

The worldwide collection of SARS-CoV-2 related information led to a large amount of data. Public health authorities such as the Swiss Federal Office of Public Health (FOPH) delegated the data collection to health institutions. Further, comprehensive data analysis and visualization were crucial to ensure the benefit of data collection. With dashboards, for example, data is accessible to the public. 'Our World in Data' collected and shared data on the SARS-CoV-2 pandemic worldwide, such as the number of cases, deaths, hospitalizations, and vaccinations. Increasing immunity mitigates symptomatic and severe COVID-19 cases worldwide. This has led to reduction of surveillance for SARS-CoV-2. In Switzerland, for example, daily reporting of SARS-CoV-2 cases has been reduced to weekly reporting since 2023. The gap in classical surveillance provides an opportunity for alternative systems, such as wastewater surveillance, for which promising early warning systems and pathogen surveillance have been proposed (Jahn et al., 2022; Karthikeyan et al., 2022). Finally, surveillance enables timely and effective interventions that mitigate the spread and contribute to well-being.

1.3.2 Genomic surveillance

Genomic surveillance helps to better inform the public health response (Alpert et al., 2021; Brito et al., 2022; Chen et al., 2022b). Global genomic surveillance of SARS-CoV-2 has been more extensive than for any other pathogen. The aim of genomic surveillance is to monitor the spread of variants and genetic changes of SARS-CoV-2. Sequencing technicians extracted and multiplied ribonucleic acid (RNA) from nasal or oropharyngeal swabs from patients using quantitative Polymerase Chain Reaction (PCR). The next-generation sequencing (NGS) approach helped to generate fragments of bases (reads) and ultimately a consensus sequence from positive samples. Consensus sequences of SARS-CoV-2 have been shared globally and in near real-time. Sequencing providers aimed to minimize the turnaround between sampling and data sharing. Brito et al. (2022) suggested sequencing about 0.5% of cases with a turnaround time of less than 21 days as a benchmark for genomic surveillance of SARS-CoV-2. The uncertainty about variants, especially after the emergence of the Alpha variant (table 1.1), led to global efforts to increase coverage in genomic surveillance. In Switzerland, members of the 'Swiss national SARS-CoV-2 genomic and variants surveillance program' increased the sequencing coverage. This program is a collaboration of the FOPH and researchers from various institutes throughout Switzerland. High sequencing coverage and speed of data sharing in publicly accessible databases is crucial for a timely public health response to emerging variants (Chen et al., 2022b).

The Global Initiative on Sharing All Influenza Data (GISAID) enabled the rapid exchange of viral sequences and related epidemiological data, including geographical information of those infected (Shu and McCauley, 2017). In addition, a data usage clause ensured that scientific credit was given to scientists generating genomic data. By June 2023, GISAID had collected more than 15 million SARS-CoV-2 sequences. 'Nextstrain', an open-source project, uses SARS-CoV-2 sequences and phylogenetic methods to visualize and communicate the spread of SARS-CoV-2 (further detail in section 1.4.4; Hadfield et al., 2018). A Nextstrain spin-off, 'CoVariants', provided an overview of the evolution of SARS-CoV-2 variants and their mutations. 'CoV-Spectrum' and 'COVID-19 Switzerland' from the Swiss FOPH were other useful dashboards and data sources for this doctoral thesis.

Dashboards are a type of data visualization to summarize different data sets to ultimately make the information easier to understand.

1.3.3 Surveillance in Switzerland

In Switzerland, the FOPH collects and reports data on infectious diseases that are of interest to public health. For instance, medical practitioners are obliged to report 54 notifiable infectious diseases or pathogens to the FOPH, including HIV, TB, and common sexually transmitted infections (STIs) such as chlamydia, gonorrhea, and syphilis (FOPH, 2023b). Following the emergence of SARS-CoV-2, its monitoring was also initiated. In 2021, for example, 912,339, 350, and 328 new SARS-CoV-2, TB, and HIV cases were reported in Switzerland, respectively (FOPH, 2023c).

In addition, since 1986 there has been a sentinel surveillance system, the Swiss Sentinel Surveillance Network, 'Sentinella' (Somaini et al., 1986). Sentinella is a collaborative project of the FOPH and around 200 general practitioners. The main aim is to monitor the course of diseases in the Swiss population and primary care. For example, the Sentinella system provides surveillance for symptomatic influenza infection, as only laboratory-confirmed cases are notifiable.

1.4 Modeling in infectious disease epidemiology

Models for infectious diseases can support experiments, help to understand observations, predict and forecast trajectories, and offer the possibility to study counterfactual scenarios, i.e., gaps in experiments and observations. For example, when no observational data on the potential effects of vaccine-induced immunity was available, Bernoulli's model in 1766 was insightful. Bernoulli calculated the gain in life expectancy at birth if smallpox were eliminated as a cause of death (Dietz and Heesterbeek, 2002). In what was probably the first compartmental infectious disease model, he grouped the study population into susceptibles (those who were not yet infected) and immune (those who were already infected). When data is available, models can also help to calculate associations. For example in 1854, Snow found the association and cause of the cholera outbreak in London with case counting and spatial mapping (*Public health kompakt* 2021). Snow's mathematical model proved his hypothesis that cholera was waterborne. This was a founding moment to combine epidemiology of infectious diseases and mathematics, including statistics, to understand diseases. Finally, modeling in epidemiology of infectious diseases helps to understand, predict, and even forecast transmission dynamics to guide and evaluate intervention strategies.

1.4.1 Statistical models in epidemiology

Statistical modeling in epidemiology aims to provide information about factors that influence diseases. The model selection depends on the study design and data collection. Regression models, for example, can help to compare groups and predict a phenomenon. The chance of a phenomenon can be expressed as probability. The (frequentist's) probability refers to the proportion of times that the condition would occur in a large number of similar repeats (Kirkwood and Sterne, 2003). Similarly, the risk refers to the chance of individuals in a defined population developing a defined condition. The frequency of this risk over time can be expressed as rates including hazards. Odds refer to the quotient of the probability of a condition occurring to the probability of it not occurring. Probabilities of an outcome can further be given as distribution, for example, a discrete uniform, normal, binomial, Poisson, negative binomial, and gamma distribution.

In Bayesian statistics, the probability is a degree of belief in the phenomenon and is given as prior and posterior distribution.

A central goal in public health is the comparison of groups. The comparison between different groups can be expressed as ratios. Ratios can be estimated with various regression models. For example, hazard ratios can be estimated using Cox's proportional hazards regression model or similarly rate ratios can be estimated using a Poisson regression model (applied in chapter 5). Odds ratios can be estimated using a logistic regression (applied in chapter 5). In addition, I used multinomial logistic regression models to quantify the relative viral growth advantage of VoCs (see figure 6 in monthly 'Swiss national SARS-CoV-2 genomic and variants surveillance program' report of February 2023).

In statistical models factors that are used to explain the outcome (= dependent variable) are called independent variables.

1.4.2 Compartmental transmission models

Transmission models aim to predict the spread within and between populations. Compartments - as introduced by Bernoulli, group the study population. The theory of the compartmental model was introduced by Kermack and McKendrick in 1927 (Kermack and McKendrick, 1991a,b,c). In the simplest model, the population is divided into the compartments of the susceptible (S), infected (I), and recovered (R) individuals. This is referred to as a SIR model. The simplest SIR model is without vital dynamics, which

TABLE 1.2: Basic reproduction number R_0 for infectious diseases ranging from 0-18. Measles is known as the disease with the largest R_0. The R_0 values are rounded.

Infectious pathogen	Transmission	R_0	
HIV	Body fluid	4–6	Eaton and Hallett (2014)
Measles virus	Aerosol	5–18	Delamater et al. (2019)
MERS-CoV	Respiratory droplets	0–1	Kucharski and Althaus (2015)
Mtb	Respiratory droplets	0-4	Ma et al. (2018)
SARS-CoV-2 (ancestral strain)	Respiratory droplets and aerosol	2–4	Leung (2021) and Riou and Althaus (2020)
SARS-CoV	Respiratory droplets	2- 4	WHO (2003)
Seasonal influenza	Respiratory droplets	1–2	Biggerstaff et al. (2014)

means that births and deaths in the population are ignored. Individuals can move compartments (S $\rightarrow$ I $\rightarrow$ R) with defined rates. These transition rates are called βI for the rate of transmission - also referred to as βI = λ = force of infection, and γ for the rate of recovery. The rate of transmission β is defined as the secondary attack rate or risk of transmission per contact of the infected with a susceptible individual. The inverse of recovery rate γ corresponds to the average infectious duration (*D*). *D* can be set equal to the generation time, which is the time between infection and transmission (fig. 1.2). The generation time for the ancestral SARS-CoV-2 strain (Wuhan strain) was estimated to be 5.2 days (Ganyani et al., 2020), which was shorter for the Delta variant and longer for Omicron, with 4.7 and 6.8 days, respectively (Hart et al., 2022; Manica et al., 2022). The movements between compartments over time can be mathematically solved using the system of ordinary differential equations (ODEs):

The concept of mass action defines that the number of new infections in a given period is proportional to the product of the number of susceptible and infected individuals.

$$dS/d_t = - \beta IS = - \lambda S,$$
$$dI/d_t = \beta IS - \gamma I,$$
$$dR/d_t = \gamma I.$$

Compartmental models assume that transmission is proportional to the number of susceptible and infected individuals (density-dependent) in a given population (N = S+I+R) and individuals are homogeneous within the population (principle of mass action). In an SIR model, the latent phase is set to zero. A model with an exposed (E) compartment contains a latent phase (fig. 1.2). This then results in an SEIR model. In addition, further stratification can be included such as age, gender, and socio-economic groups. With constant parameters the outcome of an SIR model is deterministic. This means the model gives the same output for every run.

Deterministic models are defined by their initial conditions.

Reproduction number and implication

The basic reproduction number R_0 is the average number of secondary infections arising from an individual during its entire infectious period in a fully susceptible population (N = S) (Diekmann et al., 1990; Wallinga and Lipsitch, 2007). R_0 is an interplay of human behavior and biological characteristics of pathogens (Delamater et al., 2019; Wallinga and Lipsitch, 2007). Mathematically, R_0 is the quotient of the infectious contact rate and the recovery rate,

$$R_0 = \beta \mathrm{S} D,$$

whereby we can normalize S = N = 1. Epidemic growth occurs in a fully susceptible population if the basic reproduction number R_0 is > 1. If R_0 < 1 the disease dies out and if R_0 is = 1 it is an endemic state. Thus, the R_0 value has impact on epidemic control such as vaccination strategies. In an SIR model, the interaction between susceptible and recovered is given as S = 1 $-$ R, when no infection occurs. The recovered compartment

includes immune individuals. Immunity can be acquired through infection and vaccination. Given that epidemics are not growing if R_0 < 1, the fraction p_c that needs to be immune is set as follows:

$$p_c > 1 - \frac{1}{R_0}$$

.

This threshold p_c is referred to as the herd immunity threshold (Hethcote, 1989). Prior to natural immunity R = V/VE, whereby V is the fraction of vaccinated individuals and vaccine efficacy (VE) is the fraction of those vaccinated who become immune. Theoretically,

$$V > (1 - \frac{1}{R_0})/VE,$$

need to be vaccinated that the entire population is protected from infection (Hethcote, 1989). Based on this concept, vaccinated individuals protect vulnerable and unvaccinated individuals. In summary, vaccination can be critical for preventing and controlling infectious diseases.
For example, Riou and Althaus (2020) estimated a R_0 for the ancestral SARS-CoV-2 strain of around 2.2 (table 1.2). Later, the VE was estimated to be 95% for the Pfizer/BioNTech vaccine (Polack et al., 2020). Combining these findings would suggest a herd immunity threshold p_c of 54% and at least 57% must be vaccinated to mitigate the spread of SARS-CoV-2. However, due to waning immunity, viral changes such as higher intrinsic transmissibility and immune escape, and the fact that vaccines were developed and tested to protect from COVID-19 and not to prevent transmission, the threshold for herd immunity must have been much higher.

The effective reproduction number R_e explains the transmission dynamics over time as the number of susceptible individuals changes (S_t) due to immunity in the population and NPIs.

$$R_e = \beta S_t D,$$

I.e, R_e measures the average number of secondary cases of individuals infected with a pathogen at any given time and population during an epidemic. Estimating R_e can help to assess changes in policy, population immunity, and transmissibility. A common method to estimate R_e is the renewal equation (as a branching process model), which uses the incidence of infection and the generation time distribution (Green et al., 2022; Wallinga and Lipsitch, 2007). Using the renewal theory with a gamma distributed generation interval, R_e can be estimated as follows:

$R_e = (1 + ra)^b = (1 + r\frac{\sigma^2}{\mu})^{\frac{\mu^2}{\sigma^2}}$ derived from Park et al. (2019),

whereby μ is the mean generation time with standard deviation σ and r is the epidemic growth rate. For SARS-CoV-2, Gostic et al. (2020) estimated a generation time μ of 5.2 days and a standard deviation σ of 1.7 days. The gamma distribution of the generation time is given by the rate as $1/a = 5.2/1.7^2$ and the shape as follows $b = 5.2^2/1.7^2$. There are many ways to calculate R_e, from using fixed to exponentially distributed to gamma distributed generation intervals (Park et al., 2019). Moreover, various computational tools help to estimate R_e using the renewal equation as a basis, for example `EpiNow2`(Abbott et al., 2023; Gostic et al., 2020). Overall, methods should consider different testing and surveillance schemes (over time).

The epidemic growth rate, r, is the change from one time to another. It can be positive or negative, depending on whether the epidemic is increasing or decreasing over time.

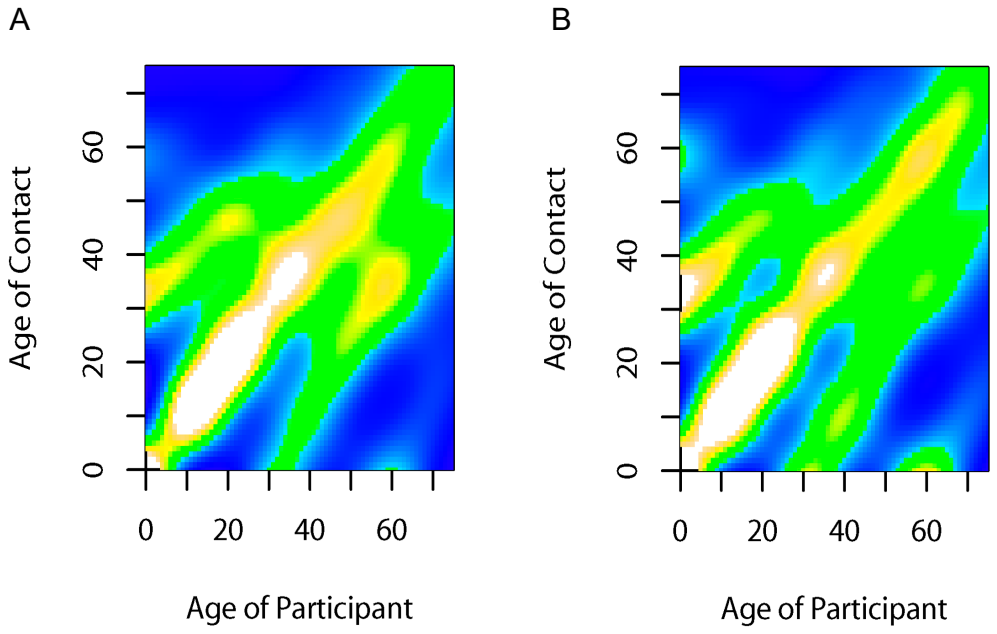

FIGURE 1.3: Social contact matrix for Belgium adapted from figure 3 reported by Mossong et al. (2008). White indicates high contact rates between participants with a specific age and a contact with a specific age, green intermediate contact rates, and blue low contact rates, relative to the country-specific contact intensity. A) All reported contacts and B) physical contacts only.

Social contact matrices

As we can observe, the number of contacts can vary, for example, due to cultural background and occupation. These heterogeneous contact rates between individuals can be crucial determinants of transmission. Contact rates influence the transmission rate of the compartment model. A comprehensive study of social contact patterns in eight European countries showed that contact rates varied by country, age group, and were highly assortative with age (fig. 1.3; Mossong et al., 2008).

Assortative contacts are non-random and are based on certain characteristics.

Contact pattern can be visualized using matrices (further detail in chapter 4). To create such matrices, participants' information about their social contacts is required. In social surveys, participants can themselves indicate how many contacts they had with another group on a particular day. They could also report the age, place, such as at work or home, the duration, and the physical distance of the contact.

Contact matrices give the mean number of contacts c_{ij} from one age group c_i with any other c_j (fig. 1.3). This matrix can then be symmetric, which reduces selection bias. Symmetry takes into account that c_{ij} have the same number of contacts with each other, which might not observed in surveys due to selection bias. The number of contacts can be normalized to the population, taking into account the ratio of age group i in the study population and the population at a certain time. The relevance of contacts also depend on the mode of transmission. For SARS-CoV-2 contacts without physical contact can still impact transmission, due to the mode of transmission being airborne.

1.4.3 Stochastic transmission models

Stochasticity influences the transmission dynamics of infectious diseases (Althaus, 2015; Riou and Althaus, 2020). Randomness is high when the number of infectious individuals

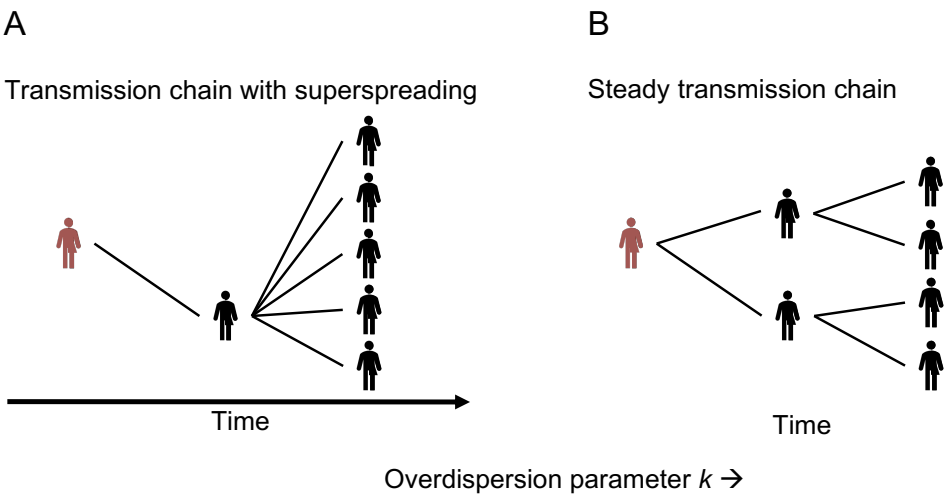

FIGURE 1.4: Overdispersion parameter k of secondary cases A) indicates that infected individuals have different numbers of secondary cases, i.e., superspreading events occur and $k < 1$ given $R_0 = 2$. B) There is no (or almost no) variability in secondary cases, i.e., $1 < k < \infty$ with basic reproduction number $R_0 = 2$. The concept is derived from Lloyd-Smith et al. (2005).

is low, for example in outbreaks or early phases of an epidemic. In computational models, parameters can be randomly taken from probability distributions to vary the outcomes. For example, a random sample of the negative binomial distribution can be used to simulate different epidemic trajectories (further detail in chapter 2). The negative binomial distribution considers overdispersion.

Overdispersion parameter k

The overdispersion parameter k gives the variability of transmission (Riou and Althaus, 2020). The higher the value, the more homogeneous the transmission and the smaller is the impact of superspreading (fig. 1.4). Often 20% of the primary cases account for 80% of the transmission, which is referred as the 20/80 rule (Woolhouse et al., 1997). The concept that few transmit to many is called superspreading (Lloyd-Smith et al., 2005). For SARS-CoV-2, Riou and Althaus (2020) estimated an median overdispersion parameter k of 0.54.

1.4.4 Phylogenetic analysis

Phylogenetics is the study of evolutionary relationships between biological groups such as viruses (Grubaugh et al., 2018). Viral sequences are more closely related if the most recent common ancestor (TMRCA) is closer in time. Insights into the evolution and transmission dynamics of viruses such as SARS-CoV-2 can be inferred and illustrated with phylogenetic trees (fig. 1.5). The beginning of the phylogenetic tree is the 'root' (left) and represents the earliest common ancestor of the sequences used for the analysis (fig. 1.5). The sequences, represented at the other end of the tree, are called 'tips'. Tips are connected with other tips via 'branches' and combined into 'nodes'. The length of the branch represents the genetic diversity. The nodes represent TMRCA of the combined tips. Phylogenetic inference relies on the molecular clock which uses mathematical models and molecular data to determine the homology of viral sequences as a function of time since their evolutionary separation (Bromham and Penny, 2003). The inference can

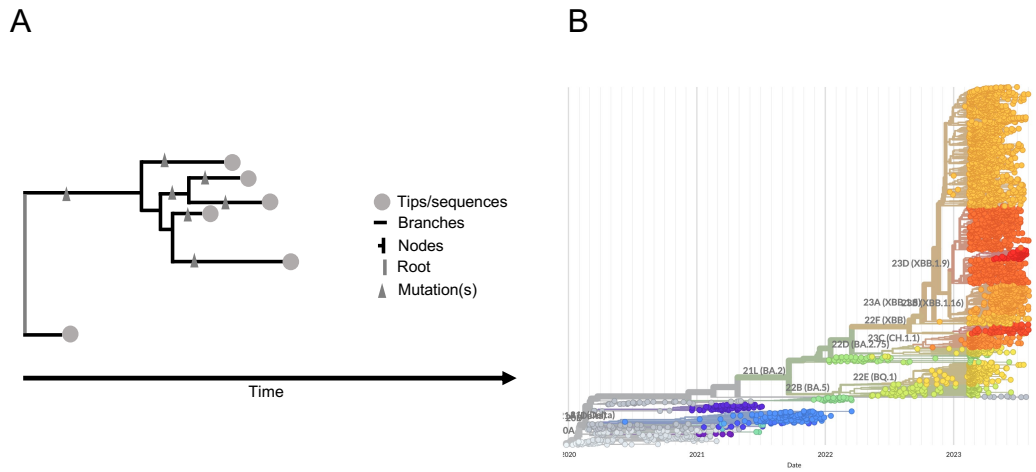

FIGURE 1.5: Phylogenetic tree in epidemiology of infectious diseases: A) A rooted, time-calibrated phylogenetic tree with branches measured in units of time using viral nucleotide sequences of a host can be used to represent transmission between hosts. B) Phylogenetic tree of SARS-CoV-2 sequences that were sequenced in Switzerland. The phylogeny was built with Nextstrain/ncov using data from GenBank by the Nextstrain team. This build shows 3,246 genomes sampled between December 2019 and August 2023.

either be drawn with maximum likelihood estimation or a Bayesian approach. Nextstrain (Hadfield et al., 2018), uses maximum likelihood trees, such as the IQ-TREE algorithm (Minh et al., 2020). Bayesian Evolutionary Analysis Sampling Trees (BEAST), on the other hand, is a phylogenetic software for Bayesian analysis and relies on Markov chain Monte Carlo (MCMC) to find a posterior tree distribution (Suchard et al., 2018). Phylogenetics that interplay with geographical information is referred to as phylogeography and the interplay with host information is referred to as phylodynamics (Grubaugh et al., 2018). In viral phylodynamics, epidemiological, immunological, and evolutionary information can be combined with phylogenies to estimate epidemic growth rates, generation times, and reproduction numbers (Volz et al., 2017).

1.5 Public health response

Public health response is crucial to mitigate the risk and impact of infectious diseases in populations. For infectious diseases, hygiene and vaccination are two of the most important interventions (further detail in section 1.5.1 and section 1.5.2, respectively). In Switzerland, interventions might have varied regionally due to the federal regulations, which entitled regional authorities to adopt policy independently.
When SARS-CoV-2 emerged little evidence was present about its impact. Evidence-based knowledge from scientific studies can lead to effective interventions. Effective and appropriate public health action is enabled with a constant feedback loop between experts and authorities (Brownson et al., 2009). In response to the threat posed by COVID-19, the World Health Organization (WHO) has identified ten global health priorities. These include strengthening countries' health systems to ultimately prevent deaths from SARS-CoV-2 (WHO, 2020a): This can be achieved by building global solidarity, addressing health inequalities, accelerating access to tests, medicines, and vaccines, promoting global leadership in science, and improving data access and sharing. Ultimately, these efforts are intended to help mitigate infectious diseases in general.

In Switzerland, the FOPH manages intervention strategies and communication to mitigate infectious diseases. The FOPH develops Swiss health policy by advising the Federal Council on public health issues. The enforcement of public health interventions during the SARS-CoV-2 pandemic was facilitated by the 'Communicable Diseases Legislation – Epidemics Act' (EpidA) (*Gesetzgebung Übertragbare Krankheiten – Epidemiengesetz (EpG)* 2010). For evidence-based interventions, the FOPH mandated Swiss scientists to advise authorities and inform the public. This 'Swiss National COVID-19 Science Task Force' provided up-to-date, evidence-based information needed to respond to the unprecedented crisis from April 2020 to early 2022. The task force consisted of a cross-disciplinary team ranging from epidemiologists to medical doctors, psychologists, economists, and communication scientists. Broad societal factors had to be included, such as physical and mental health, individual freedoms, solidarity, and economic stability.

1.5.1 Non-pharmaceutical interventions to mitigate pathogens

NPIs are preventive measures to mitigate diseases without pharmaceutical agents such as vaccines and drugs. NPIs can be particularly important to mitigate transmission chains when there is no or low immunity in the population due to lack of vaccination and previous infection. NPIs can be categorized into personal, community, and environmental NPIs (CDC, 2022). In particular, there is a wide range of NPIs against respiratory diseases. Personal NPIs include testing for diseases, isolation, quarantine, covering coughs, wearing a mask, and washing hands appropriately with soap or disinfectant. Community NPIs are physical distancing, which is often referred to as social distancing, travel regulations, bans on leisure events, and the closure of facilities such as shops, schools, and restaurants. Environmental NPIs include cleaning surfaces and ventilating rooms.

Isolation means staying away from others (staying at home) during disease, and quarantine means staying away from others because there has been close contact with a diseased person, which increases the likelihood of being diseased themselves.

While SARS-CoV-2 persisted in humans, it was necessary to determine its mode of transmission. Depending on the mode of transmission different NPIs can be more or less effective. Initially, policy-makers ignored potential airborne transmission of SARS-CoV-2 (Morawska and Cao, 2020). Emissions larger than 5 µm in diameter are considered droplets, smaller emissions are referred to as aerosols (Kutter et al., 2018). Given the small size of SARS-COV-2, <0.5 µm, the virus can be transmitted via aerosols (table 1.2; Leung, 2021). Aerosols persist longer in the air, whereas droplets fall quickly, and depending on environmental conditions, such as wind and temperature, can increase the distance of spread. Thus, the potential of airborne transmission is crucial for public health interventions. For instance, ventilation is helpful to mitigate SARS-CoV-2 transmission.

Interventions in Switzerland during the SARS-CoV-2 pandemic

In Switzerland, the use of NPIs to mitigate the impact of SARS-CoV-2 changed enormously between 2020 and 2022. The stringency of implemented NPIs was summarized with values ranging from 0 (no action) to 100 (complete lockdown) (see figs. 1.1, 4.4 and A.1). On 16 March 2020, the 'highest level of security' was announced in Switzerland. In parallel, the stringency of measures was increased to minimize social contacts to mitigate the spread of SARS-CoV-2 (fig. 1.1). Measures included border controls and entry restrictions, working from home, closing shops (except for essential shops) and restaurants, and canceling leisure activities and events. Further mitigation strategies were social distancing by at least two meters, self-isolation, and quarantine for at least ten days after contact with a confirmed case. Contact tracing helped to inform and quarantine contacts that might have been infected. On 25 June 2020, SwissCovid, a COVID-19 contact tracing app, became available (FOPH, 2023a). A couple of weeks

The SwissCovid app supported contact tracing by notifying close contacts when there was a risk of SARS-CoV-2 infection.

later the wearing of masks was introduced in public transport for all aged 12 years and older. At the beginning of the SARS-CoV-2 epidemic in Switzerland, tests were only free for symptomatic individuals but from January 2021 tests were free for everyone regardless of symptoms. From mid-March 2021, self-tests, which could be done alone at home, were also offered free of charge. At the end of May 2021, vaccinated people were exempt from quarantine. At the end of summer 2021, the 'COVID certificate' was introduced and all public venues in Switzerland were obligated to participate (FOPH, 2023a). The certificate confirmed proof of vaccination, recovery, or a negative test result which was declared mandatory to access indoor hospitality venues, cultural, sporting, leisure activities indoors, and large-scale outdoor events, which is also referred to as the '3G' rule - meaning 'geimpft', 'genesen' or 'getestet' in German. On 13 January 2022, the isolation requirement was reduced from 10 to 5 days. On 1 April 2022, all COVID-19 restrictions were lifted.

1.5.2 Vaccination to prevent diseases such as COVID-19

Vaccines save millions of lives every year (WHO, 2023a). The discovery of vaccines revolutionized public health. In 1796, the world's first vaccine for smallpox was demonstrated by inoculating a less dangerous virus - cowpox - into a human (WHO, 2023a). The first vaccinated individual felt unwell for a few days but recovered completely. Two months later when exposure to smallpox occurred, the vaccinated individual did not develop any symptoms - he was immune. Vaccines do not cause the disease but instead activate the immune system, which might lead to mild symptoms. Although most vaccinated individuals are immune to the disease in question, some might not be. The proportion of immunes among vaccinated individuals is represented as vaccine efficacy. In 1980, the WHO officially declared the first and only eradication of an infectious disease, smallpox (WHO, 2023a). Key components of the global eradication of smallpox include childhood and mass vaccination programs, as well as targeted surveillance and containment strategies during the eradication (WHO, 2023a). To maintain and progress the success of vaccines for public health, it is important to ensure access to vaccines for all and to inform the public with understandable information about vaccines (WHO, 2023a). In 2023, vaccines are available for 25 diseases (WHO, 2023a). There are three main types of vaccine; using the whole inactivated pathogen, parts of the pathogen, and the genetic material of the pathogen only (WHO, 2023a). The latter includes mRNA vaccines. Due to the short development cycle, easy industrialization, simple production process, and flexible adaption to new variants, mRNA vaccine was imperative for the SARS-CoV-2 pandemic (Fang et al., 2022).

SARS-CoV-2 vaccine in Switzerland

Due to the emergence and threat of COVID-19, a high number of resources have been invested in the rapid development and production of vaccines to protect from COVID-19. A year after the first COVID-19 cases occurred, a vaccine became available. Shortly after, in January 2021, the COVID-19 vaccination campaign started in Switzerland. The priorities for vaccination were older adults (>75 and then 65-75 years) and the chronically ill, and, secondly, healthcare workers and those living with people at risk (FOPH, 2020). In May 2021, the general population ($\geq$16 years) could get vaccinated. Children over 12 years and over five years old could get vaccinated from June 2021 and from January 2022, respectively (FOPH, 2020). In 2023, four vaccines are available in Switzerland (FOPH, 2020). Swissmedic, the Swiss agency for the authorization and supervision of

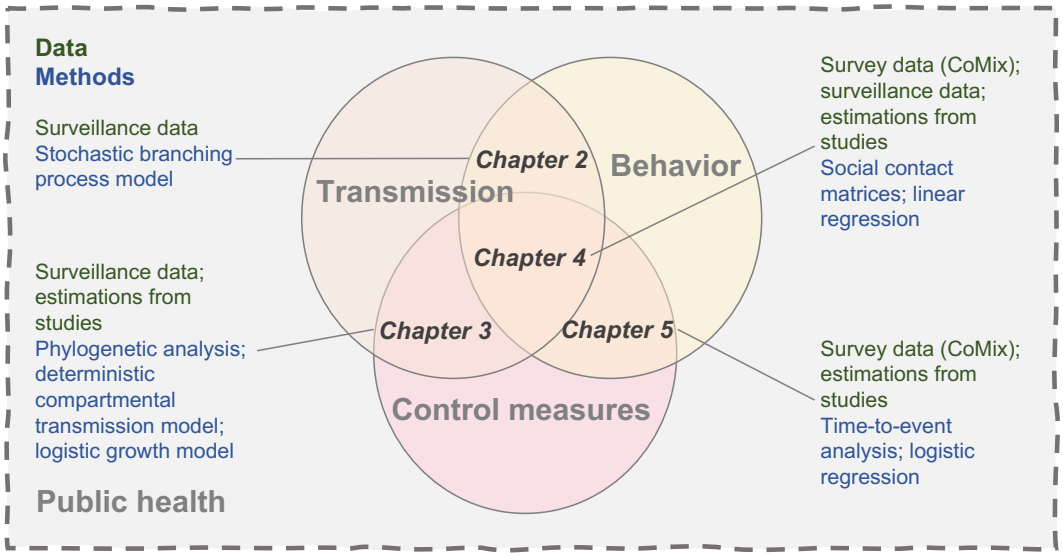

FIGURE 1.6: Doctoral thesis embedded in public health: The focus of this thesis is the spread of SARS-CoV-2 in the context of public health. Especially, chapters 2-5 link the transmission potential of SARS-CoV-2, human behavior, and implemented control measures. My approach required a cross-disciplinary approach including a variety of methods.

therapeutic products, authorized the mRNA vaccine from Pfizer/BioNTech on 19 December 2020. A few weeks later, on 12 January 2021, the mRNA vaccine from Moderna was authorized. Both, Pfizer/BioNTech and Moderna vaccines contain mRNA. Then on 22 March 2021, a viral vector vaccine was authorized from Janssen (Johnson and Johnson), which uses an adenovirus and only needed a single dose instead of two. On 13 April 2022, the Novavax vaccine was authorized, which includes proteins of SARS-CoV-2. The Swiss population became mainly vaccinated with mRNA vaccine, mainly Moderna's and then Pfizer/BioNTech's (FOPH, 2023a). Less than 1% of all doses were from Janssen (FOPH, 2023a).

1.6 Objectives of doctoral thesis

The SARS-CoV-2 pandemic has posed an unprecedented threat to public health, the economy, and society at large. To mitigate the spread of SARS-CoV-2, Switzerland, in line with many other countries, implemented NPIs such as isolation, quarantine, closure of schools, bans on gatherings, and physical distancing in general. After a year of various NPIs, the roll-out of vaccines to protect from COVID-19 began in Switzerland in early 2021. At the same time, VoCs emerged and increasingly circulated. The dynamics of transmission, human behavior, and control measures and their interaction led to many unanswered questions about transmission and the consequences of COVID-19 in Switzerland. At the beginning of my thesis in 2020, little was known about the public health consequences of SARS-CoV-2. In my thesis, I therefore applied different methods of infectious disease epidemiology to better understand the dynamics of the SARS-CoV-2 epidemic in Switzerland (fig. 1.6).
In chapter 2, I aimed to find an answer to the following question; *How was the spread of SARS-CoV-2 in Switzerland impacted by cross-border travel?* I hypothesized that cross-border mobility and associated infections strongly influence the local epidemic dynamics of SARS-CoV-2 during the summer of 2020 and 2021. I analyzed reported SARS-CoV-2 cases and their most likely country of exposure. Further, I quantified the impact of cases

exposed to SARS-CoV-2 abroad on local SARS-CoV-2 incidence and epidemic growth in Switzerland between the summer of 2020 and 2021 using a stochastic branching process model. After all, the impact of imports concerning the control measures implemented remained uncertain.

In chapter 3, I aimed to find an answer to the following question; *What was the impact of travel restrictions and surveillance in Switzerland on the spread of VoCs that emerged elsewhere?* While VoCs emerge in countries around the world, authorities in Switzerland implemented different travel restrictions to control the local SARS-CoV-2 epidemic. I hypothesized that due to globalization, newly implemented travel restrictions hardly impact the local dynamics of VoCs with higher intrinsic transmissibility. Therefore, I aimed to quantify the impact of control measures such as the closure of borders and the surveillance of travelers on the spread of Alpha and Delta variants in Switzerland. I analyzed surveillance data of cases and the SARS-CoV-2 genomes. I combined a phylogenetic approach with an SEIR transmission model to simulate the introduction of the Alpha and Delta variants. I then modeled different counterfactual intervention scenarios to quantify the potential impact of border closures and surveillance of travelers.

In chapter 3, I analyzed the impact of control measures on the transmission dynamics of SARS-CoV-2, whereas in chapter 2 I quantified the impact of travel, i.e., human behavior on the transmission. The spread of respiratory pathogens, including the public health consequences, however, is an interplay between transmission, human behavior, and control measures (fig. 1.6). In chapter 4, I therefore combined the three domains to better understand the complex interplay between transmission, human behavior, and control measures.

In chapter 4, I aimed to find an answer to the following question; *How did control measures impact the contact pattern in Switzerland and consequently the transmission of SARS-CoV-2?* I hypothesized that contact numbers decreased with the stringency of control measures. Therefore, I aimed to estimate the reduction of contacts compared with a pre-pandemic scenario and the associations of the number of social contacts with the implemented NPIs between 2021 and 2022. I harmonized 24 survey waves from an online survey in a nationally representative sample (called the CoMix study). Additionally, I made the data-set openly available to enable reproducibility and further research. The chapter 4 provides useful insights to parameterize mathematical models of infectious disease transmission. However, public health is not only about understanding and mitigating the spread but more importantly about reducing suffering of diseases. Control measures such as SARS-CoV-2 vaccines help to reduce the number of severe cases, and it is therefore important to understand the vaccination uptake and possible barriers.

In chapter 5, I aimed to find an answer to the following question; *What sociodemographic factors were associated with low vaccination uptake in Switzerland?* I hypothesized that sociodemographic factors such as region of living impacted vaccination uptake. Therefore, I aimed to estimate the rate ratio of vaccination uptake for sociodemographic factors. I used six survey waves that I harmonized in chapter 4. From this data, I analyzed sociodemographic factors, social contact behavior, and vaccination uptake in adults living in Switzerland between June 2021 and September 2021. I estimated the adjusted rate ratio with a Poisson regression model.

Impact of cross-border-associated cases on the SARS-CoV-2 epidemic in Switzerland during summer 2020 and 2021

Martina L Reichmuth[1]
Emma B Hodcroft[1,2]
Julien Riou[1,3]
Richard A Neher[2,4]
Niel Hens[5,6]
Christian L Althaus[1]

[1] Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland
[2] Swiss Institute of Bioinformatics, Lausanne, Switzerland
[3] Federal Office of Public Health, Liebefeld, Switzerland
[4] Biozentrum, University of Basel, Basel, Switzerland
[5] Interuniversity Institute for Biostatistics and statistical Bioinformatics, Data Science Institute, Hasselt University, Hasselt, Belgium
[6] Centre for Health Economics Research and Modelling Infectious Diseases, Vaccine and Infectious Disease Institute, University of Antwerp, Antwerp, Belgium

This article is published in ***Epidemics*** as Reichmuth et al. (2022). DOI:10.1016/j.epidem.2022.100654.

Contribution: I contributed to the study design, performed the analysis, created all figures, wrote the first draft of the manuscript, and integrated co-authors' comments.

Abstract

During the summers of 2020 and 2021, the number of confirmed cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections in Switzerland remained at relatively low levels, but grew steadily over time. It remains unclear to what extent epidemic growth during these periods was a result of the relaxation of local control measures or increased traveling and subsequent importation of cases. A better understanding of the role of cross-border-associated cases (imports) on the local epidemic dynamics will help to inform future surveillance strategies.

We analyzed routine surveillance data of confirmed cases of SARS-CoV-2 in Switzerland from 1 June to 30 September 2020 and 2021. We used a stochastic branching process model that accounts for superspreading of SARS-CoV-2 to simulate epidemic trajectories in absence and in presence of imports during summer 2020 and 2021.

The Swiss Federal Office of Public Health reported 22,919 and 145,840 confirmed cases of SARS-CoV-2 from 1 June to 30 September 2020 and 2021, respectively. Among cases with known place of exposure, 27% (3,276 of 12,088) and 25% (1,110 of 4,368) reported an exposure abroad in 2020 and 2021, respectively. Without considering the impact of imported cases, the steady growth of confirmed cases during summer periods would be consistent with a value of R_e that is significantly above the critical threshold of 1. In contrast, we estimated R_e at 0.84 (95% credible interval, CrI: 0.78-0.90) in 2020 and 0.82 (95% CrI: 0.74-0.90) in 2021 when imported cases were taken into account, indicating that the local R_e was below the critical threshold of 1 during summer.

In Switzerland, cross-border-associated SARS-CoV-2 cases had a considerable impact on the local transmission dynamics and can explain the steady growth of the epidemic during the summers of 2020 and 2021.

Keywords SARS-CoV-2; import; cross-border-associated cases; travel; summer.

2.1 Introduction

In early 2020, the emergence and spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Europe was facilitated by travelers (Worobey et al., 2020). A simulation study showed that targeting of air-travelers with symptom-based screening at exit or entry points of countries likely delayed the local spread of SARS-CoV-2 during the first months of the pandemic. If travel-related control measures were introduced with a delay, i.e. after local transmission had already been triggered by earlier arrivals of travelers, then control measures only delayed local spread by a few days (Clifford et al., 2020). The role of travelers in the spread of SARS-CoV-2 changed after local transmission had been established with varying levels of incidence across countries. Russell et al. (2021) showed that the contribution of imported cases on the local epidemic dynamics strongly depends on the local incidence of SARS-CoV-2, whether local epidemics are close to tipping points for exponential growth, and travel volumes.
A phylogenetic analysis reported on a novel SARS-CoV-2 variant, 20E (EU1), which was identified in Spain and subsequently spread to countries across Europe in summer 2020 (Hodcroft et al., 2021). The study estimated that 20E (EU1) was introduced multiple times into various European countries including Switzerland. This illustrated how the rising incidence in the country of origin, lack of screening and surveillance efforts, and resumption of travel can quickly establish local outbreaks and epidemics and undermine local efforts to control SARS-CoV-2 transmission. The rapid spread of 20E (EU1) revealed that travel guidelines and restrictions in Europe were mostly not sufficient to reduce cross-border transmission as holiday travel to countries with a higher incidence was not accompanied with adequate screening and surveillance efforts. These findings were supported by a phylogeographic study that showed how the impact of imported viral lineages on the local transmission dynamics was negatively associated with the local incidence (Lemey et al., 2021). Furthermore, they estimated that Belgium, the Netherlands, Norway, and Switzerland had more introductions than exports during summer 2020, highlighting that imported cases were impacting the SARS-CoV-2 epidemic in these countries.
Like most European countries, Switzerland experienced rapid spread of SARS-CoV-2 after reporting the first confirmed case on 25 February 2020 (Lemaitre et al., 2020). The federal government issued a number of major non-pharmaceutical interventions (NPIs) that included mandatory working from home, closing of schools and universities, non-essential shops, and restaurants, prohibition of gatherings of more than five people, and restricted movement across borders. Switzerland lifted major measures on 10 May 2020 and reopened its borders to countries of the Schengen Area on 15 June 2020 (Federal Council, 2020b). Switzerland lies at the heart of Europe, neighboring five countries, and has a significant fraction of foreign residents and cross-border commuters. In a survey conducted in Switzerland in May 2020, almost 80% of participants indicated that traveling is an important part of their holidays (Heim and Müller, 2020). In another survey conducted in June 2020, 15% planned to spend their summer holidays abroad compared to 49% before the pandemic (Bosshardt et al., 2020). Around 4% were planning to go to Germany, 3% to France, and 2% to Italy or Austria. More distant holiday destinations like Spain or Greece were planned to be visited by less than 1%. In summer 2020, travel-related control measures were limited. Countries with a higher incidence compared to Switzerland were typically added to a quarantine list, but often with considerable delays or not at all. The epidemic changed between the summers of 2020 and 2021 with high infection levels in winter and the start of the vaccination campaign. With the introduction of the COVID-19 certificate on 7 June 2021 (Federal Council, 2020c), travelers had to test negative for entering Switzerland, be recovered from, or be vaccinated against SARS-CoV-2. On 26 June 2021, quarantine requirement for those who had recovered from

SARS-CoV-2 or had been vaccinated was lifted (Federal Council, 2020c). Hence, in both summers travel-associated cases were to be expected, but the impact of these cases on the local level of transmission of SARS-CoV-2 in Switzerland remained unknown.
The local level of transmission can be quantified by the effective reproduction number R_e, which represents the average number of secondary cases per infected case at a given time in an epidemic (Gostic et al., 2020). Typically, estimates of R_e are based on confirmed case counts from a certain country or region and do not consider imported cases, which were infected abroad. When the proportion of imported cases among all confirmed cases is sufficiently high, conclusions about the efficacy of local control measures can be hampered. In addition, it is important to consider stochastic effects of transmission and the potential for superspreading when incidence is low and even a small number of imports can have a large impact on the local epidemic dynamics. Stochastic branching process models can account for the observed overdispersion in the number of secondary SARS-CoV-2 cases (Bi et al., 2020; Kremer et al., 2021; Laxminarayan et al., 2020), and were used to estimate the basic reproduction number R_0 during the early transmission of SARS-CoV-2 in Wuhan, China (Riou and Althaus, 2020).
In this study, we quantified the impact of cross-border-associated (imported) cases on the SARS-CoV-2 epidemic in Switzerland during the summer of 2020 and 2021. To this end, we first described routine surveillance data of confirmed cases by country of exposure to SARS-CoV-2. We then calibrated a stochastic branching process model that accounts for superspreading of SARS-CoV-2 to the observed cases in Switzerland using different scenarios for the number of imports. This allowed us to obtain estimates of the local R_e in absence and presence of imports, highlighting the potential role of travelers on the local epidemic.

2.2 Methods

Data

We analyzed routine surveillance data of confirmed cases of SARS-CoV-2 in Switzerland from 1 June to 30 September 2020 and 2021 that were provided by the Swiss Federal Office of Public Health (FOPH). Data included age, sex, case date (earliest available date of sample, test or registration), and the country of exposure, i.e., the country where confirmed cases had been within the last 14 days before they were tested or began to have symptoms. We compared the age of cases from Switzerland and abroad using Student's t-test. To compare the incidence of confirmed cases between Switzerland and other countries, we retrieved data from 'Our World in Data' (Hasell et al., 2020; Ritchie et al., 2020).

Stochastic simulations

We simulated epidemic trajectories of SARS-CoV-2 in Switzerland from 1 June to 30 September 2020 and 2021. To this end, we used a stochastic branching process model that accounts for superspreading in transmission of SARS-CoV-2 (Althaus, 2015; Riou and Althaus, 2020). The branching process was based on a negative binomial distribution to describe the number of secondary cases, with a mean of R_e and overdispersion k. The generation time for each transmission event was sampled from the gamma distribution with a mean of 5.2 days and a standard deviation (sd) of 1.72 days (Ganyani et al., 2020).
We considered different parameter combinations of R_e, k, and the seed, i.e., the number of infectious individuals during the week preceding the start of the simulation. For R_e,

we assumed a uniform prior distribution between 0.5 and 1.5. k was normally distributed between 0.49 and 0.52 (Laxminarayan et al., 2020). In a sensitivity analysis, we also considered values of 0.1 and 1 (Taube et al., 2021). To obtain the seed, we fitted a negative binomial generalized linear model with a weekend effect to account for varying testing rates to the daily number of confirmed cases during the study period. We then sampled from a uniform distribution of the 95% prediction interval of confirmed cases for the week before the study period (16-30 cases per day in 2020, and 98-300 cases per day in 2021).
We derived the number of imported cases from the routine surveillance data. In November 2020, registration procedures changed and the country of exposure was only available for hospitalized cases, deceased cases, and cases in nursing homes. Information on the place of exposure was frequently missing (table 2.1 and table A.1). To account for a potential reporting bias, we considered different scenarios for the total number of imported cases among all confirmed cases: a) we assumed imported cases among reported cases were representative and extrapolated to the total number of cases (missing at random), b) we assumed imported cases were less likely among cases with missing information ('lower limit'), c) we assumed imported cases were more likely among cases with missing information ('upper limit'). The lower and upper limits correspond to 50% and 150% of the daily imports of the first scenario. We compared these three scenarios to a baseline scenario without any imported cases, i.e., a scenario where the number of imported cases was set to 0.

Inference

We simulated 10^5 epidemic trajectories by randomly sampling parameter values. For the scenarios with imported cases, we added the imported cases to the simulations according to their case date. For the lower and upper limit scenarios, we decreased and increased the extrapolated number of imported cases by 50% and 150% for each day. We assumed that reported cases were representative of the overall infection dynamics, i.e., that the reporting rate was constant throughout each study period. Furthermore, we assumed that imported cases were equally likely to transmit and initiate new branches of transmission as did the local cases (see discussion). For computational reasons, we stopped and removed simulated trajectories that exceeded a cumulative incidence of 10^6 cases before the end of the simulation. As this value is orders of magnitude higher than the target incidence for model calibration, this did not affect our results.
To infer R_e for the different scenarios, we applied Approximate Bayesian Computation (ABC) and rejected the parameter combinations where the simulated cumulative and final incidence fell outside specific ranges. The ranges for each period were defined as the 95% prediction interval of the cumulative incidence and of the final incidence of confirmed cases, assuming a negative binomial distribution. For the final incidence, we considered the average incidence over the last week. We quantitatively compared the quality of the calibrated simulations in describing the observed number of confirmed cases in summer 2020 and 2021. To this end, we computed the sum of squared residuals (SSR) between each of 1,000 randomly selected trajectories and the daily incidence of confirmed cases (7-day moving average), and the root-mean-square error (RMSE) for each scenario. We then compared the RMSE and density distribution of the SSR between the different scenarios.
All analyses were performed using R version 4.0 with the following packages: `MASS`, `MCMCglmm`, `doParallel`, `foreach`, `lubridate`, `reshape2`, `ggplot2`, `ggpubr`, `grid`, `gridExtra`, `RColorBrewer` (R Core Team, 2020). Code is available on GitHub (https://github.com/ISPMBern/covid_summer).

2.3 Results

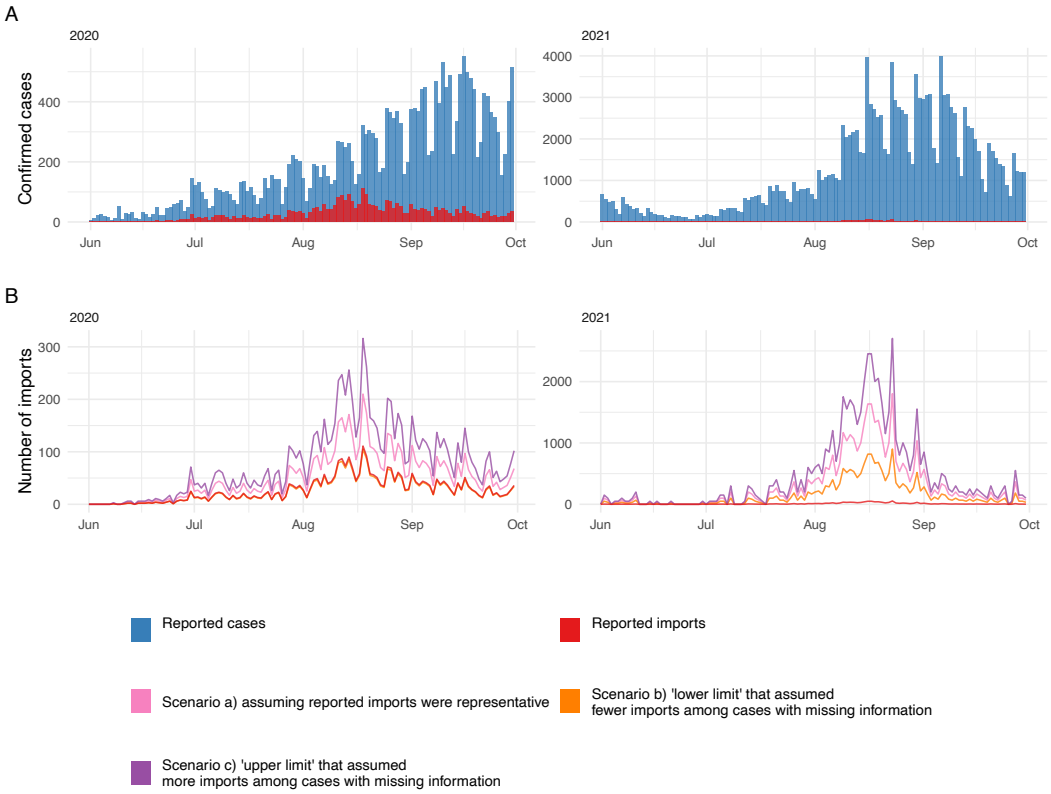

FIGURE 2.1: SARS-CoV-2 epidemic in Switzerland during summer 2020 and 2021. A) Daily number of all confirmed cases (blue) and reported imported cases (red). B) Imported cases as reported (red), and three different scenarios extrapolating the total number of imports from reported imports.

Description of the epidemic dynamics

The number of daily confirmed cases of SARS-CoV-2 increased continuously in Switzerland during early summer 2020 and 2021 before it declined in September of both years (fig. 2.1). Between 1 June to 30 September 2020, FOPH reported 22,919 confirmed cases of SARS-CoV-2 (table 2.1 and table A.1). For 12,088 (53%) cases, the reported country of exposure was available. Of these, 3,276 (27%) cases reported an exposure abroad. The highest number of imports was reported on 18 August 2020. The number of confirmed cases was considerably higher during summer 2021. Between 1 June to 30 September 2021, FOPH received 145,840 notifications of SARS-CoV-2 cases (table 2.1 and table A.1). Due to changes in the registration of cases, the country of exposure in 2021 was only available for hospitalized cases, deceased cases and cases in nursing homes (4,368 or 3%). Of these, 1,110 (25%) cases reported an exposure abroad. Extrapolation of reported imports resulted in 3,106 to 9,317 and 18,530 to 55,591 imports for summer 2020 and 2021, respectively (fig. 2.1 and table 2.1). The highest number of imports was reported on 23 August 2021. In both years, the highest number of imports coincided with the end of school holidays and resumption of school in most cantons in Switzerland (fig. A.1). Among imported cases, the countries of the reported most likely

TABLE 2.1: Cases with exposure in Switzerland and abroad. Percentages for SARS-CoV-2 cases with reported exposure correspond to all cases with known exposure. Scenario a) Missing at random. Scenario b) Lower limit (50% of imports in scenario a). Scenario c) Upper limit (150% of imports in scenario a).

	Summer 2020 (Jun-Sep)	Summer 2021 (Jun-Sep)
Total confirmed cases	22,919	145,840
Confirmed cases with known exposure	12,088 (53%)	4,368 (3%)
Confirmed cases with exposure in Switzerland	8,812 (73%)	3,258 (75%)
Confirmed cases with exposure abroad	3,276 (27%)	1,110 (25%)
Total number of imports (scenario a)	6,211	37,061
Total number of imports (scenario b)	3,106	18,530
Total number of imports (scenario c)	9,317	55,591

exposure were France and Croatia in 2020, and North Macedonia and Kosovo in 2021. During both years, the mean age of all imported cases was lower compared to local cases (table A.1 and fig. A.2). Note that the mean age of all cases for which the country of exposure was available was substantially higher in 2021 compared to 2020 due to differences in reporting guidelines.

Comparison with other countries

The incidence of SARS-CoV-2 cases in countries that were reported as a common place of exposure among Swiss cases varied widely (fig. A.3 and table A.1). In 2020, the incidence per million in the 19 countries with at least 10 reported imports was higher compared to Switzerland during 52 of 122 days (interquartile range, IQR: 40-107 days) during the study period on average. At the beginning of June 2020, testing was not mandatory to enter Switzerland and none of these 19 countries were listed on 'Ordinance on Measures to Combat the Coronavirus (COVID-19) in International Passenger Transport' (Federal Council, 2021). This list has been regularly updated by the Swiss authorities based on the global epidemiological situation and their strategy to combat SARS-CoV-2. It is important to note that quarantine for travelers in Switzerland was not enforced, but was based on trust.
Several countries were subsequently added to the quarantine list until the end of September 2020 (table A.1). In 2021, the incidence in the 14 countries with at least 10 reported imports was higher compared to Switzerland during 52 of 122 days (IQR: 26-86 days) during the study period on average. During the study period of 2021, quarantine was only mandatory for travelers returning from specific countries, i.e., countries with unreliable surveillance data, a high number of imports, and countries where the incidence per million cases during the last two weeks was 60 times higher compared to Switzerland (Federal Council, 2021).

Stochastic simulations

To understand the role of imported cases on the local dynamics of SARS-CoV-2 in Switzerland, we simulated epidemic trajectories for different import scenarios using a stochastic branching process model (fig. 2.2 and fig. A.4). Calibrating the different scenarios for the total number of imports to the confirmed number of cases allowed us to estimate the values of the effective reproduction number R_e that are most compatible with the observed epidemic dynamics. In our baseline scenario (without imports), only an R_e above the critical threshold of 1 is compatible with the observed overall increase in the daily number of cases. Hence, we estimated a local $R_e = 1.12$ (95% credible

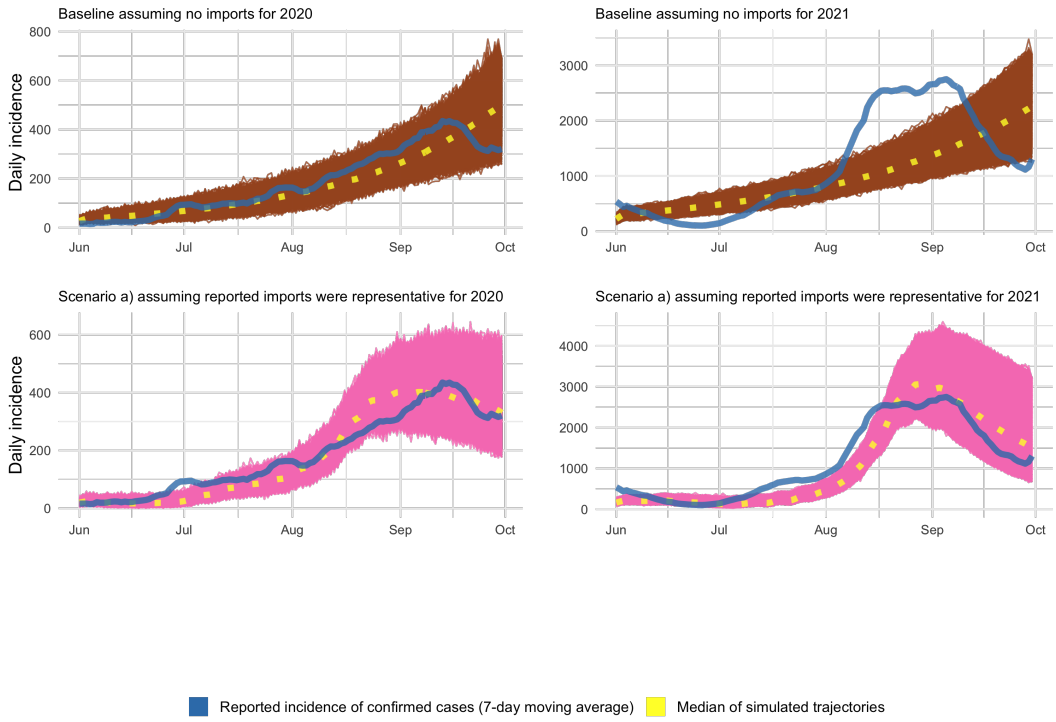

FIGURE 2.2: Simulated epidemic trajectories of the SARS-CoV-2 epidemic in Switzerland during summer 2020 and 2021. Top row: Baseline scenario without imports, which leads to an estimated local Re above one. Bottom row: Scenario a) (missing at random) assuming 27% and 25% of confirmed cases were imports in 2020 and 2021, respectively. Colored areas represent all calibrated epidemic trajectories. The median of the epidemic trajectories and the reported incidence of confirmed cases (7-day moving average) are given as yellow and blue lines, respectively.

interval, CrI: 1.08-1.16) in summer 2020 and $R_e = 1.09$ (95% CrI: 1.06-1.12) in summer 2021, suggesting that the local R_e in Switzerland was above the critical threshold of 1 during those time periods (fig. 2.3). In contrast, taking imports into account does not require a continuous exponential growth of the local epidemic to be compatible with the data. In scenario a), assuming reported imports were representative, i.e., unreported imports were missing at random, we estimated a considerably lower local $R_e = 0.84$ (95% CrI: 0.78-0.90) and $R_e = 0.82$ (95% CrI: 0.74-0.90) in summer 2020 and 2021, respectively (fig. 2.2 and fig. 2.3). Despite R_e being below the critical threshold of 1, the simulated epidemics were still growing due to imported cases and subsequently declined when imports decreased after mid-August. The additional scenarios b) (lower limit that assumed imports were overreported) and c) (upper limit that assumed imports were underreported) also resulted in estimates of R_e that were below the critical threshold of 1 (fig. 2.3 and table A.2).

In contrast to the baseline scenario, the scenarios with imported cases can qualitatively account for the initial increase in incidence during summer, and the subsequent decrease in the second half of September during both years. We further conducted a quantitative comparison of the quality of the calibrated scenarios in describing the observed number of cases (fig. A.5). For 2020, scenario a) resulted in the lowest RMSE (664) followed by scenario b) (697), scenario c) (732), and the baseline scenario (746) For 2021, the RMSE was lowest for scenario a) (6,328) and scenario c) (6,327), followed by scenario b)

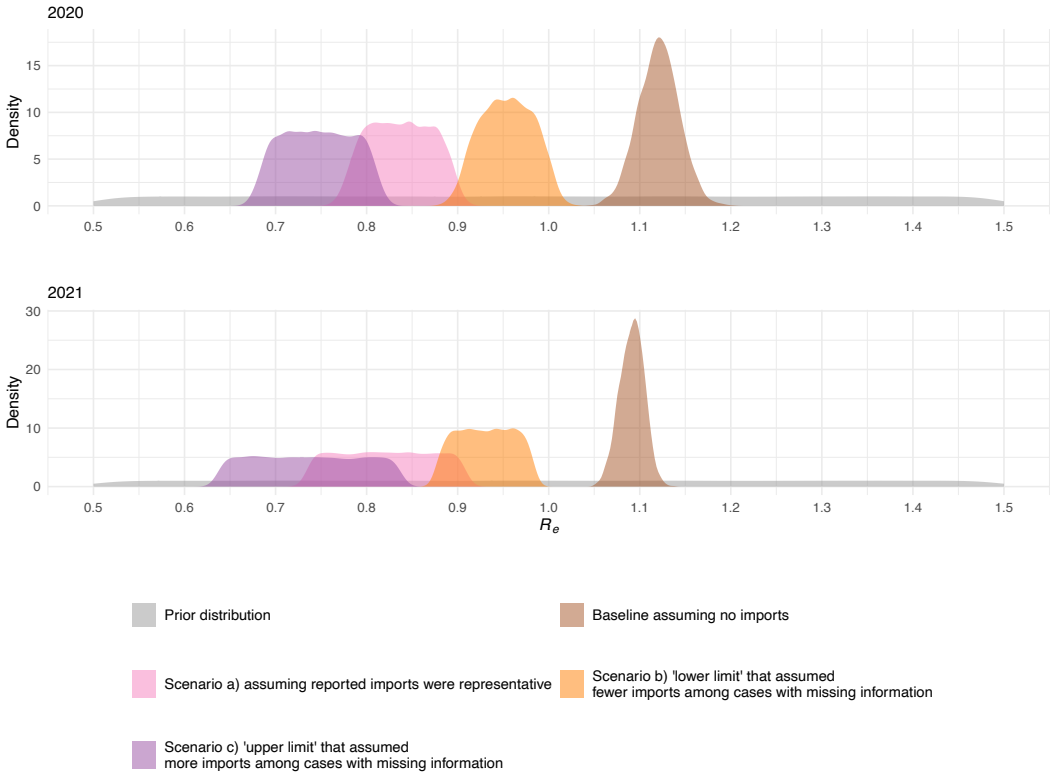

FIGURE 2.3: Estimates of the effective reproduction number R_e of SARS-CoV-2 during summer 2020 and 2021. Three different import scenarios are compared to the baseline scenario that does not consider imports.

(6,525), and the baseline scenario (8,252). The quantitative comparison of the different scenarios further illustrates that taking into account imported cases results in a better description of the initial increase in confirmed cases during summer and the subsequent decline in the second half of September during both summers.

Sensitivity analysis

In a sensitivity analysis, we evaluated the effect of different levels for the overdispersion (superspreading) on the estimated values of R_e. We hypothesized that overdispersion can strongly affect the role of imports on the local dynamics. However, we found that higher and lower values of k, representing more and less superspreading, did not result in notable differences estimates of R_e (table A.2).

2.4 Discussion

We analyzed routine surveillance data and used a stochastic branching process model to quantify the impact of imported cases on the SARS-CoV-2 epidemic in Switzerland during summer 2020 and 2021. We found that 27% and 25% of cases with a known place of exposure reported exposure abroad in 2020 and 2021, respectively. Stochastic simulations suggested that the local R_e was likely below the critical threshold of 1, highlighting that transmission within Switzerland was under sufficient control during the summers of both years. Our results indicate that imported cases caused the local epidemic to cross

the tipping point of sustained growth. Imports led to a steady rise in cases from June to August and a drop in September in both years. Together, our results highlight that the high number of imported cases had a considerable impact on the dynamics of the Swiss SARS-CoV-2 epidemic during periods when local transmission was low.

Our study relied on detailed surveillance data from FOPH that provide information about the place of exposure in a subset of all confirmed SARS-CoV-2 cases. This allowed us to track imported cases by country of exposure and over time in detail. The stochastic modeling approach was particularly suitable to describe the impact of single importation events on the epidemic dynamics in low incidence settings. Another strength of our study was that our main findings and conclusions are supported by both data sets from summer 2020 and 2021.

There are a number of limitations to our study. First, information on the place of exposure was missing for a significant fraction of confirmed cases. This was because the place of exposure was only reported via the clinical report form, which could have been filled in for all cases up to 2 November 2020 and thereafter only for hospitalized cases, deceased cases, and cases in nursing homes. Since hospitalized cases, deceased cases, and patients in nursing homes tend to be older, cross-border-associated cases were older in 2021 than in 2020. To account for uncertainty of missing data, we compared the results of our baseline scenario (missing at random) with alternative scenarios that assumed imported cases were less or more likely to have unknown place of exposure than local cases. Second, the data did not allow to distinguish between different types of traveling, like daily commuting across borders to Germany, France, Italy, Austria, and the Principality of Liechtenstein, Swiss residents returning from trips abroad, or foreign tourists. There was also no information about the modes of transport such as planes, cars, or public transport. Hence, the results of our study do not allow deriving specific interventions that would reduce the number of imported cases. Third, we assumed that the ascertainment of confirmed cases was constant and that they reflected the underlying dynamics of the SARS-CoV-2 epidemic. During the study periods, the degree of underascertainment was relatively low, suggesting that the confirmed cases represented the summer epidemics well (Nadeau et al., 2020; Stringhini et al., 2021a). Fourth, we restricted the study periods to the summer of 2020 and 2021 and assumed a constant R_e in our model simulations. We specifically chose these time periods because earlier research has shown the importance of holiday travel for the spread of SARS-CoV-2 during summer (Hodcroft et al., 2021). Furthermore, the locally implemented NPIs varied little throughout the study periods (the KOF stringency index remained largely constant from July to October of both years (Pleninger et al. 2021 and fig. A.1) and the impact of seasonal effects on virus transmission is unlikely to change substantially during summer months (Neher et al., 2020). In contrast, R_e varied considerably from autumn to spring and our stochastic modeling framework would not accurately capture the transmission dynamics during this time period. It is worth noting that the emergence of the variant Delta resulted in a higher intrinsic transmissibility of SARS-CoV-2 in summer 2021 compared to 2020 (Campbell et al., 2021). Fifth, we assumed that imported cases were as likely to generate secondary cases as local cases. In summer 2020, incoming travelers were not routinely tested but should have followed quarantine when they came from certain countries. Since quarantine was not enforced as in other countries (e.g., Australia or New Zealand) but based on trust, the adherence to this measure and its impact on further transmission of SARS-CoV-2 from imported cases - compared to local cases - remains unclear. Furthermore, mandatory quarantine for travelers from countries with many imported cases (e.g., France, Croatia, Italy, Germany) were only introduced in September 2020 or not at all. In the future, more detailed models that are informed by behavioral

data and include different transmission rates could further improve our understanding of transmission from imported and local cases (Ashcroft et al., 2021). Finally, we did not consider different age groups and age-specific contact patterns in our model (Coletti et al., 2020; Jarvis et al., 2020). Our finding that the median age of imported cases was lower compared to local cases indicates that future studies should also consider social contact patterns of travelers to better understand their impact on SARS-CoV-2 epidemics. Other estimates of the R_e for Switzerland during the same time period were similar to our baseline scenario (https://github.com/covid-19-Re; Huisman et al., 2022). However, these values likely represent overestimates. The results from our main scenario accounting for imports suggest that the local R_e was below 1 and that imported cases led to a steady growth in the number of confirmed cases. Our study therefore supports the notion that travelers play an important role in the spread of SARS-CoV-2 (Hodcroft et al., 2021; Shearer et al., 2022; Worobey et al., 2020), and provides further evidence that the contribution of imported cases on the local epidemic dynamics depends on the local incidence (Lemey et al., 2021; Russell et al., 2021). Furthermore, the risk of getting infected with SARS-CoV-2 while abroad can differ from the risk at home due to differences in incidence and behavior. Many infected travelers returned to Switzerland from countries with a similar incidence to Switzerland, but incidence levels varied widely within countries and were arguably higher in tourist hotspots. An earlier study indeed showed that the number of imported cases is typically higher than what one would expect based on the incidence and travel volume (Hodcroft et al., 2021). In addition, traveling is likely associated with leisure activities that result in a higher risk of infection (Coletti et al., 2021).

Public health measures to control the spread of SARS-CoV-2 from travelers will continue to play an important role in the global response against the SARS-CoV-2 pandemic. During the beginning of the pandemic, response strategies have varied enormously ranging from containment (e.g., Australia, New Zealand, or Taiwan) to mitigation (e.g., European countries and the United States). Compared to 2020 and 2021, the situation had changed considerably due to the increasing levels of naturally acquired and vaccine-elicited immunity that substantially reduced COVID-19-related morbidity and mortality. Hence, the continuation of travel measures such as screening, quarantine, isolation, contact tracing, vaccination passports, and travel restrictions have to be carefully balanced against the high societal and economic costs that accompany these measures (Ashcroft et al., 2021; Clifford et al., 2021; McCrone et al., 2022). The choice of an objective for (re-)implementing travel measures will likely depend on the local context and the global situation concerning SARS-CoV-2 transmission and the prevalence of variants of concern (VoCs). The expected seasonal variation in the level of SARS-CoV-2 transmission, the rise of the Omicron variant (Viana et al., 2022), and the expected emergence of future VoCs with altered transmission underlines the importance of internationally coordinated and evidence-based strategies to travel measures (Kucharski et al., 2022; McCrone et al., 2022). Though the outlook for SARS-CoV-2 may suggest that travel restrictions may play a less prominent role in the future, they are particularly critical before other methods of treatment or prevention, like vaccination, are available, or when they are limited. Thus, developing frameworks to better understand the role of imported transmissions is critical for being prepared for future pandemics, so that effective measures can be successfully implemented while minimizing disruption.

The results of this study advance our understanding of the role of imported cases on the local epidemic dynamics of SARS-CoV-2. We found that imported cases can explain the steady growth of the epidemic in Switzerland during summer 2020 and 2021, a period without strong surveillance and control measures for travelers. Improved screening and surveillance efforts targeting travelers can continue to be valuable tools for controlling

transmission of SARS-CoV-2, especially when local incidence is low.

Acknowledgment

We would like to thank the Swiss Federal Office of Public Health (FOPH) for providing surveillance data. Model simulations were performed on UBELIX (http://www.id.unibe.ch/hpc), the 'High-Performance Computing' cluster at the University of Bern.

Author contributions

MR, JR, and CA conceived and designed the study. MR performed the analysis. All authors contributed to the interpretation of the results. MR and CA wrote the manuscript. MR, JR, EB, RH, NH, and CA authors commented on the manuscript and approved the final version.

Competing interests of the authors

All authors declared no competing interests.

Funding

MR, NH, and CA received funding from the European Union's Horizon 2020 research and innovation program - project EpiPose (grant number 101003688). EH, RH, and CA were supported by the Swiss National Science Foundation (grant number 196046). JR was funded by the Swiss National Science Foundation (grant number 174281).

Importation of Alpha and Delta variants during the SARS-CoV-2 epidemic in Switzerland: phylogenetic analysis and intervention scenarios

Martina L Reichmuth[1]
Emma B Hodcroft[1,2,3]
Christian L Althaus[1,3]

[1] Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland
[2] Swiss Institute of Bioinformatics, Lausanne, Switzerland
[3] Multidisciplinary Center for Infectious Diseases, University of Bern, Bern, Switzerland

This article is published in ***PLOS Pathogens*** as Reichmuth et al. (2023). DOI:10.1371/journal.ppat.1011553.

Contribution: I contributed to the study design, performed all analysis, except the phylogenetic analysis, created all figures, except 1-3 from the supplementary material, wrote the first draft of the manuscript, and integrated co-authors' comments.

Abstract

The SARS-CoV-2 pandemic has led to the emergence of various variants of concern (VoCs) that are associated with increased transmissibility, immune evasion, or differences in disease severity. The emergence of VoCs fueled interest in understanding the potential impact of travel restrictions and surveillance strategies to prevent or delay the early spread of VoCs. We performed phylogenetic analyses and mathematical modeling to study the importation and spread of the VoCs Alpha and Delta in Switzerland in 2020 and 2021. Using a phylogenetic approach, we estimated 383-1,038 imports of Alpha and 455-1,347 imports of Delta into Switzerland. We then used the results from the phylogenetic analysis to parameterize a dynamic transmission that accurately described the subsequent spread of Alpha and Delta. We modeled different counterfactual intervention scenarios to quantify the potential impact of border closures and surveillance of travelers on the spread of Alpha and Delta. We found that implementing border closures after the announcement of VoCs would have been of limited impact to mitigate the spread of VoCs. In contrast, increased surveillance of travelers could prove to be an effective measure for delaying the spread of VoCs in situations where their severity remains unclear. Our study shows how phylogenetic analysis in combination with dynamic transmission models can be used to estimate the number of imported SARS-CoV-2 variants and the potential impact of different intervention scenarios to inform the public health response during the pandemic.

Keywords SARS-CoV-2; import; variants of concern; phylogenetics; tranmission model; travel regulation; surveillance.

3.1 Introduction

Since 2019, the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) has been spreading continuously, which has driven its evolution. Variants of concern (VoCs) have emerged which are associated with increased transmissibility, immune escape, changes in disease severity, or a combination thereof (WHO, 2023b). Alpha and Delta emerged in late 2020 and mid 2021, and their transmission dynamics were influenced by importations, the heterogeneous landscape of naturally acquired and vaccine-elicited immunity, and non-pharmaceutical interventions (NPIs) such as surveillance of travelers and travel restrictions. It was previously shown that the resumption of travel in summer 2020 after strict control interventions that - while varying by country - often involved border closures, working from home and restricting social contacts, led to the importation of a new SARS-CoV-2 variant that fueled epidemics in countries with low-incidence (Hodcroft et al., 2021; Lemey et al., 2020; Reichmuth et al., 2022b). In winter 2020/2021, Swiss authorities tightened travel restrictions again for travelers from the United Kingdom (UK) (FOPH, 2020), which were followed by overall stricter measures in Switzerland once concerns about the newly detected Alpha variant were communicated. To date, however, the impact of such travel restrictions and surveillance strategies to prevent or delay the introduction of VoCs are not well understood.

Global genomic surveillance is vital to capture the transmission dynamics of different SARS-CoV-2 variants around the world. Genomic and epidemiological data allow characterization and quantification of the spread of VoCs (Campbell et al., 2021; Chen et al., 2021; du Plessis et al., 2021; Earnest et al., 2022; Volz et al., 2021). At the end of 2020, deletions in the Alpha variant meant that Polymerase Chain Reaction (PCR) testing methods targeting a particular section of the S gene failed, leading to 'S gene target failure' (SGTF), which allowed tracking of the spread of Alpha, and in some cases, preferential sequencing of Alpha cases (Chen et al., 2021). Alpha, that was initially detected in the UK, showing a 37%-100% increase in transmissibility over previously circulating variants (Althaus et al., 2021; Campbell et al., 2021; Chen et al., 2021; Davies et al., 2021; Earnest et al., 2022; Volz et al., 2021). In early 2021, Alpha was continuously displaced by another VoC, Delta, which likely emerged in India (Vaidyanathan, 2021). For Delta, studies have estimated an increased transmissibility compared to previously circulating variants, which were predominantly Alpha in Europe and North America, Beta in South Africa, and Gamma in South America, between 40% and 167% (Campbell et al., 2021; Earnest et al., 2022). VoCs emerge in one place and spread to different countries through travel. Therefore, quantifying the impact of travel and imported SARS-CoV-2 cases can help guide pandemic responses, particularly prior to wide-spread vaccination. Routinely obtained surveillance data can provide valuable information about the place of exposure, but can be biased (Reichmuth et al., 2022b). Leveraging the wealth of genomic data offers the opportunity to integrate an additional level of information to inform the impact of travel and importation events. To try to prevent or slow the import of VoCs, some countries have introduced travel restrictions such as vaccination certificates, testing, or travel bans. Although travel restrictions have not prevented the global spread of VoCs, they could potentially mitigate the early spread and lessen the impact of new VoCs on hospitalizations and deaths until there is an improved understanding of new VoCs to then intervene appropriately.

Mathematical modeling studies and phylogenetic analyses are central to understand the transmission dynamics and evolution of infectious diseases and to inform public health decision making (Grassly and Fraser, 2008). For example, the early description of the emergence of Alpha was based on mathematical and statistical modeling approaches

and critically influenced the early response against the variant (Davies et al., 2021). Phylodynamic analyses have been used to study the evolution of infectious pathogens in intra- and inter-host systems (Grenfell et al., 2004; Volz et al., 2013). For example, BEAST (Drummond and Rambaut, 2007) can be combined with compartmental transmission models to infer epidemiological parameters such as the basic reproduction number R_0 (Stadler et al., 2012; Volz et al., 2017). Inter-host epidemiological dynamics have also been used to study the importation of infectious pathogens such as Zika virus, dengue virus or SARS-CoV-2 (Alm et al., 2020; du Plessis et al., 2021; Hodcroft et al., 2021; Ito et al., 2007; Lemieux et al., 2021; McCrone et al., 2022; Sun et al., 2017; Tayoun et al., 2020; Tegally et al., 2021). Integrating phylogenetic analyses with dynamic transmission models also has the potential to provide comprehensive inferences and projections of the SARS-CoV-2 pandemic.
In this study, we used a stepwise approach of phylogenetic analyses in combination with a dynamic SARS-CoV-2 transmission model to study the spread of VoCs in Switzerland. First, we reconstructed phylogenies of the Alpha and Delta variants to estimate the number of imported cases into Switzerland. Second, we modeled the importation and spread of Alpha and Delta in Switzerland. Finally, we simulated the impact of three counterfactual scenarios to mitigate the spread of Alpha and Delta.

3.2 Methods

Data

We used publicly available data from the Swiss Federal Office of Public Health (FOPH), CoV-Spectrum, and the Federal Statistical Office (FSO) on daily laboratory-confirmed SARS-CoV-2 cases, daily estimates of the effective reproduction number R_e, genomic metadata, and the population size (BFS, 2021; Chen et al., 2022a; FOPH, 2023a; Ganyani et al., 2020; Huisman et al., 2022; Stringhini et al., 2021a). We accessed sequencing data via GISAID (Elbe and Buckland-Merrett, 2017) on 15 February 2022, including data generated in Switzerland as part of a federal consortium (Goncalves Cabecinhas et al., 2021), to ensure the considered sequences encompass the introduction periods of Alpha and Delta into Switzerland. We used a combination of code from CoVariants.org and in-house scripts (available at https://github.com/emmahodcroft/Intros-CH-AlphaDelta) to select all Alpha (Nextstrain clade 20I) and Delta (Nextstrain clades 21A, 21I, and 21J) sequences sampled in Switzerland prior to 31 March 2021 and 31 July 2021, respectively, which are the dates when the proportion of each VoC was over 90% among all sequenced cases in Switzerland. We then ran the selected sequences through the Nextstrain ncov pipeline https://github.com/nextstrain/ncov, as modified for CoVariants.org, to generate 'focal' phylogenies (available at https://github.com/emmahodcroft/ncov_2021/tree/random_context_reduce). We minimized bias and improved phylogenetic inference by masking highly homoplastic sites and removing sequences with fewer than 27,000 bases, as recommended by De Maio et al. (2020). These focal trees contained all Alpha or Delta sequences from Switzerland before the 90% VoC representation date which passed quality control criteria. Alongside these, to maximize the chance of including closely related non-Swiss sequences, which allows detection of a putative importation, we included up to 10,000 non-Swiss, global 'context' sequences that were most genetically similar to our focal set. We chose the number of genetically similar sequences to have a dataset of approximately 15,000 to 18,000 sequences for computational tractability while resulting in 1.25 to 2 genetically similar global sequences per focal sequence. In addition, approximately 200 random 'background' sequences, distributed through time, were included to ensure the tree

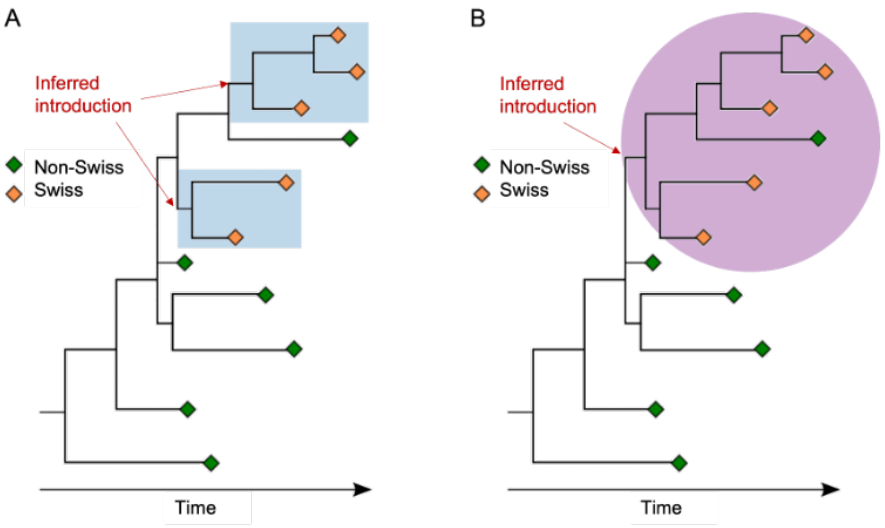

FIGURE 3.1: Illustrative example of the conservative and liberal approach to estimate the importation of VoCs to Switzerland. A) In the liberal approach, each subsequent subtree of only Swiss sequences is considered as a separate importation event. In this example, there would be two imports to Switzerland. B) In the conservative approach, subtrees with mixed Swiss and non-Swiss sequences are considered as one importation. Non-Swiss sequences are assumed to be exports from Switzerland or to originate from parallel evolution outside of Switzerland. In this example, there would be one import into Switzerland. More details are provided in the Supplementary Methods.

rooted correctly. Both of these context and background sequence sets were generated using the algorithms in the Nextstrain ncov pipeline (see Supplementary Methods), and were also sampled prior to 31 March 2021 and 31 July 2021 for Alpha and Delta respectively. The final set of sequences that we used for the analysis can be seen on GISAID under EPI_SET_221003xn (table B.2); 93% of the Swiss sequences are also available openly (table B.3). As a sensitivity analysis, we randomly downsampled all available sequences prior to our cutoff dates by 50% before selecting the most 10,000 genetically similar sequences, and repeated this ten times. The objective was to assess the influence of context sequencing coverage on our phylogenetic analysis and estimates of the imports.

Phylogenetic analysis

To estimate the number of imports of VoCs into Switzerland, we collapsed phylogenetic trees into clusters. As previously described in Hodcroft et al. (2021), we collapsed subtrees that contain only sequences from a single country into the parental node to form a polytomy. This process was repeated in a recursive 'bottom-up' fashion, such that every node eligible for collapsing was collapsed. After collapsing, we labeled internal nodes by the proportion of the geographic origin of their direct children (see Supplementary Methods for a more detailed explanation). Because both Alpha and Delta originated outside of Switzerland, the roots of these variants are non-Swiss, and thus, we inferred a putative import whenever a node without Swiss sequences led to a node with Swiss sequences. We used two approaches to estimate the number of imports, referred to as the liberal and conservative phylogenetic approach, which infer upper and lower bounds on the number of imports. The liberal approach considered any mixed Swiss and non-Swiss node as an introduction (fig. 3.1). On the other hand, when Swiss and non-Swiss sequences formed

a subtree (with mixed-country nodes leading to more mixed-country nodes), the conservative approach counted all directly linked mixed-country nodes as only one import, with further non-Swiss sequences assumed to originate from parallel evolution outside of Switzerland or exports from Switzerland (fig. 3.1). Import events were recorded and were then used to parameterize the transmission model (see next section about the transmission model).
The liberal approach may overestimate imports, as further exports from Switzerland to other countries or diversification within Switzerland could be wrongly considered imports. In contrast, the conservative approach considered only the earliest clusters with a Swiss sequence as imports, which means that further potential imports were strictly excluded. We chose the date of the earliest sequence of a cluster as the import date and shifted the date backwards by seven days to account for the delay from infection to case reporting, i.e., lag of detection. In a sensitivity analysis, we used a range of three to thirteen days for the lag of detection derived from du Plessis et al. (2021) (fig. 3.1). All code used to identify the selected sequences, to analyze the resulting phylogenies, to estimate the number of imports, and for the phylogenetic builds can be found on GitHub: github.com/emmahodcroft/Intros-CH-AlphaDelta.

Transmission model

Deterministic model
We used a deterministic, population-based transmission model for SARS-CoV-2 in Switzerland that was described by the following set of ordinary differential equations (ODEs) (fig. 3.2):

$$
\begin{aligned}
dS/d_t &= -\beta_t S I_1 - (1+\kappa)\beta_t S I_2 - \omega_t,\\
dE_1/d_t &= \beta_t S I_1 - \sigma E_1,\\
dE_2/d_t &= (1+\kappa)\beta_t S I_2 - \sigma E_2 + \omega_t,\\
dI_1/d_t &= \sigma E_1 - \gamma E_1,\\
dI_2/d_t &= \sigma E_2 - \gamma E_2,\\
dC_1/d_t &= \epsilon\gamma I_1 - \zeta C_1,\\
dC_2/d_t &= \epsilon\gamma I_2 - \zeta C_2,\\
dR_1/d_t &= (1-\epsilon)\gamma I_1 + \zeta C_1,\\
dR_2/d_t &= (1-\epsilon)\gamma I_2 + \zeta C_2,
\end{aligned}
$$

where susceptible individuals S can get infected by individuals that either carry the pre-circulating variant (I_1) or the imported VoC (I_2) at rates β_t and $(1+\kappa)\beta_t$, respectively. κ denotes the increased transmissibility of the imported VoC. We calculated κ from the estimated growth advantage ρ of the new VoC compared to the previously circulating variants using a logistic growth model (binomial regression) for the proportion of the new variant among all previously circulating variants (fig. B.5). Assuming no change in the generation time D and no immune evasion, $\kappa = \rho^* D/R_w$ (Althaus et al., 2021), where R_w is the effective reproduction number of the previously circulating variants during the time period of replacement. We sampled from that the publicly available estimates of the daily overall effective reproduction number R_e from 1 November 2020 to 31 January 2021 (early growth phase of Alpha) and from 1 April 2021 to 30 June 2021 (early growth phase of Delta), assuming the values correspond to R_w during these time periods (https://github.com/covid-19-Re, fig. 3.3, and Huisman et al. 2022). Additionally, we sampled from the estimated ρ and calculated the median κ. We then expressed the time-dependent transmission rate as a function of the overall R_e as follows:

$$\beta_t = \frac{R_e S}{(1+p\kappa)\gamma},$$

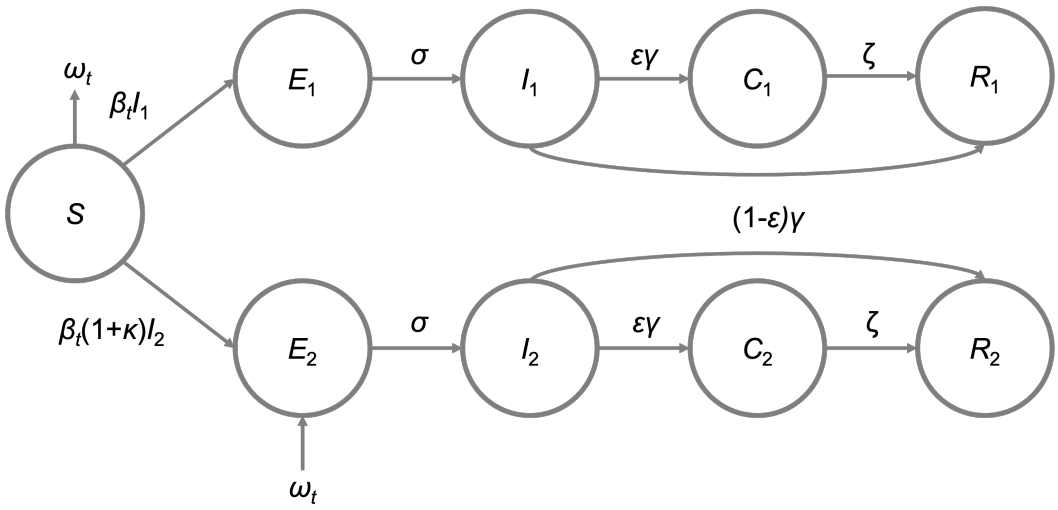

FIGURE 3.2: Scheme of the SARS-CoV-2 transmission model. The model includes individuals that were susceptible (S), exposed to the pre-circulating variant (E_1) or the imported VoC (E_2), infected with the pre-circulating variant (I_1) or the imported VoC (I_2), tested (C_1 and C_2), recovered from infection (R_1 and R_2). ω_t denotes the importation of VoCs as derived from the phylogenetic analysis.

where $p = E_2/(E_1 + E_2)$ corresponds to the proportion of the imported VoC. Exposed individuals E_1 and E_2 move through an incubation period at rate σ before they become infectious individuals I_1 and I_2 for $1/\gamma$ days. A fraction ϵ of infected infectious individuals enter a testing compartment where they get tested at rate ζ before entering the recovered compartment, whereas the remainder $(1-\epsilon)$ does not get tested and moves directly from the infected compartment to the recovered compartment. ω_t corresponds to the time-dependent rate of importation of VoCs. We parameterized the vector ω_t using the daily number of estimated imports from the phylogenetic analysis (fig. 3.4), e.g., ω_t for Alpha on 1 February 2021 was 8 and 2 for the liberal and conservative approach, respectively. We simulated importation of Alpha and Delta to Switzerland during the period from 1 October 2020 to 1 May 2021 and 1 February 2021 to 1 September. We designated variants as either 'Alpha', 'Delta' or 'other variants' and the mathematical modeling analyses started on 1 October 2020 for Alpha and 1 February 2021 for Delta and ended on 1 May and 1 September, respectively. The initial state variables and the model parameters were informed by the literature, demography, estimates, and assumptions (section 3.2). The initial number of recovered individuals infected with all previously circulating variants was informed by the Corona Immunitas study and set to 15% and 25% of the overall population for 1 October 2020 and 1 February 2021, respectively (https://www.corona-immunitas.ch). The initial numbers of exposed and infectious individuals infected with previously circulating variants were based on the number of laboratory-confirmed SARS-CoV-2 cases, the ascertainment rate, and the infectious period. The initial number of exposed and infectious individuals infected with the respective VoCs was set to zero. All other state variables, unless otherwise specified, were set to zero. Model simulations were performed in R (version 4.0.3) and code files are available on the following GitHub repository: github.com/ISPMBern/voc_imports_ch.

TABLE 3.1: Parameters for the transmission model.

Model parameter	Description	Value	**Source**
N	Population size	8,644,780	Swiss BFS (2023)
R_e	Effective reproduction number	fig. 3.3	Huisman et al. (2022)
β_t	Transmission rate of previously circulating variant		Based on R_e, where $p = E_1/(E_1 + E_1)$ corresponds to the proportion of the imported VoC
κ	Increased transmissibility of VoC	Alpha: 41% Delta: 56%	Estimated from genomic data (Chen et al., 2022a)
$1/\sigma$	Incubation period	2.6 days	Based on a generation time of 5.2 days Ganyani et al. (2020)
$1/\gamma$	Infectious period	2.6 days	Based on a generation time of 5.2 days Ganyani et al. (2020)
$1/\zeta$	Testing delay	2 days	Assumption
ω_t	Rate of importation of VoCs	fig. 3.4AB	Based on the phylogenetic analysis
ϵ	Ascertainment rate	50%	Informed by Stringhini et al. (2021a,b)

Counterfactual scenarios

We evaluated the potential impact of different intervention strategies to mitigate the spread of VoCs in Switzerland in various counterfactual scenarios:

a) Existing border closure: We assumed that borders were already closed at the time of the first estimated import. We then simulated the opening of borders 1 to 100 days after the first estimated import and introduced imports as estimated from that date forward.

b) Implemented border closure: We assumed that borders were closed on the day of the international warning about the VoCs. For Alpha and Delta, we stopped imports for 1 to 60 days after 16 December 2020 24 May 2021 (ECDC, 2021b; Wise, 2020).

c) Increased surveillance of travelers: We assumed improved surveillance, quarantine, and isolation of travelers. We performed simulations where we reduced the number of simulated imports by randomly selecting 1 to 99% of the estimated imports from the phylogenetic analysis.

We calculated the time to dominance (>50%) of the VoC and compared it to the time to dominance as observed in Switzerland. Counterfactual scenarios that did not reach dominance within the predefined period were excluded from the analysis.

Stochastic model

We used a generic branching process model to investigate the impact of stochastic effects during the early growth phase of variants. The model accounts for superspreading of SARS-CoV-2 and simulates epidemic trajectories with 1, 10, and 100 seeds, which can be interpreted as imports. The branching process was based on a negative binomial distribution to describe the number of secondary cases, with a mean corresponding to R_e and overdispersion parameter κ (Althaus, 2015; Reichmuth et al., 2022b; Riou and Althaus, 2020). The generation time was sampled from the gamma distribution with a mean of 5.2 days and a standard deviation of 1.72 days (Ganyani et al., 2020). For R_e

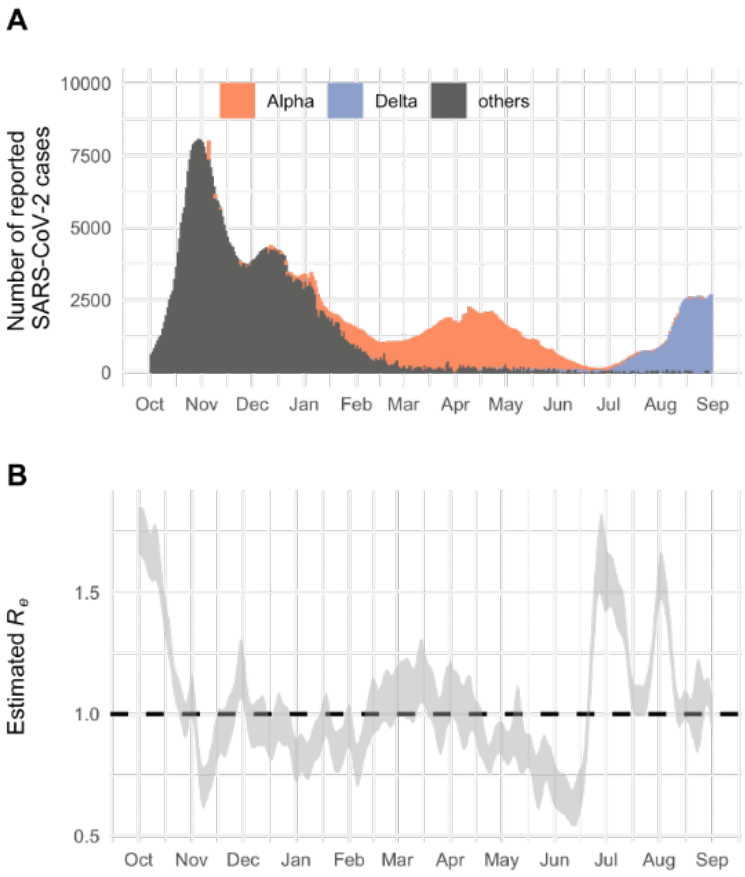

FIGURE 3.3: SARS-CoV-2 epidemic in Switzerland from October 2020 to September 2021. A) Number of laboratory-confirmed SARS-CoV-2 cases per day. B) Effective reproduction R_e number of SARS-CoV-2 in Switzerland.

of the variant, we randomly drew 10^4 values from a uniform distribution between 1.05 to 1.15. For each seeding scenario, we simulated 10^4 epidemic trajectories.

3.3 Results

In autumn 2020, the effective reproduction number R_e of SARS-CoV-2 increased substantially which led to a rapid exponential increase in laboratory-confirmed cases in Switzerland (fig. 3.3). In the following weeks and months, cantonal and federal authorities strengthened control measures that led to a reduction of R_e (fig. B.6). On 16 December 2020, researchers in the UK announced a newly discovered SARS-CoV-2 variant with a potentially increased transmissibility (Alpha). In response to these findings, the Swiss federal authorities introduced travel restrictions to travelers from the UK and increased sequencing coverage of SARS-CoV-2 (FOPH 2023a and fig. B.6). Nevertheless, Alpha then replaced the previously circulating variants during a period of high incidence from January to March 2021, pushing R_e above 1 again. Based on genomic sequencing, we estimated that Alpha reached dominance (>50%) in Switzerland on 5 February 2021. In May 2021, Delta was identified as a new VoC. Subsequent growth of Delta in June and July 2021 led to an increase of laboratory-confirmed SARS-CoV-2 cases during summer 2021. We estimated that Delta reached dominance in Switzerland on 27 June 2021. The simulated timing of dominance lagged estimates from sample data more for Alpha than

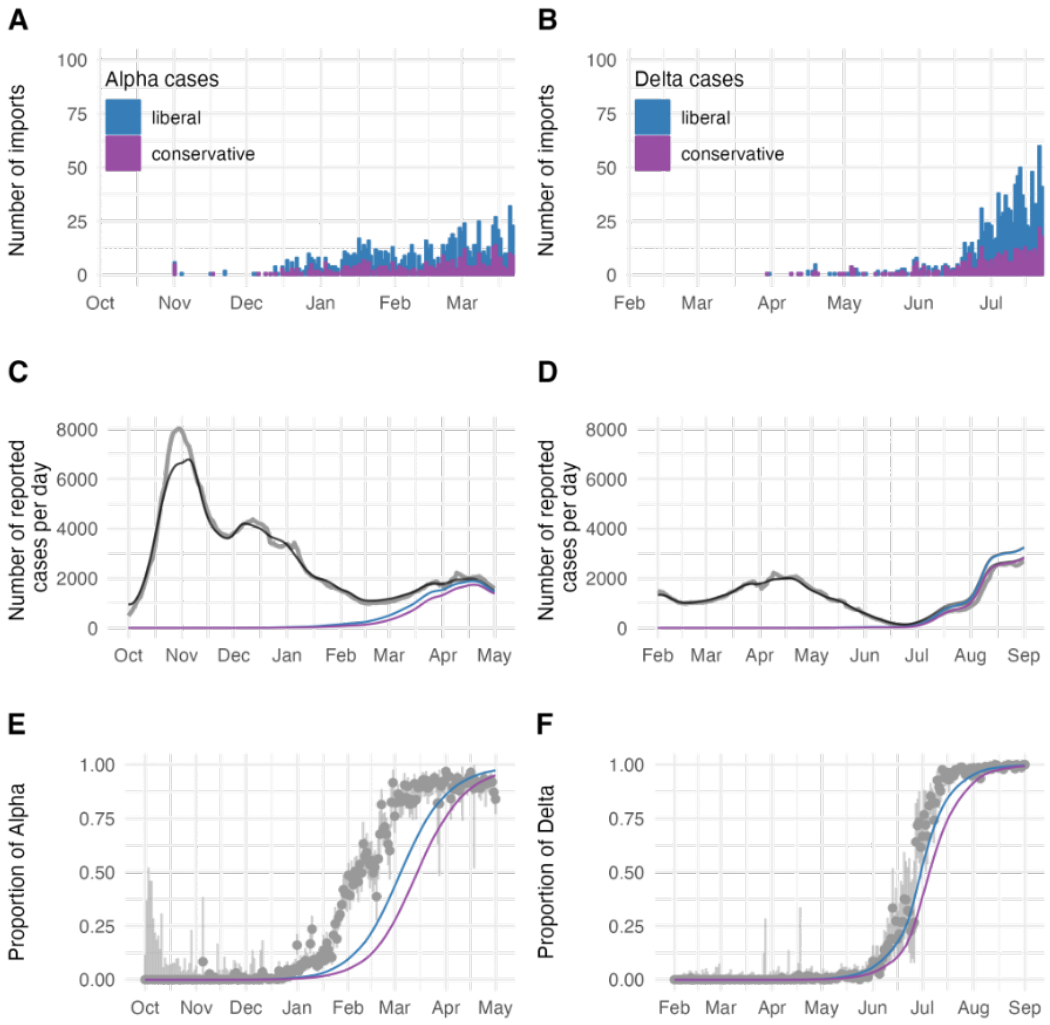

FIGURE 3.4: Dynamics of Alpha and Delta importation to Switzerland. A-B) Number of imports estimated with the phylogenetic analysis. C-D) Number of laboratory-confirmed SARS-CoV-2 cases per day (gray). The black lines show the overall simulated number of reported cases. The blue and purple lines show the simulated number of VoC cases. E-F) Proportion of reported Alpha and Delta among all SARS-CoV-2 infections. Gray: Genomic surveillance data. Blue: Liberal approach. Purple: Conservative approach.

for Delta, which might have been influenced by missing early imports indicated by larger clusters for Alpha than for Delta at the beginning (fig. B.7).

We estimated the number of Alpha and Delta importations to Switzerland using two phylogenetic approaches. The Alpha tree contained 7,988 Swiss Alpha sequences, 9,901 non-Swiss context sequences, and 162 background sequences. The Delta tree contained 5,210 Swiss Delta sequences, 9,973 non-Swiss context sequences, and 147 background sequences. Using the liberal approach, we found 1,038 and 1,347 imports of Alpha and Delta into Switzerland, respectively (fig. 3.4 and table B.1). With the conservative approach, we found 383 and 455 imports of Alpha and Delta into Switzerland, respectively. In our sensitivity analysis where we removed half of the available non-Swiss sequences before identifying the most genetically similar sequences to our Swiss sequences, the liberal and conservative approach had similar results as using the baseline sampling method (fig. B.8).

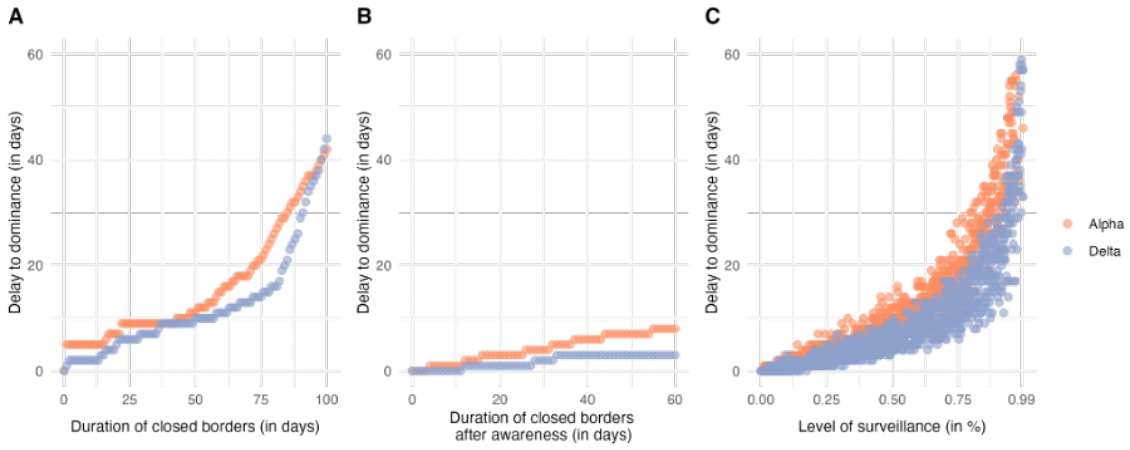

FIGURE 3.5: Counterfactual scenarios for mitigating the spread of VoCs in Switzerland. A) Existing border closure. B) Implemented border closure after warning about VoC. C) Increased surveillance of travelers.

We then introduced these estimated imports in the deterministic SARS-CoV-2 transmission model, which resulted in 593,418 and 592,768 simulated reported cases from 1 October to 1 May with the liberal and conservative approach, respectively, compared to 606,575 cases reported by the FOPH (fig. 3.4 and table B.1). For 1 February to 1 September, we simulated 288,397 and 271,702 SARS-CoV-2 cases with the liberal and conservative approach, respectively, compared to 260,933 cases reported by the FOPH (fig. 3.4 and table B.1).

To better understand the dynamics of VoCs replacing previously circulating variants, we estimated the time VoCs reached dominance. With the liberal approach, Alpha reached 50% of all infections on 5 March 2021 and Delta reached 50% on 30 June 2021 (fig. 3.4). With the conservative approach, dominance was reached somewhat later, namely on 22 March 2021 and 9 July 2021, respectively. Compared to genomic monitoring data, the model lagged 28 to 45 days behind for Alpha and 3 to 12 days behind for Delta, respectively. This suggests that either the liberal approach better approximates the true number of imported cases that resulted in subsequent transmission chains, that certain events during the early phase of importation accelerated the growth of VoCs, or both. Stochastic simulations of imported variants highlight that the expected variation in the early growth phase can shift the epidemic trajectories by several weeks (fig. B.9).

We investigated different counterfactual scenarios to assess the impact of border closures and increased surveillance of travelers on the early spread of VoCs. Existing border closures at the time of the first estimated import could delay the time to dominance from a few days to several weeks (fig. 3.5). Longer border closures result in increasing returns, e.g., doubling the time of closed borders from 50 to 100 days increases the time to dominance roughly 4-fold. Complete border closure for 100 days delayed the time to dominance by around 40 days. The effect of closed borders is substantially reduced when implemented after the international warning (fig. 3.5). Increased surveillance of travelers that reduces the number of imported VoCs that result in a subsequent transmission chain by 25%, 50%, and 75% would delay the time to dominance of Alpha for 4, 10, and 19 days (95% confidence interval, CI: 2-6, 7-14, and 13-28 days) and of Delta for 3, 6, and 14 days (95% CI: 2-5, 5-10, and 8-18 days) (fig. 3.5).

3.4 Discussion

We used a combination of phylogenetic analysis and dynamic transmission modeling to estimate the number of imported VoCs and simulate the impact of counterfactual intervention scenarios in Switzerland. In the phylogenetic analysis, we found that single importation events happened early, and at least several hundred Alpha (383-1,038) and Delta (455-1,347) cases were introduced into the Swiss SARS-CoV-2 epidemic during the study period. The actual number of imports is likely between these estimates. From our sensitivity analysis, we saw that even if there had been substantially less sequencing outside of Switzerland to help infer imports, we would still detect around the same number of introductions. The integration of these importation events into a transmission model accurately described the subsequent spread of VoCs. We estimated a 41% and 56% increased transmissibility of Alpha and Delta compared to previously circulating variants, which is in the range of previously reported estimates (Althaus et al., 2021; Campbell et al., 2021; Chen et al., 2021; Davies et al., 2021; Earnest et al., 2022; Volz et al., 2021). Applying our transmission model using counterfactual intervention scenarios showed that only very strict or existing control measures would substantially delay the time to dominance of VoCs. In contrast, implementing border closures after international warnings delayed the time to dominance of VoCs by a few days only. Increased surveillance of travelers - which is less disruptive than border closures - could prove effective for delaying the spread of VoCs in situations where their severity remains unclear. These findings have important implications for informing intervention strategies in the case of newly emerging SARS-CoV-2 VoCs and future pandemic preparedness.

The major strength of our study is the combination of phylogenetic analyses with a dynamic transmission model. This not only allowed us to estimate the number of imports but also to investigate counterfactual intervention scenarios. Our phylogenetic approach to estimate imported variants is standardizable and thus applicable to other countries with similar genomic surveillance and other emerging pathogens.

Our study also has a number of limitations. First, we used a deterministic transmission model for our main analysis and ignored the potential effects of stochasticity during the importation and early growth phase of VoCs. In the model, we assumed that all imported VoCs enter a deterministic growth trajectory. In contrast, some imported VoCs might not result in continuous transmission chains and go extinct even with R_e >1. We showed that stochastic effects during importation and the early growth phase can cause a variation in the time to dominance of several weeks. With the phylogenetic analysis, we found sufficiently large transmission clusters and imports of VoCs that were successfully established in the local population. Second, we fixed the generation time for Alpha, Delta, and earlier circulating variants to 5.2 days. There is some evidence that the generation time of Delta is somewhat shorter (Hart et al., 2022), but we do not expect this to affect our results substantially. Third, we did not consider the importation of other variants that could compete with the new VoCs. Since the new VoCs were characterized by an increased transmissibility, we do not expect this assumption to substantially affect the dynamics of the new VoCs replacing previously circulating variants. Fourth, we did not consider co-infection with different variants (Rockett et al., 2022). As we focus our analysis on the spread of VoCs and not on their evolution, we do not expect this to affect our results substantially. Fifth, we assumed a constant ascertainment of SARS-CoV-2 infections of 50%, which was informed by seroprevalence studies (Stringhini et al., 2021a,b). During the study period, test positivity varied and ascertainment might have fluctuated as well. Thus, our transmission model cannot precisely describe the overall number of infections, which was not the objective of our study. In addition, the high variation in genomic sequencing among different countries can influence the estimated number of imports

from the phylogenetic analysis. For example in Switzerland, the sequencing coverage increased from 2% in December 2020 (just after the first importation of Alpha) to 10% in April 2021 (during the first importation of Delta) (Dong et al., 2020; FOPH, 2023a), and was on average 14% for our study period (1 October 2020 to 1 September 2021). The limited sequencing efforts during the introduction of the Alpha variant may hinder the detection of early imports and splitting clusters accurately. Sixth, the lag time of detecting an import and the true introduction might vary by testing and sequencing strategies, e.g., du Plessis et al. (2021) reported a detection lag of 3 to 13 days of the introduced cluster time of the most recent common ancestor (TMRCA) to the true importation (du Plessis et al., 2021). Finally, the phylogenetic analysis has intrinsic limitations due to the fact that not every infection is detected or sequenced, and interpretation during outbreaks requires caution (Lemey et al., 2020; Villabona-Arenas et al., 2020), which was also highlighted at the beginning of the pandemic by Morel et al. (2021). This is specifically true for Alpha, which appeared at the end of 2020, prior to sequencing in Switzerland being scaled up considerably during 2021. To further mitigate the impact of sequencing error and unreliable sequences, as highlighted by Turakhia et al. (2020), we excluded sequences with poor coverage and low quality control scores and masked homoplastic sites. There is currently no gold standard for estimating imports. Uncertainty in creating and interpreting phylogenies can lead both to imports being underestimated due to considering only one importation event per cluster and overestimated due to within-country diversification or further exports. In our analysis, we aimed to address this issue, by using two approaches to estimate lower and upper bounds on the number of imports. The liberal approach considered any cluster containing Swiss sequences as an importation event. If the sequencing coverage was low, the liberal approach would thus overestimate imports and exports could cause Swiss sequences to be falsely classified as imports. In contrast, the conservative approach considered only the earliest clusters with Swiss sequence as imports, which means that further potential imports were strictly excluded.
For monitoring the transmission dynamics of SARS-CoV-2, it is important to differentiate between locally-acquired and imported infections, particularly in situations when the local incidence of infections is low (Reichmuth et al., 2022b). Scalia Tomba and Wallinga (2008) emphasized the significance of estimating the impact of travel on infectious disease transmission and the potential effectiveness of interventions on the local spread, particularly highlighting that initial importation events will eventually lead to a local epidemic if not contained, whereas importations after local expansion have begun are less impactful (Scalia Tomba and Wallinga, 2008). Using an example of pandemic influenza, they estimated that a 90% reduction of imports would delay the first importation event by 11.5 days. Based on routine surveillance data from FOPH, we previously extrapolated a total of 6,211 and 37,061 imported cases in Switzerland during summer 2020 and 2021, respectively. Using genomic data to estimate the number of imports might have the advantage of being less prone to the bias in routine surveillance data. Other studies also using phylogenetics estimated the number of imported infections during the early phase of the SARS-CoV-2 pandemic. For example, 13 and 101 introductions were estimated to South Africa over two and eight months (Pung et al., 2023; Tegally et al., 2021), 120 introductions were estimated in Boston over three months (Lemieux et al., 2021), and more than 1,000 introductions were estimated to the UK over three months (du Plessis et al., 2021). During summer 2020, we estimated 34 to 291 introductions of the SARS-CoV-2 variant EU1 to Switzerland over four months (Hodcroft et al., 2021). Phylogenetics offers an advantage in estimating imports by leveraging sequence data that was readily produced by many countries in the pandemic, but can be limited by insufficient coverage to detect importations, fluctuations in coverage, and dependence on other countries to

also sequence sufficiently. Methods such as that employed by Pung et al. (2023) in Singapore can incorporate detailed case finding and contact tracing data to break down the impact of different measures even further, but the availability of such data varies widely across countries and pandemic stage.

Global genomic surveillance is essential to monitor the emergence and spread of VoCs. As of February 2023, more than 14 million SARS-CoV-2 sequences have been submitted to GISAID (Elbe and Buckland-Merrett, 2017). This effort facilitated the early identification of several VoCs, such as Omicron in November 2021 (Viana et al., 2022). Early detection of variants with substantial immune evasion or altered severity can inform policy makers to adjust control measures, vaccination programs, and health systems. For example, several countries imposed controversial travel bans for visitors from South Africa to prevent importation of Omicron (Mallapaty, 2021). In our analysis, we found that complete border closures following warnings of VoCs have limited impact and delay their spread by a couple of days only. Hence, travel bans and any time they may buy for certain interventions, such as increasing the uptake of booster vaccines, have to be carefully balanced against the societal and economic costs that accompany them. Similar to our findings, McCrone et al. (2022) reported that control measures that had just been introduced in response to warnings about Delta were late, as introductions have already occurred to other countries. In addition to studying importation and exportation events of VoCs, it is important to better understand the spread of VoCs in the local context. Variations in naturally-acquired and vaccine elicited levels of immunity, local control measures, mobility, and behavior can strongly influence the local spread of VoCs. Taking these factors into account will be critical to inform country-specific strategies to respond to the emergence of new VoCs.

Integrating phylogenetic analyses with dynamic transmission models can provide critical insights into the importation and early spread of SARS-CoV-2 VoCs, and how they are impacted by different intervention scenarios. In this study, we showed that border closures would have had a limited impact on the spread of Alpha and Delta in Switzerland. In contrast, increased surveillance of travelers can potentially delay the spread of VoCs by several weeks, which can buy time for health systems to prepare for new epidemic waves.

Data and code availability

The data of confirmed SARS-CoV-2 cases are openly shared by the Swiss FOPH and sequence data are available on GISAID after registration, as EPI_SET_221003xn. Most Swiss sequences (93%) that we used are also available openly. Our code is openly accessible in the following repositories: github.com/ISPMBern/voc_imports_ch (https://doi.org/10.5281/zenodo.7994708) for the transmission modeling, https://github.com/emmahodcroft/ncov_2021/tree/random_context_reduce (https://doi.org/10.5281/zenodo.7970773) for the phylogenetic analysis and github.com/emmahodcroft/Intros-CH-AlphaDelta (https://doi.org/10.5281/zenodo.7970756) for the inference of importations.

Acknowledgements

We gratefully acknowledge all data contributors, i.e., the authors and their originating laboratories responsible for obtaining the specimens, and their submitting laboratories for generating the genetic sequence and metadata and sharing via the GISAID Initiative, on which this research is based. We also gratefully acknowledge and thank all labs around the world that have collected and shared SARS-CoV-2 sequences we used in our study. A complete list of the labs that generated the data we used from GISAID can be found at doi.org/10.55876/gis8.221003xn. In particular, we want to especially thank the Swiss laboratories that perform SARS-CoV-2 sequencing, namely 'Hôpitaux Universitaires Genève' (HUG), the 'Centre hospitalier universitaire vaudois' (CHUV), the 'Universitätsspital Basel', the 'Institut für Infektionskrankheiten' (IFIK) of the University of Bern, 'Institute of Medical Virology' (IMV) of the University of Zurich, the 'Ente Ospedaliero Cantonale' (EOC) in Bellinzona, and 'Institut Central des Hôpitaux du Valais'.

Author contributions

MR, EH, and CA conceived and designed the study. EH estimated the imports using a phylogenetic analysis. MR performed mathematical modeling and wrote the first draft of the manuscript. MR, EH, and CA contributed to the interpretation of the results, and writing of the manuscript, and approved the final version.

Competing interests of the authors

MR, EH, and CA declare no competing interests.

Funding

MR and CA were supported by the European Union's Horizon 2020 research and innovation program - project EpiPose (No 101003688). CA and EH received funding from the Swiss National Science Foundation (No 196046).

Social contacts in Switzerland during the COVID-19 pandemic: insights from the CoMix study

Martina L Reichmuth[1]
Leonie Heron[1]
Philippe Beutels[2]
Niel Hens[2,3]
Nicola Low[1,4]
Christian L Althaus[1,4]

[1] Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland
[2]Centre for Health Economic Research and Modelling Infectious Diseases, Vaccine and Infectious Disease Institute, Antwerp, Belgium
[3]Data Science Institute, I-BioStat, Hasselt University, Hasselt, Belgium
[4]Multidisciplinary Center for Infectious Diseases, University of Bern, Bern, Switzerland

This article is *under review* and the data is available as Reichmuth et al. (2023). DOI:10.5281/zenodo.10147647

Contribution: I contributed to the study design, performed all analyses, made all figures, and partly wrote the first draft of the manuscript.

Abstract

To mitigate the spread of SARS-CoV-2, the Swiss government enacted restrictions on social contacts from 2020 to 2022. In addition, individuals changed their social contact behavior to limit the risk of COVID-19. In this study, we aimed to investigate the changes in social contact patterns of the Swiss population.

As part of the CoMix study, we conducted a survey consisting of 24 survey waves from January 2021 to May 2022. We collected data on social contacts and constructed contact matrices for the age groups 0-4, 5-14, 15-29, 30-64, and 65 years and older. We estimated the change in contact numbers during the COVID-19 pandemic to a synthetic pre-pandemic contact matrix. We also investigated the association of the largest eigenvalue of the social contact and transmission matrices with the stringency of pandemic measures, the effective reproduction number (R_e), and vaccination uptake.

During the pandemic period, 7,084 responders reported an average number of 4.5 contacts (95% confidence interval, CI: 4.5-4.6) per day overall, which varied by age and survey wave. Children aged 5-14 years had the highest number of contacts with 8.5 (95% CI: 8.1-8.9) contacts on average per day and participants that were 65 years and older reported the fewest (3.4, 95% CI: 3.2-3.5) per day. Compared with the pre-pandemic baseline, we found that the 15-29 and 30-64 year olds had the largest reduction in contacts. We did not find statistically significant associations between the largest eigenvalue of the social contact and transmission matrices and the stringency of measures, R_e, or vaccination uptake.

The number of social contacts in Switzerland fell during the COVID-19 pandemic and remained below pre-pandemic levels after contact restrictions were lifted. The collected social contact data will be critical in informing modeling studies on the transmission of respiratory infections in Switzerland and guiding pandemic preparedness efforts.

Keywords SARS-CoV-2; contact pattern; Switzerland; survey; CoMix; control measures; human behavior.

4.1 Introduction

The spread of respiratory pathogens, such as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is largely influenced by human contact behavior and mobility (Tomori et al., 2021). SARS-CoV-2, which causes COVID-19, is mainly transmitted via respiratory droplets, aerosols, and close contact, with varying levels of susceptibility and transmissibility across different age groups (Davies et al., 2020; Leung, 2021; Richard et al., 2020). Understanding the number of close contacts between different communities is crucial for estimating and evaluating transmission dynamics (Mossong et al., 2008). This requires empirical data on social contacts that provide information on the mixing behavior of communities over time (Kiti et al., 2023). More specifically, age-stratified matrices of social contacts can provide important information for mathematical models of disease transmission and allow an assessment of the potential impact of physical distancing measures, such as working from home or restrictions for gatherings and events (Jarvis et al., 2020; Wallinga et al., 2006). Hence, it is critical to collect and analyze age-specific social contact data for individual countries (Mossong et al., 2008), across different settings (Leung, 2021), in the presence of different interventions (Backer et al., 2021; Coletti et al., 2020; Gimma et al., 2022; Hens et al., 2009; Jarvis et al., 2020, 2021; Wong et al., 2023), and over time (Verelst et al., 2021).
As part of the CoMix study, 19 European countries collected empirical social contact data using a common survey design (Verelst et al., 2021). Within this collaboration, (Jarvis et al., 2020) estimated a 74% decline in age-specific social contact data in the UK in early 2020 (Jarvis et al., 2020). They used the largest eigenvalue approach (Diekmann et al., 1990). The largest eigenvalue of a transmission matrix of the next-generation matrix scales linearly with the reproduction number, the average number of secondary cases from an infected individual (Munday et al., 2021). Thus, the largest eigenvalue approach enables a comparison of the number of contacts between different time points. Consequently, they were able to estimate the change in the reproduction number under different distancing measures using contact information from the CoMix study in the UK and showed that physical distancing measures adopted by the UK population have substantially reduced contact levels, which by affecting the reproduction number can lead to a substantial decline in COVID-19. Coletti et al. (2020) also estimated an 80% reduction in contacts for March and April 2020 in Belgium (Coletti et al., 2020).
While detailed data on social contact patterns has been collected for many countries (Coletti et al., 2020; Feehan and Mahmud, 2021; Jarvis et al., 2021; Kiti et al., 2023; Mossong et al., 2008; Verelst et al., 2021; Wong et al., 2023), there has been no nationwide study on contact patterns for Switzerland to date. Smieszek et al. (2012) and Smieszek (2009) showed in a sample of around 50 participants that heterogeneity in transmission of respiratory pathogens also matters in a Swiss context. But due to the lack of a nationwide study on contact patterns, mathematical modelers have relied on either synthetic contact matrices or on social contact data from neighboring countries, such as Germany (Brugger and Althaus, 2020; Mossong et al., 2008; Prem et al., 2021).
The COVID-19 pandemic highlighted that longitudinal monitoring of detailed contact data for Switzerland is necessary for better understanding the impact of interventions on contact behavior and transmission, modeling the spread of respiratory infections across age groups, and guiding decision making during the pandemic response. Therefore, Switzerland participated in the CoMix study.
Here, we present the results of the CoMix study in Switzerland. We collected and analyzed social contact data and estimated the change in contact numbers during January 2021 to May 2022 compared to a synthetic pre-pandemic baseline. Moreover, we investigated the association of the largest eigenvalue of the social contact and transmission

matrices with the stringency of pandemic measures, the effective reproduction number Re, and vaccination uptake. Finally, we discuss the implications of our findings for the future study of social contacts in Switzerland.

4.2 Methods

Data

CoMix is a social contact survey that followed participants in 19 European countries throughout the COVID-19 pandemic (Verelst et al., 2021). The design of the CoMix survey is largely based on the POLYMOD study from Mossong et al. (2008). For CoMix, the market research company, Ipsos, enrolled participants for online panels through multi-source recruitment methods, including referral by online suppliers, website banners and advertisements, and search engine marketing. Volunteers who were part of an online panel were sent an email invitation to join the CoMix survey. In Switzerland, we conducted 24 survey waves from 22 January 2021 to 19 May 2022. The waves were clustered in 6 panels where participants were followed longitudinally. The aim was to include 1,000 participants per panel. Due to the lack of participants, new participants were also included after the first wave of each panel. The panels were selected to be nationally representative for quotas on age, gender, and region of residence. Participants could answer the questionnaire in three national languages, i.e., German, French, or Italian. The survey included adults aged 18 years and older (in panels A, B, and F) and parents (at least 18 years old) who completed the surveys on behalf of their children (younger than 18 years old; panels C, D, and E). For parents, quotas were set on region only. Participants reported their social contacts made on the day prior to survey participation. A contact was defined as anyone who met the participant in person with whom at least a few words were exchanged, or physical contact was made. The survey data include the gender and exact age of participants or the median age if the exact age was unknown (8.2%). All adult participants reported their ages, but parents only provided an age range for their children, namely 0-1, 1-4, 5-11, 12-15, and 16-17 years. The data also include information on residence (26 Swiss cantons), place of contact (at home, at work, at school, in a means of transport, or during leisure activity), age range of contacts, contact frequency, contact duration, whether contacts were within the household, whether contacts were individual or in a group, and the date of the contact. The social contact data used for this study are openly available on Zenodo (doi.org/10.5281/zenodo.10147647) and can be analyzed using the R package `socialmixr` (Funk and Willem, 2022).
For our study, we used CoMix data on social contacts and supplemented the analysis with additional data. We have reported the number of hospitalized patients from FOPH data to describe the Swiss SARS-CoV-2 epidemic over time. We estimated the effective reproduction number R_e from the number of laboratory-confirmed SARS-CoV-2 cases provided by the Swiss Federal Office of Public Health (FOPH) (https://www.covid19.admin.ch/api/data/context) (Prem et al., 2021). We estimated the proportion of SARS-CoV-2 variants during the study period from genomic data and combined the proportions with estimates of the growth advantage of the variants from the literature (https://cov-spectrum.org/) (Campbell et al., 2021; Chen et al., 2022a; Suzuki et al., 2022). We used the KOF ('Konjunktur-Forschungsstelle', meaning economic research center in English) Stringency Index from Pleninger et al. (2021) (https://datenservice.kof.ethz.ch) as a proxy measure for the stringency of control interventions. We extracted seroprevalence estimates for SARS-CoV-2 of the Swiss population from the Corona Immunitas studies (www.corona-immunitas.ch) (Amati et al., 2022; Frei et al., 2023; Tancredi et al., 2023). We extracted data of the synthetic contact matrix for Switzerland from Prem et al. (2021)

as a pre-pandemic baseline. The synthetic matrix includes the number of contacts for one day. The contacts are divided into 16 age groups (starting at 0 and continuing in 5-year steps). The synthetic contact matrices are based on country-specific demographic and contact data collected as part of the POLYMOD study, which was conducted in eight non-Swiss European countries. We used demographic information of the Swiss population from the Federal Statistics Office (FSO or BFS in German) (www.bfs.admin.ch) (BFS, 2022).

Analysis

For the analysis of social contact data, we considered five groups of 0-4, 5-14, 15-29, 30-64, and 65+ year olds, which correspond to the age groups used for reporting by Sentinella, the Swiss Sentinel Surveillance Network (Somaini et al., 1986). Note, as we had no exact age for children, we used the median of reported age groups to assign for Sentinella age groups. Thus, we assigned to the 5-14 years cohort 1/10 extra, and to the 15-29 years cohort 1/15 less. We converted the age groups of the synthetic contact matrix for Switzerland from Prem et al. (2021). To estimate the number of contacts per survey wave, we split the age group of 15-29 years into two groups of 15-17 and 18-29 years. We randomly truncated the number of reported contacts at 50 contacts to reduce bias from outliers. If participants did not report the exact age of the contact, we sampled their age based on the reported range.
We estimated the crude mean number of contacts per day. Then, we constructed social contact matrices using the R package `socialmixr` (Funk and Willem, 2022). To account for the weekend effect, we weighted the contacts according to the day of the week, i.e., weekends and weekdays were weighted differently. The weighting compensates for the uneven distribution of five working days and two weekend days. Noting, the number of contacts during working days may differ from the number of contacts during leisure time. Weights for the days were calculated as follows:

$$w_{dayofweek} = 5/7/(N_{weekday}/N) \text{ or } 2/7/(N_{weekday}/N),$$

where N is the overall sample size and $N_{weekday}$ and $N_{weekend}$ the number of participants that were surveyed during weekdays and weekends, respectively. We adjusted the daily mean number of contacts (of the survey data and the synthetic contact matrices) using the age distribution of the Swiss population for the year 2021. Data for 2022 was not available while conducting the analysis. We further accounted for reciprocity of contacts. Reciprocity may be lost due to sampling differences in age groups. Contacts should be based on reciprocity, i.e., $m_{ij}N_i$ should be equal to $m_{ij}N_j$:

$$m'_{ij} = (m_{ij}N_i + m_{ij}N_j)/(2N_i),$$

where m_{ij} is the mean number of contacts of age group i with age group j, and N_{iorj} is the total number of people in age group i or k. Finally, we generated 100 bootstrap samples of the contact data and followed the same procedure to calculate matrices to account for uncertainty in the reported number of contacts in the survey sample.
From the matrices, we summed the overall number of contacts for survey contacts for the following panels, A and C (22 January to 17 May 2021), B and D (3 June to 15 September 2021), and E and F (9 December 2021 to 19 May 2022). We compared this number to a synthetic pre-pandemic baseline and calculated the relative number of contacts by age group.
Next, we adapted the next generation approach and calculated the effective contact rate c_{eff} from the largest eigenvalue of the contact matrix C_t from survey wave t (Diekmann et al., 1990):

$$c_{eff} = Eig(C_t).$$

In the main analysis, we calculated the largest eigenvalue of the contact matrix for each survey wave of the adults pooled with all survey waves of the children. We investigated the association of the largest eigenvalue of the contact matrix with the stringency of pandemic measures and the vaccine coverage using linear regression.
We also calculated the largest eigenvalue of the transmission matrix that accounts for susceptibility, the level of immune protection, and the relative growth rate of different SARS-CoV-2 variants in proportion to their monitored occurrence (table C.1). Precisely, we calculated the largest eigenvalue of the transmission matrix β by multiplying the contact matrices with the outer product ($\otimes$) of the infectiousness and susceptibility vectors for the different age groups and scaled with the relative growth rate κ:

$$\beta = \kappa\ Eig(C_t \circ (i \otimes s)).$$

For simplicity, we set the infectivity i to 1 and the baseline susceptibility s to 0.5 and 1 for children and adults, respectively (Munday et al., 2021). The susceptibility vector was then multiplied by one minus the seroprevalence times the level of immune protection, which we assumed to be at 90% in the main analysis (table C.1). We investigated the association of the largest eigenvalue of the transmission matrix with R_e using linear regression. We estimated R_e from the daily number of laboratory-confirmed SARS-CoV-2 cases using the R package `EpiNow2` (Abbott et al., 2020, 2023). For computational and content reasons, we run intervals of 1.5 months covering the time of survey waves and intervals overlapped for 2 weeks with the previous run. We used an incubation time of 5.2 days with a standard deviation (sd) of 2.8 days (Zhang et al., 2020), a generation time of 5.2 days (sd = 1.72 days) (Ganyani et al., 2020), and assumed a reporting delay of 2 days (sd = 2 days). `EpiNow2` takes the weekly noise into account by explicitly considering a weekend effect in reported case numbers.
In a sensitivity analysis, we also considered contact and transmission matrices that included survey waves in adults (participants $\geq$18 years) with the wave in children (participants younger < 18 years) closest in time, and varied our assumptions for susceptibility and the level of immune protection (table C.1). All R code is publicly available on GitHub (https://github.com/ISPMBern/comix).

4.3 Results

Over 24 survey waves from 22 January 2021 to 19 May 2022, we recorded 18,428 observations from 7,084 participants who reported 83,515 contacts (table 4.1). Study participants completed a median of 2 (range: 1-7) survey waves. The responses were not always recorded in consecutive survey waves. In the study, 3,609 (50.9%) participants were females, 3,452 (48.7%) were males, and 23 (0.4%) did not specify. The gender ratio was more balanced in adults (49.7% females and 49.9% males) than children (58.2% females and 41.8% males). The median age of participants was 41 (interquartile range: 26-58) years. Children constituted 14.7% of the sample while older adults (65+ year olds) represented 16.7%. Participants came from all 26 Swiss cantons. The highest proportion came from Zurich (1,253, 17.7%) and the fewest came from Appenzell Innerrhoden (9, 0.1%), which is proportional to the cantonal population sizes. The survey panels A and C were dominated by the SARS-CoV-2 Alpha variant, panels B and D by the Delta variant, and panels E and F by the Omicron variant (fig. 4.1). During the study period, the predicted seroprevalence levels for Switzerland overall increased from 17.3% to almost 99.0% due to infection- and vaccine-induced immunity (fig. C.1).

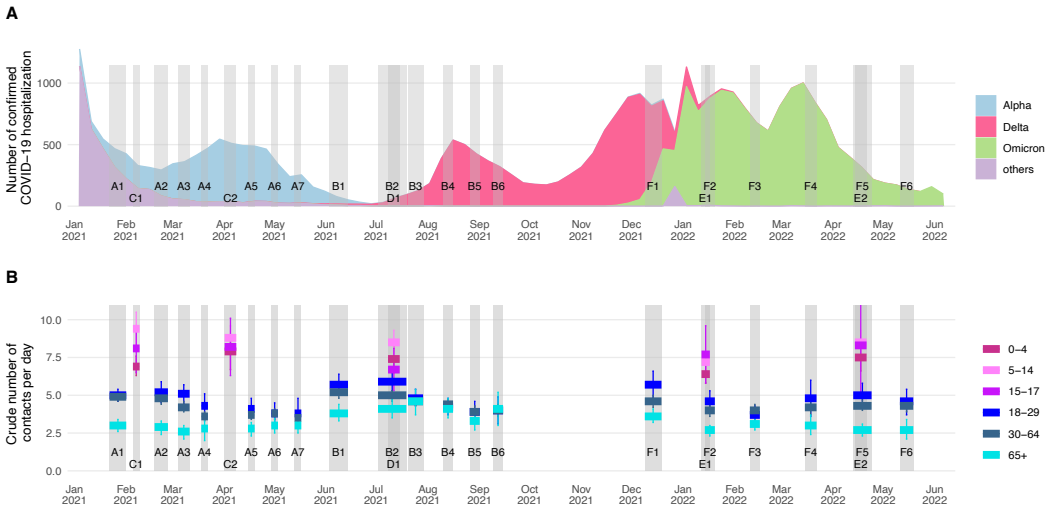

FIGURE 4.1: COVID-19 epidemic and social contact survey in Switzerland. A) Reported number of hospitalized COVID-19 cases reported by the FOPH colored by the proportion of variants sequenced. Gray bars and digits represent each CoMix survey wave. B) Mean number and 95% confidence interval of social contacts by age group and wave.

The number of contacts overall was on average 4.5 (95% confidence interval, CI: 4.5-4.6) per day. Over the entire study period, no statistically significant difference was found between the average number of contacts at the weekend and on weekdays (p-value = 0.6). The number of contacts varied by survey wave (table 4.1) and age group (fig. 4.1). Children aged 5-14 years had the highest overall number of contacts with 8.5 (95% CI: 8.1-8.9) per day, whereas 65 years and older reported the fewest (3.4, 95% CI: 3.2-3.5) per day. The numbers of contacts were similar between women (4.2 per day, 95% CI: 4.1-4.3) and men (4.3 per day, 95% CI: 4.2-4.4) (fig. C.2). The number of contacts also depended on the location where the contact took place, i.e., at home, at work, at school or at another location, as well as the number of waves in which participation took place (fig. C.2). Overall, 57% of contacts occurred at home (fig. C.3). Contact frequency between adults and children mainly differed at work (9% and 1%), and school (1% and 9%), respectively.

TABLE 4.1: Description of study population of the CoMix survey. CI, confidence interval.

Survey wave	Time period	Number of participants	Mean number of contacts (95% CI)	Number of newly enrolled participants	Number of missing participants who had been previously enrolled	Number of returning participants after missing at least one wave
A1	22 January 2021 to 01 February 2021	1555	4.50 (4.3-4.7)	1555	0	0
A2	18 February 2021 to 26 February 2021	842	4.50 (4.1-4.8)	562	1275	0
A3	04 March 2021 to 11 March 2021	662	4.10 (3.8-4.3)	327	737	230
A4	18 March 2021 to 22 March 2021	707	3.60 (3.3-3.9)	32	296	309
A5	15 April 2021 to 19 April 2021	649	3.60 (3.3-3.9)	31	311	222
A6	29 April 2021 to 03 May 2021	544	3.60 (3.3-3.9)	27	272	140
A7	13 May 2021 to 17 May 2021	465	3.40 (3.2-3.7)	17	206	110
B1	03 June 2021 to 14 June 2021	996	5.00 (4.7-5.3)	996	0	0
B2	02 July 2021 to 19 July 2021	1559	4.90 (4.7-5.2)	800	237	0
B3	20 July 2021 to 29 July 2021	1324	4.70 (4.4-4.9)	88	392	69
B4	10 August 2021 to 16 August 2021	1120	4.30 (4-4.6)	0	393	189
B5	26 August 2021 to 01 September 2021	953	3.70 (3.5-4)	0	354	187
B6	09 September 2021 to 15 September 2021	806	4.00 (3.7-4.4)	0	367	220
C1	05 February 2021 to 09 February 2021	303	8.40 (7.7-9.1)	303	0	0
C2	01 April 2021 to 08 April 2021	296	8.40 (7.8-9)	150	157	0
D1	08 July 2021 to 15 July 2021	300	8.00 (7.4-8.5)	300	0	0
E1	12 January 2022 to 17 January 2022	307	7.00 (6.6-7.4)	307	0	0
E2	14 April 2022 to 21 April 2022	308	8.10 (7.5-8.8)	140	139	0
F1	09 December 2021 to 19 December 2021	1001	4.50 (4.2-4.8)	1001	0	0
F2	14 January 2022 to 20 January 2022	899	3.80 (3.5-4)	158	260	0
F3	10 February 2022 to 16 February 2022	813	3.70 (3.5-4)	14	209	109
F4	15 March 2022 to 22 March 2022	727	4.00 (3.6-4.3)	51	137	0
F5	13 April 2022 to 24 April 2022	700	4.10 (3.8-4.4)	236	297	34
F6	11 May 2022 to 19 May 2022	592	4.00 (3.7-4.4)	151	300	41

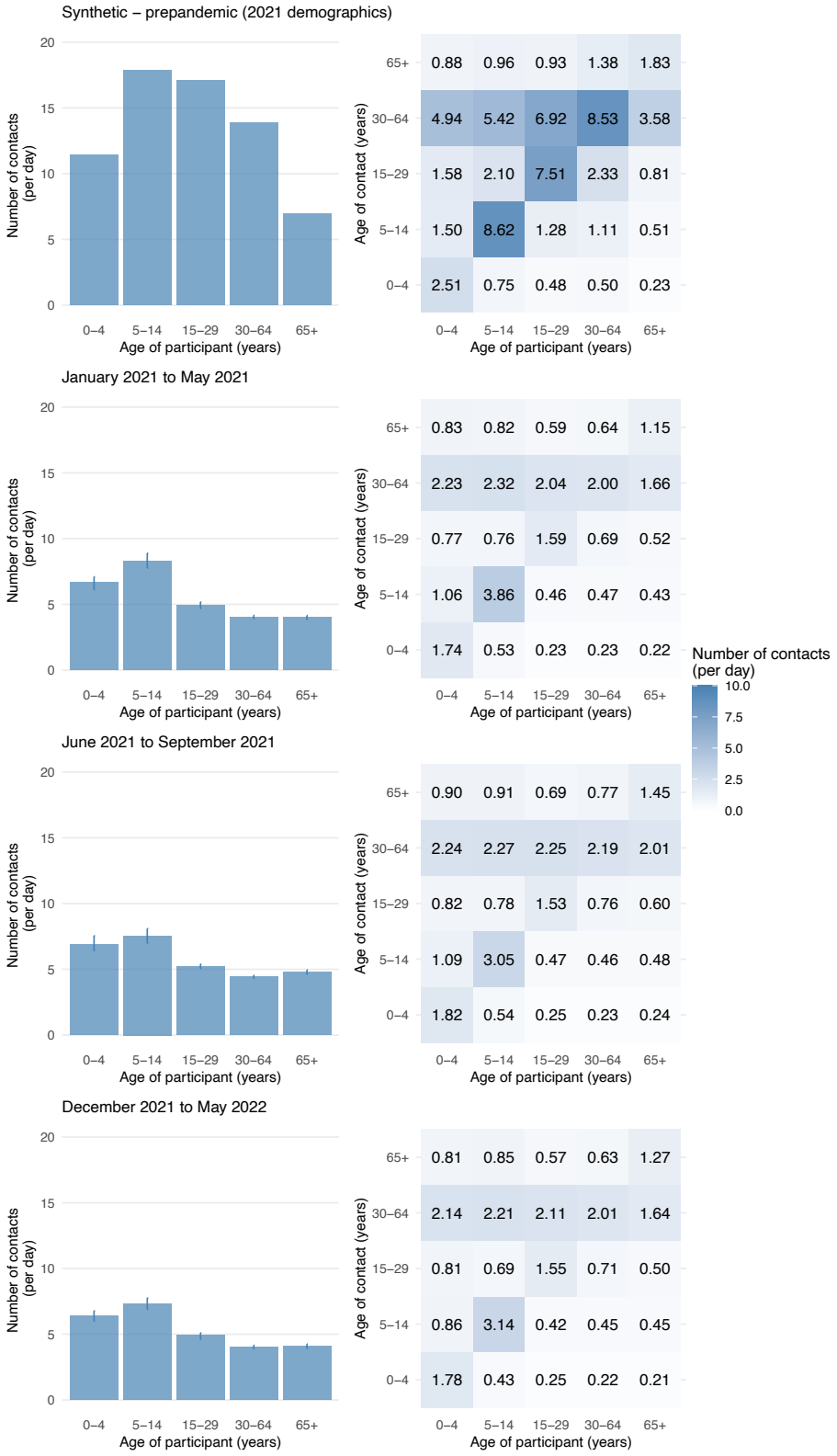

FIGURE 4.2: Number of social contacts per day (left) and social contact matrices (right) for Switzerland. The number of contacts was normalized to the Swiss population in 2021. The top row corresponds to the synthetic data representing a pre-pandemic baseline and the other rows correspond to the CoMix data over different survey periods.

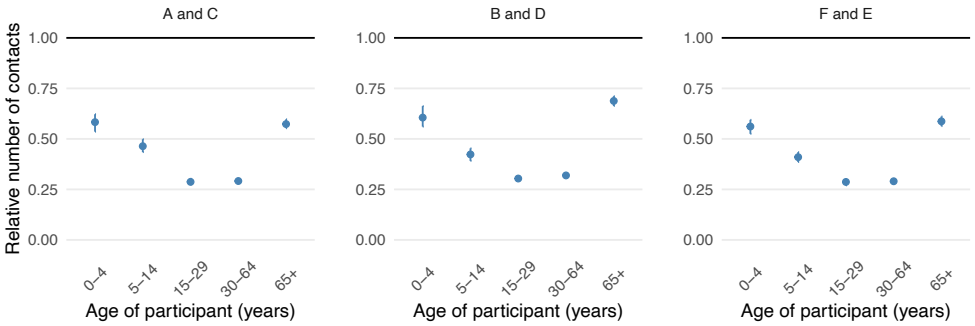

FIGURE 4.3: Relative number of social contacts by age group during the COVID-19 pandemic in Switzerland. The number of contacts from the CoMix study at different survey periods is shown relative to a pre-pandemic baseline. Participants aged 18 years and older (in panels A, B, and F) and children younger than 18 years old (in panels C, D, and E). Bars correspond to the 95% confidence interval of 100 bootstrap samples.

Comparing the number of contacts to a pre-pandemic baseline, contacts were substantially reduced during the COVID-19 pandemic in Switzerland (fig. 4.2). The reductions were similar over all three survey panels (fig. 4.3). The range of reduction was 34-47% in 0-4 year old children, 51-61% in 5-14 year old children, 68-73% in 15-29 year olds, 67-72% in 30-64 year old adults, and 29-45% in those aged 65 years or older.
We investigated whether the properties of the social contact matrix were associated with the stringency of pandemic measures and vaccination uptake. The largest eigenvalue of the contact matrix only decreased moderately (-0.1, 95% CI: -0.5-0.3) and increased moderately (0.1, 95% CI: -0.3-0.5) with higher stringency of measures and vaccination uptake, respectively (fig. 4.4). We further tested whether the properties of the transmission matrix were associated with R_e during the course of the COVID-19 pandemic in Switzerland. The degree of association strongly depended on the underlying assumptions (fig. C.4). For the main analysis, we found a positive but non-significant association between the largest eigenvalue of the transmission matrix and R_e with a coefficient of 0.5 (95% CI: -0.4-1.4) (figs. 4.5 and C.5).

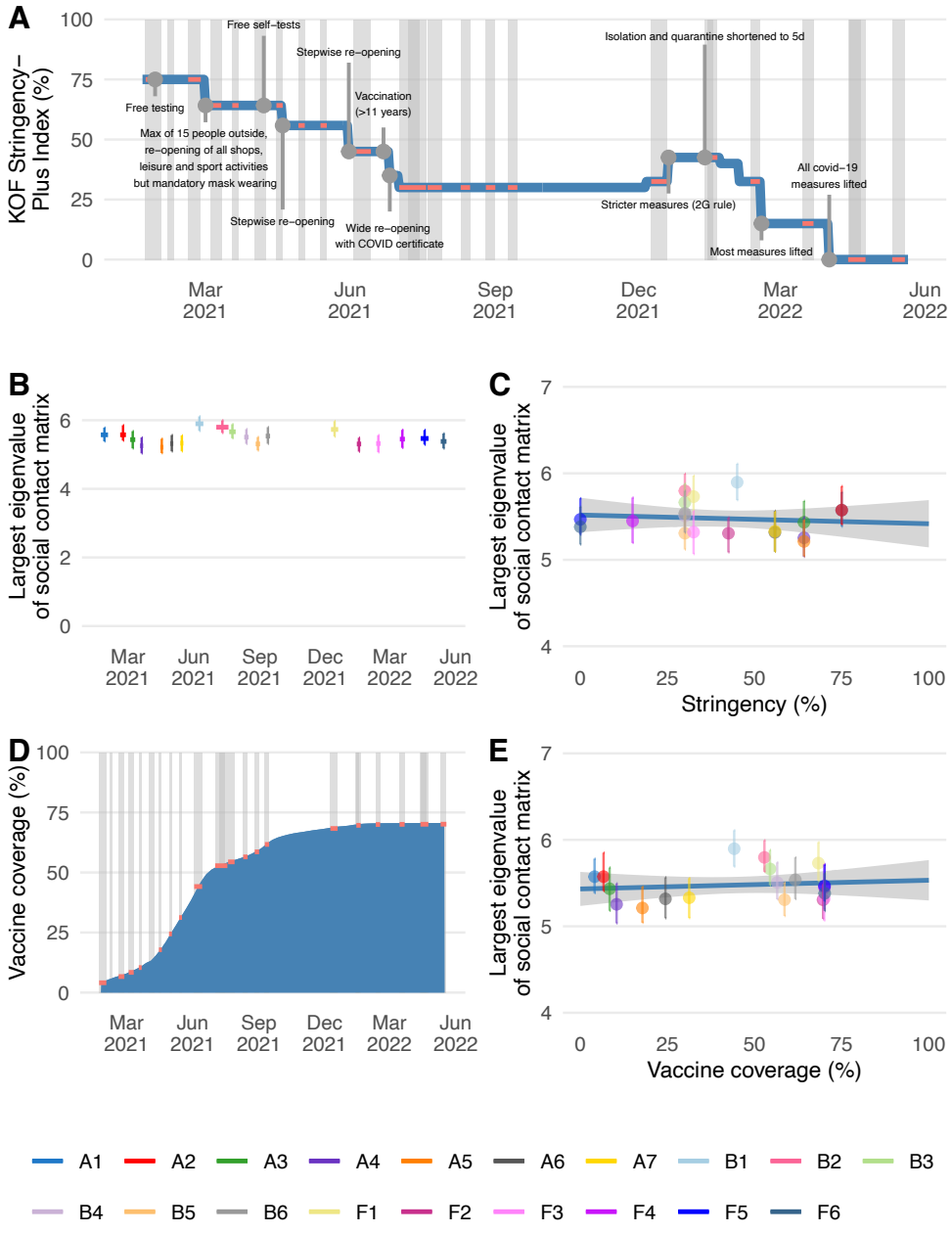

FIGURE 4.4: Largest eigenvalue of social contact matrix. A) The KOF Stringency Index and major events during the COVID-19 pandemic in Switzerland (Pleninger et al., 2021). The values range from 0 (no measures) to 100 (full lockdown) and were adapted from Hale et al. (2021). The gray areas indicate the CoMix survey wave periods and the red bars the median of the KOF Stringency Index for the corresponding survey waves. B) Largest eigenvalue of the social contact matrix by adult survey wave. C) Linear association of stringency of measures with largest eigenvalue of social contact matrix for corresponding survey period. D) Vaccine coverage with the first dose in Switzerland. Red bars indicate the median vaccine coverage for corresponding survey waves. E) Linear association of vaccine coverage with largest eigenvalue of social contact matrix for corresponding survey period. Shaded areas of the linear association correspond to the 95% confidence interval.

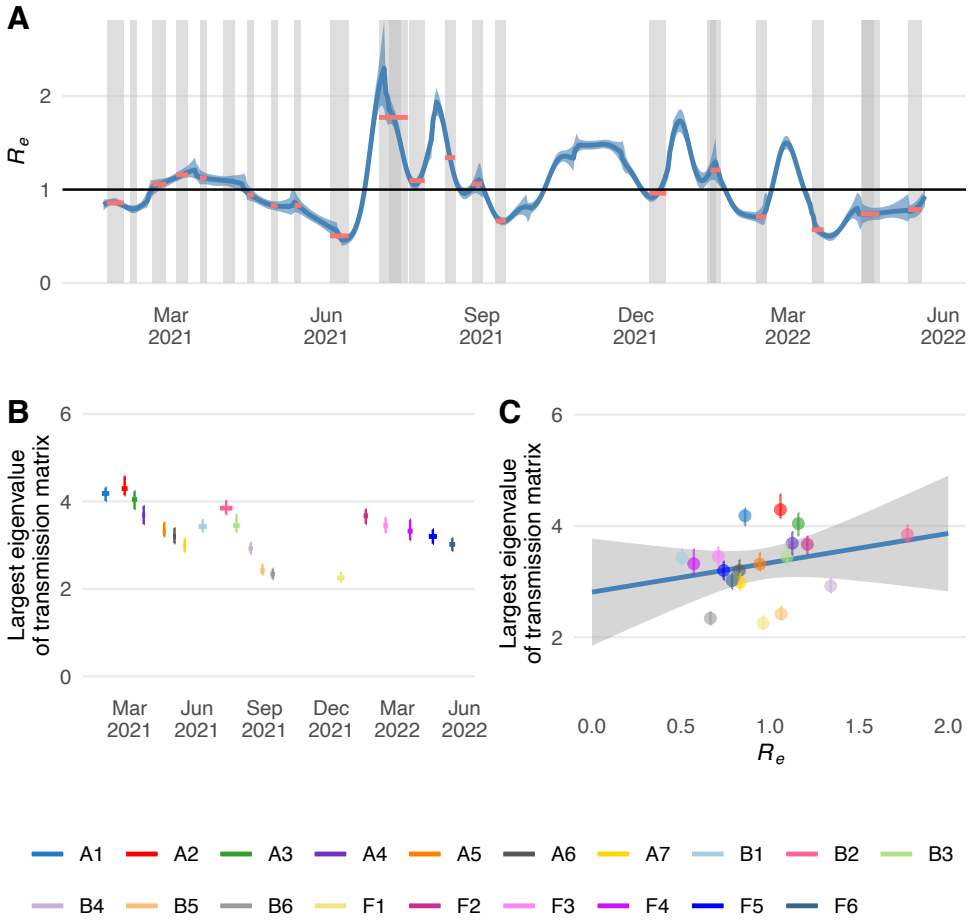

FIGURE 4.5: Largest eigenvalue of transmission matrix. A) Median (blue line) effective reproduction number Re and 90% confidence interval (blue shades) per day. The median R_e (red lines) for the corresponding survey wave (gray area). B) Largest eigenvalue of transmission matrix per survey period. C) Linear association of the largest eigenvalue of transmission matrix with the median R_e for corresponding survey period.

4.4 Discussion

In our study, we analyzed social contacts reported by a total of 7,084 participants across five age groups and over 24 survey periods from 22 January 2021 to 19 May 2022. The average number of contacts overall was 4.5 (95% CI: 4.5-4.6) per day and varied by age group and survey wave. The number of reported contacts during the pandemic was substantially lower than before the pandemic. We did not find strong associations between the largest eigenvalue of the social contact and transmission matrices and the stringency of measures, vaccination uptake, or R_e.

This is the first study that includes detailed social contact data by age in a large study population that is representative of the Swiss population in regard to age, gender, and geographical region of residence. The study includes multiple survey waves during critical phases of the COVID-19 pandemic when restrictions were lifted and the vaccination program was rolled out. Furthermore, the data were collected during the circulation of different SARS-CoV-2 variants, namely Alpha, Delta, and Omicron. Lastly, the publicly available social contact data represent an important resource for the future study of the transmission of respiratory infections in Switzerland.

Nevertheless, our study has several limitations. First, as previously mentioned this is the first empirical Swiss study from which social contact matrices for Switzerland could be directly constructed. Consequently, there were no pre-pandemic surveys and we had to rely on the synthetic contact matrix by Prem et al. (2021) to generate a pre-pandemic baseline. The synthetic contact data is based on country-specific demographic and contact data collected as part of the POLYMOD study (Mossong et al., 2008). However, Switzerland was not part of the POLYMOD survey. In addition, participants used a prospective diary and did not record contacts retrospectively, which differs from the CoMix study. The type of data collection can influence the number of contacts (Mikolajczyk and Kretzschmar, 2008). Thus, collecting data and comparisons between different studies have limitations. For example, synthetic matrices could extrapolate artifacts and thus overestimate the number of contacts, or the CoMix method could systematically underestimate them. Second, social contact surveys are prone to biases. Not all participants that were recruited in a panel participated in the same number of waves. We previously showed in the context of vaccination uptake between June and September 2021 that the number of drop-outs increased in later survey waves (Reichmuth et al., 2023b). Survey fatigue can result from various reasons. For example, participants with more contacts need to invest more time in filling out the survey and thus might be more likely to stop. Loedy et al. (2023) analyzed the impact of drop-outs on the number of contacts and found that drop-outs did not depend on the number of contacts in Belgium. We have therefore not adjusted the number of contacts for drop-outs. Third, we conducted fewer waves for children and also had a smaller number of participants compared to adults. To overcome this limitation, we pooled all survey waves in children to increase the number of participants. Fourth, we did not investigate differences in viral characteristics for different circulating variants and susceptibility and infectivity between the age groups. We used viral characteristics, such as incubation and generation time of the wild-type of SARS-CoV-2 to estimate R_e and not for different circulating variants. We also only assumed that children are half as susceptible as adults (Davies et al., 2020). Fifth, there is considerable heterogeneity in the number of secondary SARS-CoV-2 cases which can result in superspreading events (Riou and Althaus, 2020; Wegehaupt et al., 2023). We did not include superspreading when calculating transmission contact matrices, which could influence the comparison with Re. In addition, SARS-CoV-2 can be transmitted through aerosols. Aerosol transmission can affect secondary transmissions, i.e., Re, without increasing social contacts that consider only close contacts (Leung, 2021). Sixth, we might miss the impact of regional differences in control measures, vaccination uptake, and adherence because there were too few participants to stratify by region. Finally, constructing a transmission matrix at different time periods of the COVID-19 pandemic is challenging. The spread of SARS-CoV-2 strongly depends on the infectiousness of index cases, the susceptibility of the hosts, the transmissibility and immune evasion of variants (Althaus et al., 2021; Davies et al., 2021; Perez-Guzman et al., 2023; Tan et al., 2023; Viana et al., 2022; Viner et al., 2021), and seasonality (Wiemken et al., 2023). Most of these factors are difficult to estimate and come with considerable uncertainty.

The CoMix study in Switzerland is part of a larger Europe-wide project, which enables a comparison of the results between the countries (Jarvis et al., 2023; Wong et al., 2023). For example, Wong et al. (2023) compared contact data among 21 European countries including data from 22 January to 17 May 2021 from Switzerland. They showed a reduction in contacts in all countries after the onset of the COVID-19 pandemic. We added with our study that the reduction in contacts in Switzerland persisted at least until 19 May 2022. Further, compared to other countries, the CoMix data from Switzerland (22

January to 17 May 2021) suggested that contact behavior in Switzerland is in line with the European average. However, for Switzerland more contacts were reported than in neighboring countries, namely Germany, Italy, France, and Austria, which underlines the importance of country- and context-specific contact data. Wong et al. (2023) also showed that the number of contacts in children that attended school or not was similar within Switzerland. The reason for this could be that the schools in Switzerland were only closed in spring 2020 and not during the study period. In addition, the school holidays varied regionally (i.e., also within the study population) and were relatively short. There were fewer interventions in schools than in workplaces, which likely led to smaller reduction in contacts with children than adults. Moreover, Jarvis et al. (2023) compared post-pandemic contact behavior using CoMix data in four European countries including Switzerland and concluded that the pre-pandemic number of contacts had not been reached again by May 2022. Future contact surveys, including different seasons, will give insights on social contact behavior in Switzerland to better assess the risk of infection with SARS-CoV-2 and other respiratory diseases such as influenza. Additionally, Munday et al. (2023) suggested the use of contact data for forecasting incidences of infections.

We showed that the number of social contacts in Switzerland fell substantially from January 2021 to May 2022. Contacts remained below the pre-pandemic baseline despite the gradual lifting of contact restrictions during this period. Social contact surveys should be continued to monitor changes in social contact patterns by age group and over time. In addition to monitoring contact data, further studies are needed to clarify why the number of contacts remains lower than pre-pandemic levels. Finally, openly available contact data will be crucial for modeling studies on the transmission of respiratory infections in Switzerland and guiding future pandemic preparedness measures.

Declarations

The CoMix study protocols and questionnaires were approved by the local ethics committee of the Canton of Bern (project number 2020-02926). All methods were performed in accordance with regulations and informed consent of participants was obtained.

Data and code availability

Data and R code are available on Zenodo (doi.org/10.5281/zenodo.10147647) and GitHub (https://github.com/ISPMBern/comix).

Acknowledgements

We like to thank the European Centre for Disease Prevention and Control (ECDC) and the CoMix Europe Working Group for setting up the CoMix study across more than 20 European countries, and the partners at Ipsos MORI for running the survey.

Author contributions

MR, NL, and CA conceived and designed the study. MR and CA performed the analysis and wrote the manuscript. All authors contributed to the interpretation of the results, commented on the manuscript, and approved this version.

Competing interests of the authors

All authors declare no competing interests.

Funding

This study received funding from the European Union's Horizon 2020 research and innovation program - project EpiPose (No 101003688), the Swiss Federal Office of Public Health (No 142004995), and the Swiss National Science Foundation (No 176233).

Sociodemographic characteristics associated with COVID-19 vaccination uptake in Switzerland: longitudinal analysis of the CoMix study

Martina L Reichmuth[1]
Leonie Heron[1]
Julien Riou[1,2]
André Moser[3]
Anthony Hauser[1]
Nicola Low[1,2]
Christian L Althaus[1,2]

[1] Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland
[2]Multidisciplinary Center for Infectious Diseases, University of Bern, Bern, Switzerland
[3] CTU Bern, University of Bern, Bern, Switzerland

This article is published in ***BMC Public Health*** as Reichmuth et al. (2023). DOI:10.1186/s12889-023-16405-0

Contribution: I contributed to the study design, performed all analyses, made all figures, wrote the first draft of the manuscript, and integrated co-authors' comments.

Abstract

Vaccination is an effective strategy to reduce morbidity and mortality from coronavirus disease 2019 (COVID-19). However, the uptake of COVID-19 vaccination has varied across and within countries. Switzerland has had lower levels of COVID-19 vaccination uptake in the general population than many high-income countries. Understanding the sociodemographic factors associated with vaccination uptake can help to inform future vaccination strategies to increase uptake.

We conducted a longitudinal online survey in the Swiss population, consisting of six survey waves from June to September 2021. Participants provided information on sociodemographic characteristics, history of testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), social contacts, willingness to be vaccinated, and vaccination status. We used a multivariable Poisson regression model to estimate the adjusted rate ratio (aRR) and 95% confidence intervals (CI) of COVID-19 vaccine uptake.

We recorded 6,758 observations from 1,884 adults. For the regression analysis, we included 3,513 observations from 1,883 participants. By September 2021, 600 (75%) of 806 study participants had received at least one vaccine dose. Participants who were older, male, and students, had a higher educational level, household income, and number of social contacts, and lived in a household with a medically vulnerable person were more likely to have received at least one vaccine dose. Female participants, those living in rural areas and smaller households, and people who perceived COVID-19 measures as too strict were less likely to be vaccinated. We found no significant association between previous SARS-CoV-2 infections and vaccination uptake.

Our results suggest that sociodemographic factors as well as individual behaviors and attitudes played an important role in COVID-19 vaccination uptake in Switzerland. Therefore, appropriate communication with the public is needed to ensure that public health interventions are accepted and implemented by the population. Tailored COVID-19 vaccination strategies in Switzerland that aim to improve uptake should target specific subgroups such as women, people from rural areas, or people with lower sociodemographic status.

Keywords Vaccine, COVID-19, contact survey, social contact, sociodemographic characteristics, Switzerland.

5.1 Introduction

Vaccines can prevent symptomatic infections, severe disease, and death from coronavirus disease 2019 (COVID-19). The evidence of vaccine effectiveness comes from randomized clinical trials and real-world data (Dickerman et al., 2022; Pouwels et al., 2021). Although effective vaccines with a favorable safety profile are available against a wide range of pathogens, public confidence in vaccination has declined in some countries, and some population groups are increasingly reluctant to be vaccinated (Black and Rappuoli, 2010). The World Health Organization (WHO) ranks vaccine hesitancy among the top ten global health threats (WHO, 2020a). Investigating the factors associated with vaccine hesitancy and lower vaccination uptake could help to develop strategies to minimize the impact of COVID-19 and future epidemics.
Several studies have reviewed factors that may be associated with COVID-19 vaccination uptake. A systematic review indicated that sociodemographic factors and perceptions of risk and susceptibility to COVID-19 were associated with the intention to get vaccinated and that vaccine attributes influenced vaccination intention while receiving negative information about vaccines and working in healthcare resulted in lower intentions to get vaccinated (Al-Amer et al., 2022). Switzerland has had lower levels of COVID-19 vaccine uptake in the general population than many other high-income countries (Ritchie et al., 2020). A prospective cohort study in Switzerland found that vaccination uptake was multifactorial and associated with sociodemographic characteristics, health status, trust in institutions, fears of side effects, and expected risk of severe COVID-19 (Heiniger et al., 2022). A further understanding of how sociodemographic and behavioral factors were associated with vaccine uptake while accounting for the age-dependent roll-out during the COVID-19 vaccination program in Switzerland, will help to improve future vaccination strategies.
The objective of this study was to analyze the association of sociodemographic and other factors with COVID-19 vaccination uptake during the roll-out of the vaccination program in the general population in Switzerland. First, we conducted an online survey with six survey waves from June to September 2021. Second, we studied vaccination uptake in the survey population using a Poisson regression model. Finally, we investigated whether the participants' characteristics were associated with missed survey waves.

5.2 Methods

This study was conducted as part of the CoMix study, which is a longitudinal online survey about social contact patterns during the COVID-19 pandemic in more than 20 countries in Europe and is described in detail elsewhere (Jarvis et al., 2020; Verelst et al., 2021). The questionnaire included sociodemographic characteristics, attitudes, and practices toward public health interventions against COVID-19 and social contact behaviors. Questions about social contacts were based on the POLYMOD survey, conducted in 2008 (Mossong et al., 2008).
In the longitudinal CoMix study design, a sample of the adult ($\geq$18 years) Swiss population was invited by the market research company Ipsos MORI to take part in repeated survey waves. We aimed to include 1,000 participants per survey wave, who were representative of the population in Switzerland using quotas on age, gender, and region of residence. We compared the characteristics of the participants with Swiss demographic data as reported by the Federal Statistical Office (FSO or BFS in German) and the vaccination uptake of the participants with the vaccination monitor from the Federal Office of Public Health (FOPH) (BFS, 2023; FOPH, 2023a). We used data from six online surveys

from June to September 2021 (B1-B6). Enrollment of new participants continued over the first three waves, primarily due to inconsistent participation and to ensure a sufficient sample size.
Participants provided sociodemographic information, including age groups (categorized as 18-29, 30-39, 40-49, 50-59, 60-69, and 70+ years), gender (female or male), region (urban or rural), Swiss region of residence (nomenclature of territorial units for statistics (NUTS) regions of Switzerland), country of birth (Switzerland, European Union (EU), or non-EU), educational level (low (obligatory school and vocational education), middle (high school and advanced vocational education), and high (bachelor or higher)), employment level (unemployed, student, homemaker, retired, or unemployed due to health reasons), net household income (<5,000, 5,001-10,000, or >10,000 CHF, preferred not to answer), household size, and whether they were living in a household with a medically vulnerable individual, and testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (tested positive, tested, never tested, preferred not to answer). They also reported social contact behaviors (number of physical contacts per day), vaccination status, willingness to be vaccinated, and attitudes toward COVID-19 measures. Participation in the study was voluntary but each participant received 5 CHF per survey wave. We conducted all analyses using anonymized data in R version 4.2.1 and the code is available on GitHub: https://github.com/ISPMBern/comix. The study was approved by the ethics committee of the Canton of Bern (project number 2020-02926), all methods were performed in accordance with relevant guidelines and regulations, and informed consent of participants was obtained. We followed the 'strengthening the reporting of observational studies in epidemiology' (STROBE) Statement to report this study (Vandenbroucke, 2007).
The primary outcome of the analysis was having received the first dose of the COVID-19 vaccine. In Switzerland, the first COVID-19 vaccine was approved in December 2020 (Swiss Agency for Therapeutic Products, Swissmedic; table D.1), and mRNA vaccines (Moderna and Pfizer-BioNTech) were most widely used. In addition, we reported the prevalence of fully vaccinated individuals in Switzerland by the end of our study period in September 2021 (defined as having received at least two doses).
We described vaccination uptake over time. First, we reported the willingness to be vaccinated as reported in the survey. Second, we modeled the primary outcome (vaccination uptake) as a point process using Poisson regression with the logarithm of the observation time (the length of the interval between follow-up surveys per participant, i.e., t_i - t_i-1) as offset (or denominator) for vaccination uptake (Aalen et al., 2008). Thus the unadjusted rate ratios (RR) are given as follows:

$$log(E(Y_i)/(t_i - t_{i-1})) = \beta_0 + \beta_x$$

.

We set time zero to be 1 January 2021, shortly after the administration of the first vaccinations. All participants' observations were included until they reported having received the first dose, if applicable, and were censored thereafter. We included data recorded on unvaccinated participants at all time points. We derived rates from the exponentiated coefficients of the Poisson regression model.
Vaccination status was the dependent variable, and the following factors were covariates: time (survey wave), age, gender, region, residence, country of birth, education level, employment level, net household income, household size, vulnerable group within the household, testing for SARS-CoV-2, number of contacts, and attitude towards COVID-19 measures. The last three covariates could change over time for participants. We

performed univariable and multivariable regression models and reported the RR and adjusted RR (aRR) with 95% confidence intervals (CI), controlling for all covariates. We included time by survey waves and modeled an interaction with age to account for the different times at which vaccines became available for different age groups. We calculated the cumulative vaccination uptake for a given interval as one minus the product of all probabilities of not being vaccinated until that interval.
In a sensitivity analysis, we set time zero to 1 June 2021, which was just before the first survey wave. We performed further sensitivity analyses and compared the results from the Poisson regression model to those derived using Cox proportional hazards regression models. We ran Cox regression models, first with all participants included in the main analysis and second for individuals with an exact date of vaccination (86%) or who had not been vaccinated during the study period, with and without inverse probability weighting cumulatively over time (IPWC) to account for dropouts (Fewell et al., 2004). We estimated the probability of censoring with each observation or up to the time point of vaccination. Probabilities were then derived with a logistic regression model adjusting for all covariates as described in our main analysis. Further, we subtracted estimated probabilities from 1, which resulted in an estimate of the probability of being uncensored for a given observation. We accumulated these probabilities over time for each participant. Finally, we derived stabilized weights using a logistic regression model without covariates for the nominator. We defined missingness as when a participant was absent in any survey wave after recruitment. To estimate these probabilities, we used logistic regression with all observations and all covariates from the main regression model plus the primary outcome. Further, we use each participant's last observation to test whether the missingness of a survey wave was associated with covariates that we previously described.

5.3 Results

This study included six survey waves from 3 June 2021 to 9 September 2021, with participants enrolled during the first three waves (table 5.1 and figs. D.1 and D.2). We followed participants for 55 days on average (range: 0-103 days). The study included 6,758 observations from 1,884 participants. Overall, 918 (49%) were females and 956 (51%) were males. Participants' age ranged from 18 to 90 years with a median of 47 years. The study population was largely representative of the Swiss population (table D.2). For the regression analysis, we included 1,883 participants (one participant had missing data for vaccination status; table 5.2). Further, we identified missing data for six observations from three participants (four for vaccination status and two for contact information). We excluded these observations from regression analyses. Of all who participated from June to September 2021, 443 (24%) did not miss any waves, 363 (19%) missed at least one survey wave, and 1,078 (57%) dropped out before the last wave.

TABLE 5.1: Overview of survey waves.

Survey wave	Start date, year-month-day	End date, year-month-day	Number of participants	Number of newly enrolled participants	Number of missing participants who had been previously enrolled	Number of returning participants after missing at least one wave	Number of participants with no missing variables
B1	2021-06-03	2021-06-14	996	996	0	0	996
B2	2021-07-02	2021-07-19	1,559	800	237	0	1,558
B3	2021-07-20	2021-07-29	1,324	88	392	69	1,322
B4	2021-08-10	2021-08-16	1,120	0	393	189	1,119
B5	2021-08-26	2021-09-01	953	0	354	187	952
B6	2021-09-09	2021-09-15	806	0	367	220	805

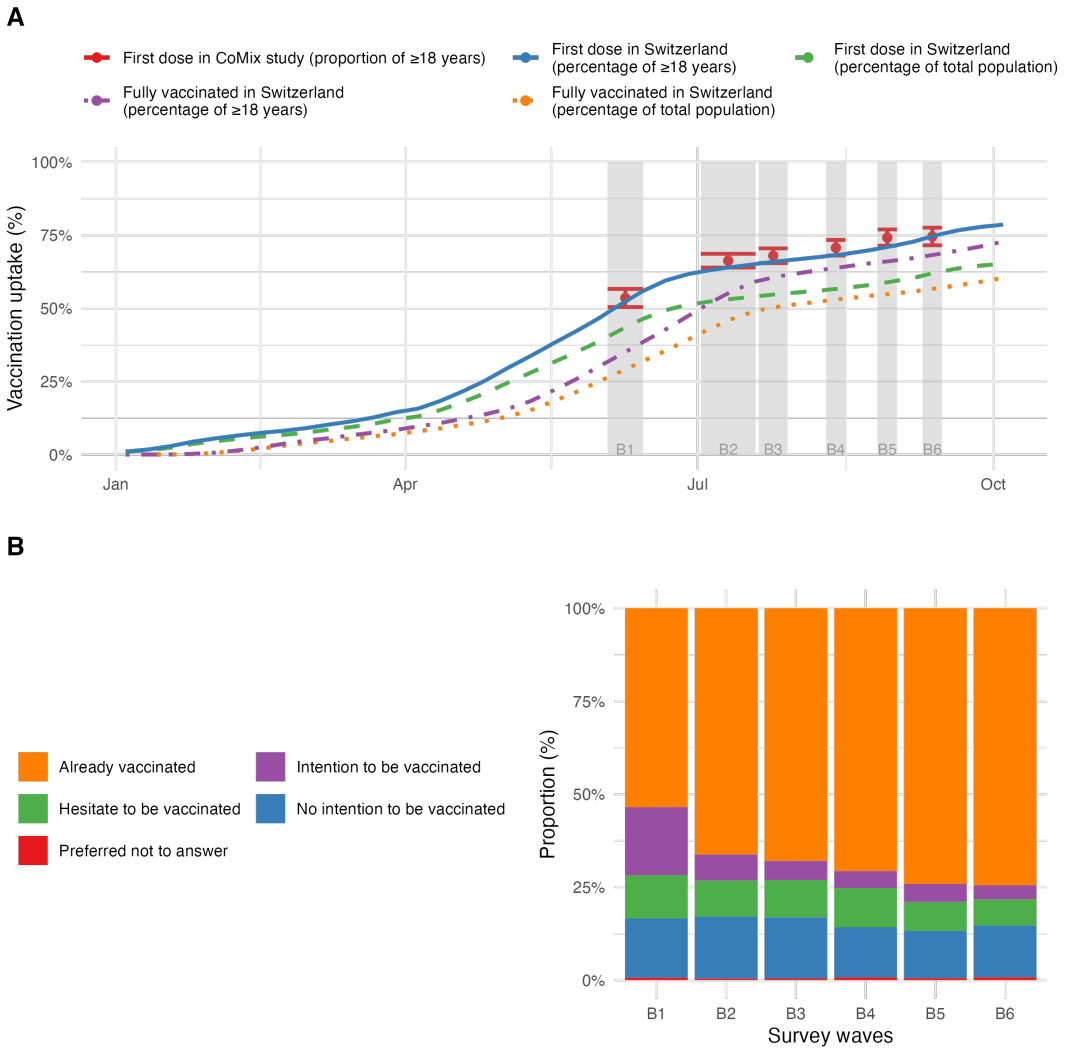

FIGURE 5.1: COVID-19 vaccination uptake in Switzerland. A) Comparison of vaccination uptake in the CoMix survey participants (red dots with 95% confidence intervals) and general population of Switzerland. B) Willingness to receive COVID-19 vaccination

From May 2021 onwards, the COVID-19 vaccination campaign in Switzerland targeted the entire adult population and uptake increased during the study period (fig. 5.1). Vaccination uptake in our study population was higher than in the overall population of Switzerland. In the first survey wave of June 2021, 533 (54%) had at least one vaccine dose compared with 43% of the general Swiss population. This increased to 75% by the sixth survey wave, compared with 70% in the general adult population (fig. 5.1). Participants who had not already been vaccinated indicated their willingness as to whether they intended, were hesitating, or had no intention to get vaccinated. The increase in vaccine uptake within the CoMix study occurred mainly amongst those who wanted to get vaccinated (18% in the first wave to 4% in the last wave) rather than those that had no intention (16% in the first wave to 14% in the last wave) or were hesitant (12% in the first wave to 7% in the last wave) (fig. 5.1).

In the unadjusted Poisson regression model, we found that people in all older age groups were more likely to get vaccinated than those in the youngest age group (18-29 years; fig. 5.2). In the adjusted Poisson regression model, the vaccination uptake per interval

TABLE 5.2: Overview of the study population: Sociodemographic characteristics, history of testing for SARS-CoV-2, social contact behavior, and perception of COVID-19 measures in all study participants and in study participants who got vaccinated by the end of the study. * For time-dependent variables, the last observation of the participant is given. Abbreviations: EU, European Union; CHF Swiss Francs.

Category	All participants, N (%)	Vaccinated participants, N (%)
Total	1,883 (100%)	1,321 (100%)
Age groups, years		
18-29	358 (19%)	216 (16%)
30-39	358 (19%)	234 (18%)
40-49	308 (16%)	203 (15%)
50-59	363 (19%)	263 (20%)
60-69	289 (15%)	226 (17%)
70	207 (11%)	179 (14%)
Gender		
Female	918 (49%)	613 (46%)
Male	955 (51%)	699 (53%)
Other	10 (1%)	9 (1%)
Region		
Urban	1,426 (76%)	1,039 (79%)
Rural	457 (24%)	282 (21%)
Swiss region of residence		
Espace Mittelland	406 (22%)	273 (21%)
Zurich	351 (19%)	260 (20%)
Lake Geneva region	337 (18%)	235 (18%)
Eastern Switzerland	263 (14%)	186 (14%)
Northwestern Switzerland	262 (14%)	181 (14%)
Central Switzerland	182 (10%)	129 (10%)
Ticino	82 (4%)	57 (4%)
Country of birth		
Switzerland	1,331 (71%)	927 (70%)
EU	249 (13%)	176 (13%)
Non-EU	156 (8%)	113 (9%)
Unknown	147 (8%)	105 (8%)
Education level		
Obligatory school and vocational education	805 (43%)	531 (40%)
Gymnasium and advanced vocational education	639 (34%)	439 (33%)
Higher education (e.g., Bachelor, Master or PhD)	439 (23%)	351 (27%)
Employment status		
Employed	1,161 (62%)	789 (60%)
Unemployed	110 (6%)	67 (5%)
Student	116 (6%)	83 (6%)
Homemaker	75 (4%)	43 (3%)
Retired	377 (20%)	313 (24%)
Other unemployed situation	44 (2%)	26 (2%)
Household income, net		
0-5,000 CHF	592 (31%)	380 (29%)
5,001-10,000 CHF	762 (40%)	539 (41%)
10,000+ CHF	248 (13%)	200 (15%)
Preferred not to answer	281 (15%)	202 (15%)
Household size		
Median (Range)	2 (range: 1-10)	2 (range: 1-10)
Household with medically vulnerability		
No person in a risk group	1,305 (69%)	871 (66%)
One or more person in a risk group	578 (31%)	450 (34%)
Testing for SARS-Cov-2*		
Tested positive	31 (2%)	25 (2%)
Tested	543 (29%)	336 (25%)
Never tested	1,277 (68%)	941 (71%)
Preferred not to answer	32 (2%)	19 (1%)
Number of contacts per day*		
0-2	767 (41%)	547 (41%)
3-5	527 (28%)	377 (29%)
6	589 (31%)	397 (30%)
Attitudes towards COVID-19 measures*		
About right	913 (48%)	737 (56%)
Too lenient	423 (22%)	356 (27%)
Too strict	501 (27%)	204 (15%)
No comment	46 (2%)	24 (2%)

in adults 30 years and older was highest before the first survey wave and declined afterward (fig. 5.3). The vaccination uptake per interval in younger adults (18-29 years) peaked at the second survey wave, then declined and increased again at the last survey wave. The modeled cumulative vaccination uptake over the entire study period depended less on age than expected from the crude vaccination uptake in the CoMix study, i.e., the effect of other covariates became more important (fig. D.3). Being male was associated with higher vaccination uptake (aRR 1.09, 95% CI: 1.04–1.15) (fig. D.2). We found geographical differences in vaccination uptake. Living in rural areas was associated with lower vaccine uptake than in urban areas (aRR 0.85, 95% CI: 0.80–0.90). Vaccination uptake varied slightly between regions. Most regions were associated with higher vaccine uptake than Espace Mittelland. We did not find statistical evidence of an association between country of birth and vaccination uptake.

We found that the highest education level (having a Bachelor, Master or PhD), was associated with a higher vaccination uptake (aRR 1.18, 95% CI: 1.10–1.27) than with the lowest education level (completed obligatory school and vocational education only). Unemployed participants were less likely (aRR 0.86, 95% CI: 0.76–0.97) and students were more likely (aRR: 1.33, 95% CI: 1.17–1.51) to get vaccinated than employed participants. In addition, higher income was associated with higher vaccination uptake. A household income between 5,001 CHF and 10,000 CHF compared with less than 5,000 CHF resulted in an aRR of 1.15 (95% CI: 1.08–1.23) and an income of at least 10,000 CHF resulted in an aRR of 1.34 (95% CI: 1.23–1.46). Living in smaller households was associated with lower vaccination uptake (aRR 0.96, 95% CI: 0.94–0.99). In contrast, living with a medically vulnerable individual was associated with a higher aRR of 1.16 (95% CI: 1.10–1.23). We found no association between previous SARS-CoV-2 infections and vaccination uptake. Individuals with six or more contacts per day had higher vaccination uptake than those with fewer than three contacts (aRR 1.08, 95% CI: 1.01–1.16). We also found that the perception of COVID-19 measures was associated with vaccination uptake. Participants who thought that the control measures were too strict were less likely to be vaccinated compared to those who thought that the control measures were about right (aRR 0.56, 95% CI: 0.53–0.61).

Setting time zero to 1 June 2021 did not substantially change the results of the Poisson regression model (table D.3). The results from the Cox regression model were similar compared to those from the Poisson regression model (table D.3 and D.4). However, we deemed the Cox regression model less appropriate for the analysis of the data because the strong correlation between age and the time point of vaccination as a result of the age-specific vaccination campaign violates the proportional hazard assumption.
We also studied whether certain characteristics of participants were associated with missed survey waves (n=1,441, 76%). We found that individuals between 40 and 69 years were less likely to have missed survey waves than the youngest age group (18-29 years). Participants living in Geneva and Ticino were more likely to have missed survey waves compared to those living in Espace Mittelland. The same was found for those born in an EU country than those born in Switzerland. Participants with six or more contacts were also more likely to have missed survey waves than those with fewer than three contacts. We did not find strong statistical evidence for associations between missingness and gender, region, education level, employment status, household income, history of testing for SARS-CoV-2, or vaccination (table D.5). Participants who missed survey waves had little impact on the results from the Cox regression model, as the unweighted and weighted hazard ratios (HR) were similar (table D.3).

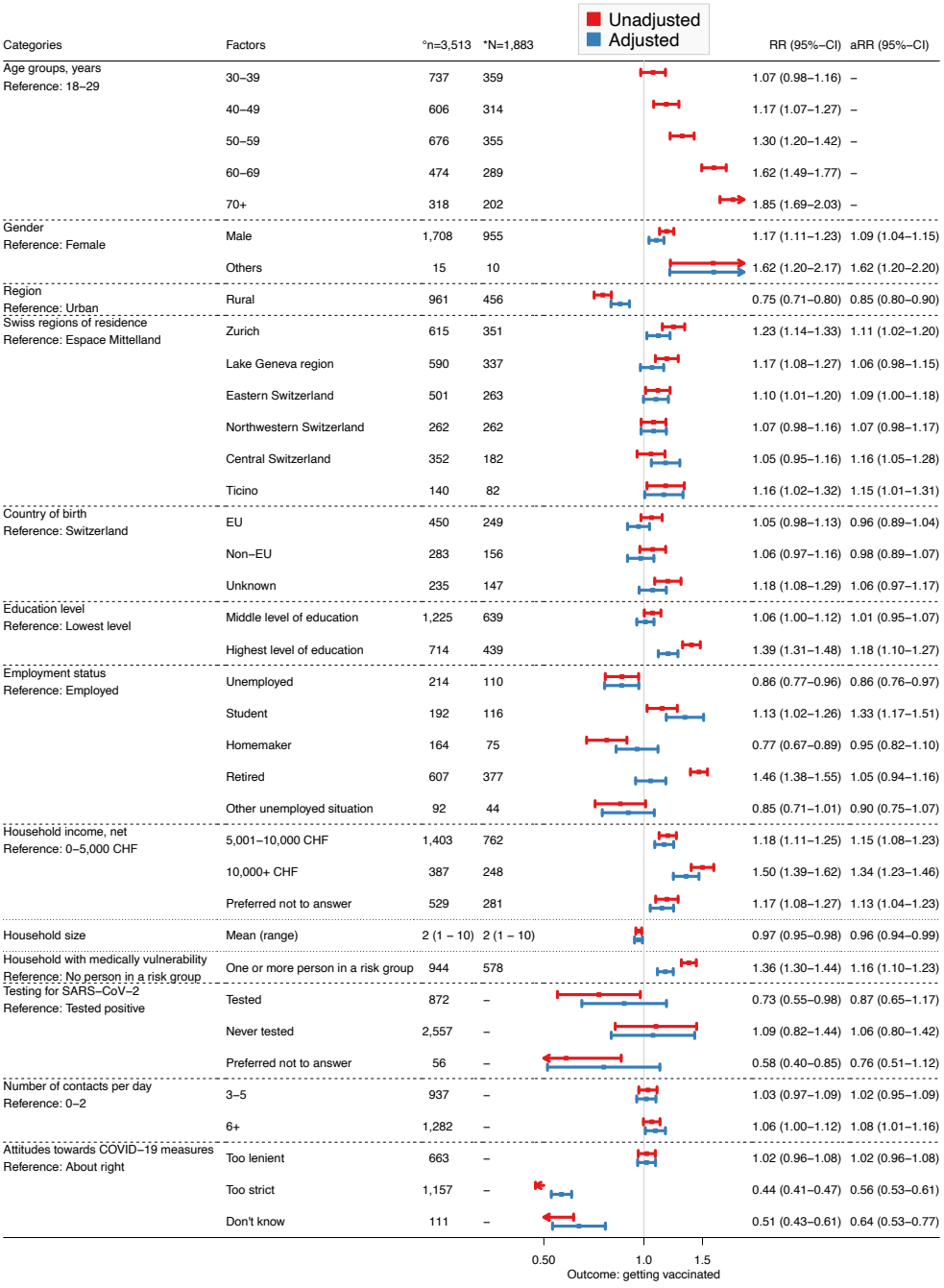

FIGURE 5.2: Rate ratios from the univariable and multivariable Poisson regression models. The primary outcome of the analysis is having received the first dose of a COVID-19 vaccine. °Number (n) of observations included in the regression analysis. *Number (N) of participants included in the regression analysis. Abbreviations: EU, European Union; CHF, Swiss Francs; CI, confidence interval; RR, rate ratio; aRR, adjusted rate ratio.

5.4 Discussion

This study presents findings from analyses investigating factors associated with COVID-19 vaccination uptake in participants in the CoMix study in Switzerland. We found that vaccination uptake differed between subgroups from June to September 2021, a period

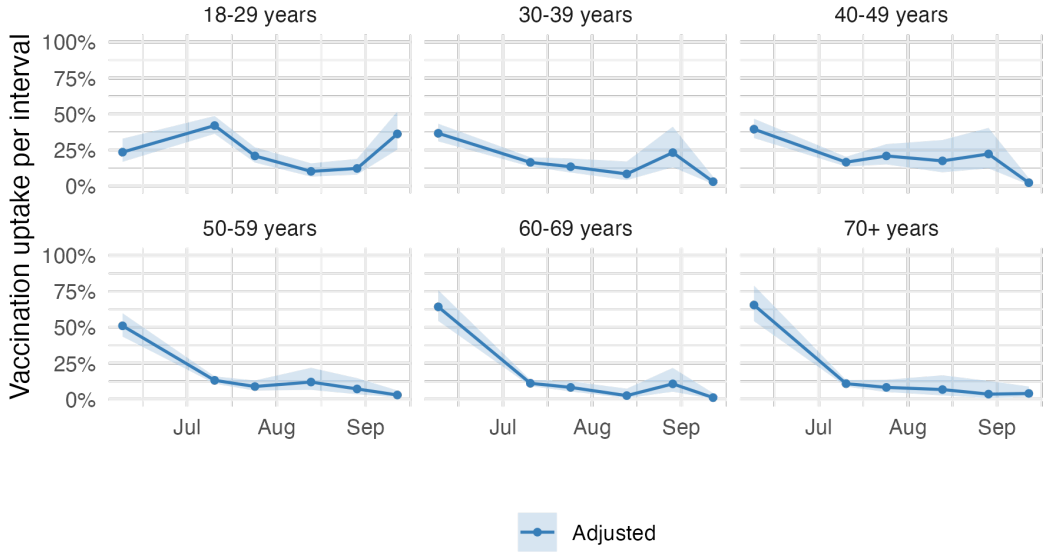

FIGURE 5.3: Vaccination uptake per interval by age group. Vaccination uptake corresponds to the percentage receiving the first vaccine dose amongst those who have not already received it. The estimates were adjusted for gender, region, Swiss region of residence, country of birth, education level, employment level, net household income, household size, household with a medically vulnerable individual, testing for SARS-CoV-2, number of contacts per day, and attitude towards COVID-19 measures, with an interaction between age and survey wave. The shaded area indicates the 95% confidence interval.

during which COVID-19 vaccines were available to the entire adult population in Switzerland. Individuals who were older, male, and students, had a higher educational level, household income, and number of social contacts, and lived in a household with a medically vulnerable person were associated with higher vaccination uptake. In contrast, individuals who lived in rural areas, smaller households, and who perceived COVID-19 measures too strict were associated with lower uptake. There was no significant association between previous SARS-CoV-2 infections and vaccination uptake. Together, these results suggest that sociodemographic factors as well as individual behaviour and attitudes shaped COVID-19 vaccination uptake in Switzerland.

A major strength of our study is the use of the longitudinal CoMix survey to study multiple factors that are associated with COVID-19 vaccination uptake. The survey was based on quotas on age, gender, and region of residence and aimed to be representative of the Swiss population. As a result of the longitudinal data collection over six survey waves and modeling vaccination uptake as a point process using a Poisson regression model, we were able to capture changes in social contacts and attitudes on control measures over time. In France, Germany, and Italy, the introduction of COVID-19 vaccine passports in September 2021 resulted in an increase in vaccination uptake (Oliu-Barton et al., 2022). In our study, the increase in vaccination uptake in 18-49 year olds during the last two survey waves at the end of summer 2021 coincided with the introduction of a COVID-19 vaccination certificate, which was required for participation in certain activities (table D.1). Another possible reason for the increase in vaccination uptake in late summer 2021 could be the easier scheduling of vaccination appointments after the summer holidays. In contrast to the study by Heiniger et al. (2022), we were also able to study the association

between previous SARS-CoV-2 infections and the number of social contacts with COVID-19 vaccination uptake in Switzerland.

Our study also comes with a number of limitations. The potential inclusion of participants from the same household may influence our findings due to shared behaviors among household members. However, we think that such an event would be highly unlikely due to the survey design and the recruitment of participants. Further, the overall vaccination uptake in the study population by September 2021 (75%) was somewhat higher compared to the Swiss adult population (70%). This difference could be a result of the recruitment method within which the CoMix study was biased towards individuals with access to the internet, who may be reached by banner ads, email campaigns, and social media advertisements. In addition, survey participants are likely to be healthier than the general population (Keyes et al., 2018). In the context of the CoMix study, participants might be more health-conscious and more likely to be vaccinated than the general population. Moreover, we found that individuals from the youngest and oldest age groups, non-German speaking regions, who were born in an EU country, and who had a higher number of contacts were more likely to have missed a survey wave. Therefore, the vaccination uptake and the aRR for these categories could be slightly underestimated. Although accounting for missing data from participants who missed survey waves hardly affected estimated HRs, associations between the place of residence, place of birth, and contact number with vaccination uptake should be interpreted with caution. As indicated by Moser et al. (2018), relative outcome measures like RRs may be less prone to bias than absolute quantities. Further, we did not collect information about the political orientation of participants, which may have an association with COVID-19 vaccination uptake as found for the United States but not for the United Kingdom (Albrecht, 2022; Klymak and Vlandas, 2022).

Our analysis indicated that older age and higher sociodemographic status were associated with higher COVID-19 vaccination uptake in Switzerland, similar to the findings of some other studies (Dubé and MacDonald, 2022; Heiniger et al., 2022; Klymak and Vlandas, 2022; Leos-Toro et al., 2021; Terry et al., 2022). Lazarus et al. (2021) have, however, observed considerable heterogeneity in vaccine acceptance between countries. Vaccine hesitancy has also been shown to vary substantially at county level within the US (Larson et al., 2014). For example, gender as a predictor of COVID-19 vaccine acceptance and hesitancy varied globally (de Figueiredo and Larson, 2021; Detoc et al., 2020; Heiniger et al., 2022; Lazarus et al., 2021). In our study, women reported lower vaccination uptake than men, possibly due to the mixed guidance for pregnant women or women wanting to become pregnant (Stock et al., 2022; Wong et al., 2022). Among women, Skjefte et al. (2021) also found that younger age, lower income, lower level of education, being unmarried and not having health insurance were associated with vaccine hesitancy. We did not find a significant association between place of birth and vaccination uptake, but systematic reviews indicated low intent to get vaccinated and low uptake in some migrant population groups (Crawshaw et al., 2022; Dubé et al., 2014). We asked participants about their perception of current COVID-19 measures, which might reflect trust in the government, which was found to be decisive in vaccine uptake (de Figueiredo and Larson, 2021). Moreover, Lazarus et al. (2021) stated that vaccine hesitancy is associated with a lack of trust in COVID-19 vaccine safety and science, and scepticism about vaccine efficacy. Finally, we found that individuals with a higher daily number of social contacts had a higher vaccination uptake. This could either be a result of participants increasing their number of contacts after vaccination, or that participants with a higher number of contacts are more willing to get vaccinated to protect themselves and others from infection, severe disease, and death.

Decision-making about vaccination strategies often occurs in the presence of uncertainties (Larson et al., 2022). To develop tailored and effective vaccination strategies, it is important to understand the multifactorial causes and context of vaccination hesitancy (Dubé and MacDonald, 2022). Factors associated with vaccine hesitancy or uptake, often encompass political, religious, and socioeconomic aspects, but might vary across time, location, and specific vaccines (Larson et al., 2014; MacDonald, 2015). Despite the difference in time and context, a study examining the uptake of human papillomavirus (HPV) vaccines in Switzerland also found that individuals living in rural areas tended to be vaccinated less frequently (Riesen et al., 2018). Vaccination strategies need to be carefully planned to ensure readiness of both the public and the health community, including the need for effective communication about the complexities of vaccination, such as the recognition that side-effects may occur shortly after vaccination while protection from severe disease only follows later. Vaccination strategies also require a broad range of approaches on the individual, provider, health system, and national levels, which is difficult to properly coordinate and promote (McIntosh et al., 2016). Policymakers have historically considered multiple options to increase vaccine uptake, ranging from communication and outreach strategies to monetary (dis)incentives, encouraging parental responsibility, and minimizing distrust of expertise (WHO, 2014). Experts, such as physicians and other health care providers, are still among the most trusted individuals when it comes to health care advice, including for vaccination (Albrecht, 2022; Featherstone et al., 2019; Larson et al., 2022). Both, science, and health professionals, should be adequately trained in knowledge communication. Low vaccine uptake might be due to access and communication barriers and highlight that it is key to have outreach, and credible, consistent, and unified information about vaccines (Black and Rappuoli, 2010), such as that vaccines are among the most effective measures ever achieved through medical intervention. Engaging with and comprehending individuals skeptical about vaccination is of importance. In our study, we observed minimal changes in the attitudes of individuals who expressed no intention to get vaccinated (16% vs. 14% maintained their attitude throughout the study). We showed, within another panel of participants in the CoMix study in Switzerland, that almost half of individuals who did not intend to be vaccinated lacked trust in vaccines or feared side effects Reichmuth et al. (2022a). Horne et al. (2015) underscored the positive influence of factual information on people's attitudes towards vaccination in relation to communicable disease risks. Future research should focus on exploring effective social intervention strategies to enhance the uptake of vaccination. Finally, transparency about vaccine effectiveness and adverse events to set public expectations should improve trust in vaccines, but messaging should take care to avoid unintentionally overemphasizing the risk of rare adverse events (Schaffer DeRoo et al., 2020).

Our analysis suggests that women and individuals from rural areas, people with lower levels of education and lower household income, those who were unemployed, and who perceived the pandemic measures as being too strict were less likely to get vaccinated against COVID-19 in Switzerland. Tailored vaccination strategies towards these communities with lower vaccination uptake can be decisive as COVID-19 vaccination remains an important pillar in preventing severe disease and death.

Declarations

Ethics approval and consent to participate The CoMix study protocols and questionnaires were approved by the local ethics committee of the Canton of Bern (project number 2020-02926), all methods were performed in accordance with regulations, and informed consent of participants was obtained.

Availability of data and materials

Scripts used for the analysis are available on GitHub: https://github.com/ISPMBern/comix.

Competing interests

All authors declare no competing interests.

Funding

This study received funding from the European Union's Horizon 2020 research and innovation program - project EpiPose (No 101003688), the Swiss Federal Office of Public Health (No 142004995), and Swiss National Science Foundation (No 176233). JR was supported by the Swiss National Science Foundation (No 189498).

Author contributions

MR, LH, AM, NL, and CA conceived and designed the study. MR performed the analysis and wrote the first draft. MR, LH, AM, JR, AH, NL, and CA contributed to the interpretation of the results. MR, LH, and CA wrote the manuscript. MR, LH, AM, JR, AH, NL, and CA commented on the manuscript and approved the final version.

Acknowledgements

We like to thank the European Centre for Disease Prevention and Control (ECDC) and the CoMix Europe Working Group for setting up the CoMix study across more than 20 European countries, and the partners at Ipsos MORI for running the survey.

Discussion

6.1 Summary and outlook

During the pandemic, an enormous amount of SARS-CoV-2 related data was available in near real-time. By combining data with modeling methods epidemiologists could estimate important epidemiological parameters such as the effective reproductive number R_e and the growth advantage of SARS-CoV-2 variants (Althaus et al., 2021; Davies et al., 2021; Huisman et al., 2022; Viana et al., 2022). This doctoral thesis especially contributes evidence on the transmission dynamics of SARS-CoV-2 and behavioral changes in humans, including vaccination uptake. Collaboration with authorities such as the FOPH might have facilitated the translation of these findings into action.

An epidemic in a specific geographical region cannot be seen independently of the neighboring areas' interactions. As a result of cross-border activities including travel, infections acquired abroad can impact the local epidemic. The findings in chapter 2 quantified that imported cases can explain the growth of the SARS-CoV-2 epidemic in two summers. For summer 2020, Hodcroft et al. (2021) highlighted that travel likely increased the rapid spread of a SARS-CoV-2 variant detected in Spain that had no intrinsic transmission advantage. During this time imported cases successfully thrived into transmission chains mostly when local SARS-CoV-2 incidence was low (Lemey et al., 2021). The impact of travelers on the local epidemic can be reduced by maintaining and improving cross-border measures. For instance, certificates, testing, and quarantine can help mitigate the growth of the epidemic, especially when local incidence is low, as it was in summer 2020. Improved surveillance of travelers can not only help to mitigate the epidemic growth but also delay the spread of VoCs. Emerging VoCs fueled epidemic waves. A variant is defined as VoCs when genomic changes lead to a significant increase in growth advantage of the variant compared to existing variants or more severe disease (Carabelli et al., 2023). VoCs can thoroughly impact global health, including healthcare capacity. Thus, authorities attempted to control the impact of VoCs with various control measures such as travel bans.

Global, coordinated efforts are needed to prevent SARS-CoV-2 transmission worldwide. Testing and quarantine may be more effective than travel bans to mitigate local spread. We showed that border closures implemented after alerts of new variants are likely too late, as variants such as Alpha and Delta had already spread in the country (chapter 3). Similarly Tsui et al. (2023) highlighted that Omicron had been introduced undetected into England before scientists alerted the WHO. By the time authorities reacted with stricter control measures, such as travel bans, the variant had already spread globally and nationally. Therefore, the subsequent travel restrictions imposed on countries in southern Africa hardly impacted local introduction and spread. Tegally et al. (2023) showed that countries where VoCs emerged, had a declining role in their global dispersal, for example, India contributed <15% and South Africa <2% of Delta and Omicron exports, respectively. Travel bans and border closures can hinder rapid scientific research, and

collaboration on global health interventions and can also lead to social and economic damage for the banned countries.
The Swiss government implemented various other interventions to mitigate transmission and the severity of COVID-19 between 2020 and 2022. For example, working from home became mandatory in March 2020 and aimed to reduce the average number of social contacts. From 2021 until mid-May 2022, we showed a significantly reduced number of social contacts in Switzerland (chapter 4). The largest reduction in contact was in 30-64 year old adults and the smallest reduction in children aged 0-4 years. Jarvis et al. (2023) indicated that the pandemic caused long-term changes in contact patterns in Switzerland and other countries. Differences in contact patterns impact the spread of respiratory pathogens such as SARS-CoV-2 and influenza (Mousa et al., 2021). For the future, access to data, that is setting-specific and up-to-date, is crucial to guide effective pandemic interventions. Such data combined with models helps to predict the transmission of respiratory pathogens and to evaluate the effectiveness of NPIs in mitigating the burden of disease. The most recent social contact data for Switzerland is available on an open repository Zenodo (Reichmuth et al., 2023a).
In addition to NPIs, increasing immunity, specifically through vaccination, is crucial to mitigate the burden of COVID-19. Vaccines protect against severe disease and death, but they are less effective in preventing transmission (Wilder-Smith, 2022). Harris et al. (2021) found that among household contacts vaccinated cases were around 50% less responsible for symptomatic cases than without vaccination. While transmission of disease is still a concern, NPIs should reduce SARS-CoV-2 transmission and vaccinate the severity of COVID-19 in the community. High vaccination coverage in Switzerland can be achieved by focusing on sociodemographic factors and individual behavior (chapter 5). We reported survey findings on vaccination willingness to the FOPH every month (further detail in our final report Reichmuth et al. (2022a)). This feedback loop between researchers and the government can lead to a better understanding among all stakeholders to ultimately implement more effective public health measures.

6.1.1 Further research directions on the SARS-CoV-2 pandemic

The SARS-CoV-2 pandemic is not over and still raises unresolved questions. Further research on SARS-CoV-2 is needed. For example, to better understand transmission dynamics, research should focus on the waning immunity in humans and the evolutionary origin of VoCs, including their properties such as immune escape. VoCs can trigger epidemic waves that can overburden the health system. Especially if the acquired immunity in the population does not protect against serious diseases. Acquired immunity in the population increased over time. Thus, immune escape mutations are progressively selected. Likely due to immune evasion, Pulliam et al. (2022) indicated an increase in reinfection in the Omicron-era. The heterogeneous immunity in South Africa was confirmed by Sun et al. (2023) for the 4^{th} wave (after October 2021). Together with waning immunity, the population immunity level increased in complexity.
The need to include a global perspective while studying pandemics further increases the complexity. For example, the spread of SARS-CoV-2 differs in geographical regions, in particular when comparing Switzerland and South Africa. In contrast to Switzerland, South Africa has poorer access to health care, including access to vaccines, one of the highest HIV prevalence in the world, and an increasing number of people living with diabetes (Magliano et al., 2021; Zuma et al., 2022). Co-existing epidemics potentially interact with SARS-CoV-2 and influence its evolution and severity of COVID-19 (Corey et al., 2022; Danwang et al., 2022; Pal and Bhadada, 2020). Jassat et al. (2021) identified in a nationally representative cohort study in South Africa that older individuals, those

with chronic co-morbidities, and people living with HIV, particularly those not on ART are at high risk of COVID-19 in-hospital mortality. By the beginning of 2022, the population attributable fraction of diabetes was around 10% for severe COVID-19 and even higher for COVID-19–related deaths (Li et al., 2023). In line with these findings and investigating all COVID-19 hospital admissions in South Africa between 5 March 2020 and 28 December 2022, we estimated an adjusted fraction of deaths in hospitalized COVID-19 patients attributable to HIV to be around 5%, which was slightly higher due to diabetes (unpublished work from Reichmuth ML, Tegally H, Poongavanan J, Abimiku A, Baxter C, de Oliveira T, Naranbhai V, and the INFORM-Africa team).

Given differences in host health status including vaccine and natural infection-induced immunity which resulted in heterogeneous immunity within populations, the spread of variants within communities is becoming increasingly complex. Overall, with uncertainty in immunity levels and viral evolution, it is only to speculate about the future course of the pandemic. For example, in many years, SARS-CoV-2 could be seasonal, similar to influenza, and might lead to mild respiratory illnesses such as the other four hCoVs (Markov et al., 2023).

Markov et al. (2023) elaborated on three hypotheses for the evolutionary origin of VoCs and could be part of further research, namely I) undetected circulation in humans, II) circulation in animal reservoirs, and III) chronic infections, also known as persistent infection. Continuous and representative (genomic) surveillance of cases and viral diversity is crucial to detecting the circulation of new viral pathogens and variants timely. Moreover, population-scale data, such as those built and maintained by the 'Role of Data Streams in Informing Infection Dynamics in Africa' (INFORM Africa) initiative, can help to understand health-related associations and thus improve public health (Poongavanan et al., 2023).

In addition to undetected circulation in humans, circulation in various zoonotic reservoirs is of concern. Lu et al. (2021) provided evidence for circulation in animals, e.g., farmed minks, and for animal-to-human transmission, also known as zooanthroponotic transmission. Pickering et al. (2022) confirmed zooanthroponotic transmission from wildlife such as white-deer. Host-specific adaptation and potential recombination with other viral lineages may occur in animals and threaten the health of wildlife, domestic animals, and humans through multi-host transmission (Kuchipudi et al., 2023). Coordinated surveillance efforts in humans but also among animals can help to guide evidence-based response to SARS-CoV-2 (Kuchipudi et al., 2023).

Persistent infections enable SARS-CoV-2 to accumulate multiple mutations (Carabelli et al., 2023). Harari et al. (2022) found evidence for dynamic polymorphic viral populations in chronically infected patients, which suggests that a compromised immune system selects for antibody evasion. For example, Maponga et al. (2023) highlighted a case were SARS-CoV-2 of a women living with uncontrolled HIV accumulated over twenty additional mutations. Reoccurred mutations in persistent infection escape the immune system, increase ACE2 affinity, and improve viral packaging (Wilkinson et al., 2022). Thus, persistent infection can contribute to antigenic shifts when these variants get transmitted to others. Ghafari et al. (2023) estimate that 0.1-0.5% of SARS-CoV-2 infections can persist. They suggested that 70% of the persistent SARS-CoV-2 infections had long periods of no consensus changes in the viral sequences, which indicates the presence of a non-replicating virus (Ghafari et al., 2023). Overall, characterizing the host-viral dynamic and identifying persistent infection and controlling co-morbilities including health promotion can help to mitigate COVID-19 and reduce the occurrence of SARS-CoV-2 variants.

Another field of research that requires further study - as data is becoming available - is long COVID. Long COVID is a multisystemic condition with often severe symptoms that

are physically and mentally distressing (Davis et al., 2023). Symptoms impact individuals and society as a whole, such as absence from work. At least 10% of SARS-CoV-2 infections experienced long COVID (Davis et al., 2023). This is dramatically, given the high number of infections. Moreover, chronically infected individuals were more likely to report long COVID than shorter infections (Ghafari et al., 2023). Finally, continuous research on the evolution of SARS-CoV-2 and its outcomes combined with public health research will benefit the well-being of all.

6.1.2 Strengths and limitations

During my thesis, I used several data sources and models. My multi-method approach has both strengths and limitations. On the one hand, the use of multiple data sources and methods allows for increased hypothesis testing, for example, due to missing data, compared to an inflexible approach. Missing data is common in epidemiological studies. In chapter 5, missing data occurred, for instance, because of inconsistent participation and reporting. Data might also be unavailable for ethical reasons. For example, data on human mobility which was used in chapter 2 is rare or confidential.
The spread of SARS-CoV-2 is a multidimensional process that depends on the interaction between human genetics and behavior, the viral genetics, and the environment. In addition, data presents only a snapshot of the complex global health problems. Depending on the research question and data availability, different models can provide insights to understand, explain, and predict observed phenomena and dynamics. A scientist should be open to learn about many different methods to support rigorous evidence-gathering and ultimately improve public health. In chapter 3, we illustrated that combining different data sources such as sequence data, case numbers, and results from observational and modeling studies, with different models such as phylogenetic and mathematical transmission models, can inform public health response during pandemics. In addition, chapter 4 offers the potential to improve mathematical transmission models in Switzerland by including heterogeneity in transmission rates. In summary, data availability and hypotheses require flexible use of different data sources and methods.
On the other hand, knowledge of various methods and disciplines can lead to generalizations that contradict specific knowledge. No single person can be an expert in all disciplines, and few can be conversant in all of them (Lipsitch, 2020). Even in a single discipline, scientific information is extensive. Science including academic career opportunities favors specialization. However, specialization should not lead to disciplines that accept and follow only one method to progress (Lipsitch, 2020).
Cross-disciplinary approaches are important for progress in health science, but collaboration is fraught with challenges. For example, I collaborated with molecular and computational epidemiologists, physicians, policymakers, statisticians, and social scientists. It was challenging to create a knowledge base with experts from a wide range of disciplines. Regular joint discussions need to combine different concepts, interests, knowledge, and communication channels - which have the risk of getting lost and being time-consuming. However, I learned about more methods than I would have otherwise. I have broadened my view on aspects of public health - from qualitative to quantitative perspectives.
Moreover, being surrounded by wealth of knowledge can be overwhelming and I wonder if this reinforces impostor syndrome. Impostor syndrome describes the failure to objectively assess their accomplishments and co-occurs with persistent self-doubt and fear of being exposed as a fraud (Huecker et al., 2023). Academics, especially students, are particularly at risk of developing an impostor syndrome species as they are assessed multidimensional (Huecker et al., 2023).

6.2 Modeling impacts decision making

Effective decision-making needs evidence. Computational modeling can provide needed evidence in times of uncertainty and threats. During the emergence of pathogens such as SARS-CoV-2 authorities have to react promptly to ensure global health. During the SARS-CoV-2 pandemic, scientists worked with comprehensive data to provide evidence-based advice. For instance in January 2020, Riou and Althaus (2020) predicted pandemic potential using stochastic transmission models. The data and models indicated the pandemic potential, and at the same time, the WHO declared a public health emergency of international concern (WHO, 2020b). Nevertheless, in Switzerland, for example, drastic control measures, i.e. the 'extraordinary situation', were introduced only one and a half months later (Federal Council, 2020c).
The emergence of SARS-CoV-2 in China and the predicted pandemic potential raised uncertainties about the impact of globalization, particularly travel, on the burden of COVID-19. Worobey et al. (2020) demonstrated using phylogenetic models that travelers facilitated the early spread of SARS-CoV-2 in Europe when intensive testing and contact tracing were hardly implemented. Chinazzi et al. (2020) used a global transmission model to conclude that early travel restrictions helped to slow the spread of the pandemic for few days. They suggested that quarantines, self-isolation, and early detection will probably be more successful in mitigating the SARS-CoV-2 pandemic than travel restrictions.
Nevertheless, Tegally et al. (2023) highlighted using a phylogeographic approach that many countries imposed severe travel bans during the pandemic, especially for countries where VoCs were detected, although surveillance and quarantine could benefit greatly. Without a zero-COVID policy, the introduction and spread of a new variant will occur. Therefore, travel control measures focus on delaying the spread. Delaying the dominance of a variant may be beneficial to allow more time to accelerate vaccination uptake, implement local control measures, and increase health care capacities. For example, with the emergence of Alpha in Switzerland, authorities introduced quarantine for travelers from the UK as well as stricter local measures. When Delta and Omicron were detected, travel restrictions were introduced, but vaccination coverage and local measures were hardly increased.
Moreover, research on social contact models suggested in early 2020 that premature and sudden lifting of NPIs would lead to rapid increases in the epidemic curve, which could be flattened by a gradual relaxation of NPIs (Prem et al., 2020). Switzerland lifted the control measures in June 2020 rather abruptly, in contrast to March 2021 and February 2022 when it was more gradual.
With the surge in cases, the need for hospital and intensive care units (ICU) also increased. Grasselli et al. (2020) forecast the ICU demand over the first weeks of the first outbreak in Italy. A couple of months later, Zhao et al. (2020) forecast the ICU demand for Switzerland to inform decision-makers with various counterfactual scenarios regarding hospital occupancy. Subsequent during the critical phase of the SARS-CoV-2 pandemic and to react with measures, the FOPH monitored and visualized the hospital occupancy online on dashboards (www.covid19.admin.ch).
In general, a well-integrated continuous surveillance system combined with a modeling approach at the FOPH would help to ensure a rapid response and pandemic preparedness. Before the SARS-CoV-2 pandemic, statisticians and modelers were hardly engaged within the FOPH, whereas the Netherlands is a pioneer in integrating science and public health at the 'National Institute for Public Health and the Environment' (RIVM). In Switzerland, scientific engagement only increased and was complemented by the scientific task force during the pandemic. Thus, their communication channels were developed

and improved due to the lack of pandemic preparedness during the emergency. In improving pandemic response after the pandemic, the FOPH invests in pandemic response and for example, established a new online dashboard to inform about the circulation of respiratory infectious diseases in Switzerland (more detail at idd.bag.admin.ch).

6.2.1 Pandemic preparedness

Preparedness enables an early and effective response in an emergency of 'diseases X' to reduce needs, mitigate suffering, and help to save lives (ECDC, 2021a; Van Kerkhove et al., 2021). The effectiveness of a response depends on investment in preparedness, i.e., relies on pre-existing capabilities (ECDC, 2021a). Capabilities in public health, health systems, and communities aim to prevent, protect, and enable quick response and recovery from health emergencies (Nelson et al., 2007). Nelson et al. (2007) defined sixteen key elements involved in preparedness. They categorized the elements into having preplanned and coordinated crisis response capabilities, having experts and a fully staffed workforce, and constantly evaluating accountability and quality. For instance, capabilities include public engagement by educating and involving communities in health-related topics, but also the monitoring of diseases.
Epidemiological surveillance is important to monitor, detect, and investigate infectious diseases. During the SARS-CoV-2 pandemic, enormous and previously unseen global genomic surveillance enabled effective public health response. For instance, global genomic sequencing helped to detect and track the spread of VoCs. Although global sequencing data are available, Brito et al. (2022) and Chen et al. (2022b) highlighted the heterogeneity of global sequencing coverage, sharing, and time to its availability. The continuous, globally homogeneous and representative (genomic) surveillance of cases and viral diversity is crucial to monitor the circulation of new viral pathogens and variants timely. Cases, viral genomes from cases, and wastewater samples provide information on the occurrence of epidemiologically and clinically relevant mutations (Karthikeyan et al., 2022). In addition, sequencing from wastewater can improve the early detection of pathogens. Early detection of VoCs is key to pandemic preparedness.
The FOPH aimed to evaluate their performance during the SARS-CoV-2 pandemic. On behalf of the FOPH, Althaus et al. (2022) evaluated the Swiss escalation model: They concluded that the operational epidemiological criteria were missing during the epidemic but are needed for effective epidemic response. For instance, incidence in hospitals can help transient to different escalation levels. Further, the work process and division were inefficient within the escalation model. Althaus et al. (2022) also highlighted that a predefined expert group can help during crisis management. In an emergency, the federal authority should take over a leading role in assigning duties. For example, experts should be included in decision-making of the FOPH. Decision-making and implementation need effective communication between different levels, of federal and regional authorities.
Appropriate communication is needed at all stakeholder levels to act and implement measures. Effective science communication should aim to help others understand the evidence and demonstrate its relevance, bearing in mind that other factors such as beliefs influence action (Committee on the Science of Science Communication: A Research Agenda et al., 2017). The context, especially the target audience, i.e., their prior knowledge and beliefs, the place, and time should be taken into account when communicating (Committee on the Science of Science Communication: A Research Agenda et al., 2017). Furthermore, the transfer of knowledge should be transparent. I.e. communication should include the evidence, but also the uncertainties, but not be confusing. Public engagement offers opportunities to facilitate transparency (Committee on the Science of Science Communication: A Research Agenda et al., 2017). For example, the 'Swiss

Meeting for Infectious Disease Dynamics' (SMIDDY) aims to organize regular networking events to provide the opportunity for researchers and policy-makers such as members of the FOPH to share their work and foster scientific collaborations across Switzerland. Within such a community, mutual learning from other insights and barriers can eventually create a common statement between scientists and policy-makers, which could facilitate the communication of evidence and the potential for public engagement in infectious disease control.
In my opinion, communication skills and the assessment of sources must be properly learned in obligatory school. The public needs to be able to assess trustworthy sources in the age of artificial intelligence and fake news. Worrying, in the study of the Program for International Student Assessment (PISA) from the Organisation for Economic Co-operation and Development (OECD), on average only one in ten students was able to distinguish between fact and an opinion (Schleicher, 2019). Public understanding and involvement in pandemic response can strengthen joint efforts. For example, the understanding of vaccination and its health benefits can help to increase trust and willingness in vaccination uptake. The implementation of capabilities must be in quiet times to be prepared for threats.

6.2.2 Interdisciplinary approach in public health

Health problems are multidimensional. Public health is, thus, an interplay of natural sciences, social sciences, and humanities. Collaboration between different disciplines helps to create joint strategies to expand knowledge and health (The Academy of Medical Sciences, 2016). For example, intervention, such as implementing vaccination and increasing its uptake, needs to consider psychological, economic, cultural, and health policy factors.
Depending on the division and combination of disciplines, this results in a multi-, inter-, and transdisciplinary approach (Choi and Pak, 2006). The 'Multidisciplinary Center for Infectious Diseases' (MCID) at the University of Bern, for instance, includes several disciplines, namely epidemiology, patient-focused research, society and law, neglected diseases, immunity, economics, and microbiology. Disciplines are additive. In an interdisciplinary approach such as public health multiple disciplines interact into one activity. Unifying disciplines results in a transdisciplinary approach such as aimed by the 'One Health' approach (OHHLEP et al., 2022).
One Health is an integrated, unifying strategy to balance and optimize the health of humans, animals, and ecosystems. It acknowledges that the health of humans, domestic and wild animals, plants, and ecosystems are inextricably interrelated and interdependent. Effective communication, collaboration, and coordination are needed to co-benefits for fair and holistic solutions (OHHLEP et al., 2022).
For global problems such as pandemics and ultimately improving global health, international collaborations are needed. Successful international research relies on mutual trust and respect (Ko et al., 2023). Science and global health can only continue and improve with research integrity such as objectivity, accountability, openness, fairness, and honesty.

Acknowledgements

Over the past three years, our society faced several hurdles. Hurdles that shaped society directly influenced my doctoral thesis. Thanks to the fruitful collaboration and support, I learned to overcome and solve problems that not only determined my academic path, but also my personal life. My doctoral thesis including all experiences was only possible with the financial support of the Epipose project, the University of Bern (UniBE DoC.Mobility), the FOPH, and all social interactions. Despite many hours that I was allowed to (and had to) work from home, I was able to meet friends again as colleagues and found new friends. Judith Bouman, Selina Wegmüller, Leonie Heron, Diana Buitrago-Garcia, Martin Wohlfender, Anthony Hauser, Julien Riou, Eliane Rohner, and Kathrin Zürcher made my life as doctoral student sweet and 'sporty'. The academic and personal advice and edits from Judith and Leonie on my thesis were also indispensable. I also like to thank Emma Hodcroft for inspiring me, for the warmth, and for admiring science (and) communication. Thanks to everyone who taught me about science, laughed with me, and caught my tears in Bern, Zurich, and Stellenbosch. I am also grateful to have met all CERIer during my UniBE Doc.Mobility at Stellenbosch University and will keep as friends, in particular Houriiyah Tegally, Graeme Dor, and Monika Moir for your kindness and comments on my thesis. I would also like to thank my co-advisor Niel Hens, who inspired me with his great knowledge and composure, and Nicola Low for her nuanced perspective on my projects. Above all, I would like to thank my supervisor, Christian Althaus, for all the knowledge transfer in modeling and epidemiology of infectious diseases, uncomplicated support and guidance with all the freedom that taught me to think independently and critically, and your engagement and patience. Last but not least, I like to thank my friends, my parents, Gertrud Reichmuth and Martin Reichmuth, and Anina Reichmuth including your plus one, Janis Matthys, for always giving me the best support for my life.

Supplementary material for chapter 2

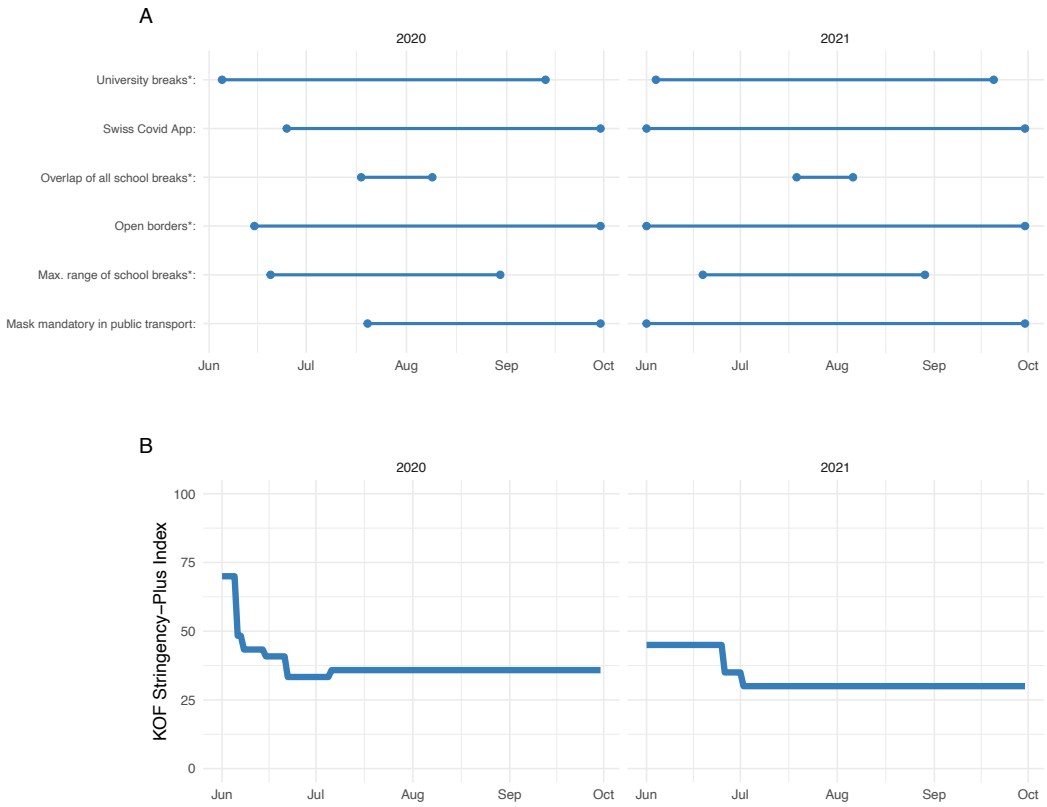

FIGURE A.1: Control measures during summer 2020 and 2021. The KOF Stringency Index records the stringency of COVID-19 policy measures in Switzerland over time (Pleninger et al., 2021). The values range from 0 (no measures) to 100 (full lockdown). Asterisks indicate variability between regions.

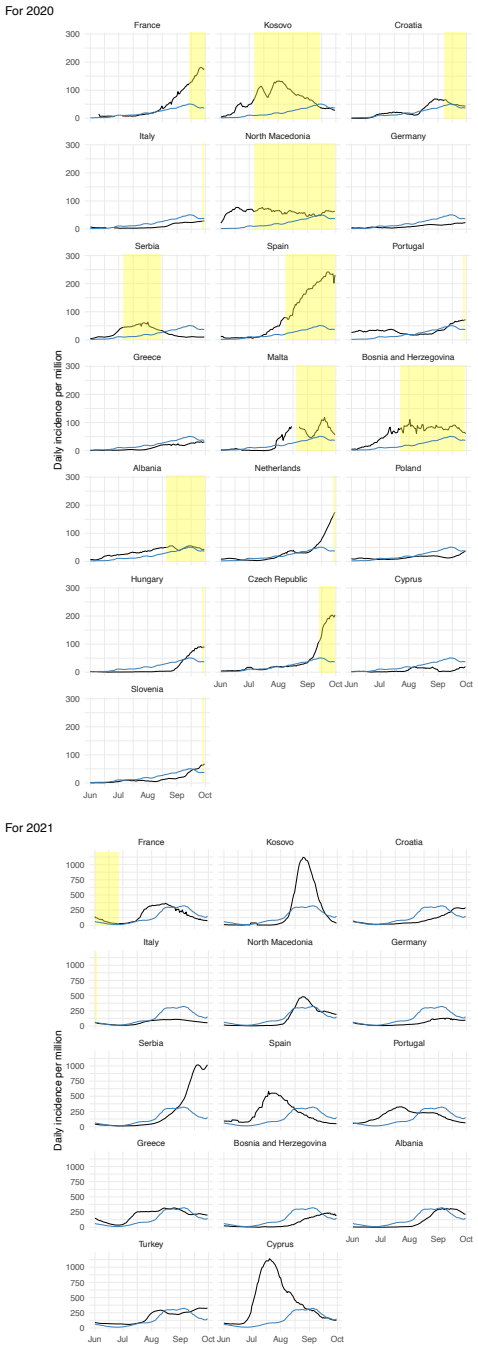

FIGURE A.2: Age of SARS-CoV-2 cases during summer 2020 and 2021. Crosses in the boxplots correspond to the mean age of cases by country of exposure. The blue line corresponds to the mean age of cases with likely exposure in Switzerland. Countries of exposure are ordered by the reported number of cases (indicated with numbers above each countrz). Asterisks indicate significance level from Student's t-test: * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$.

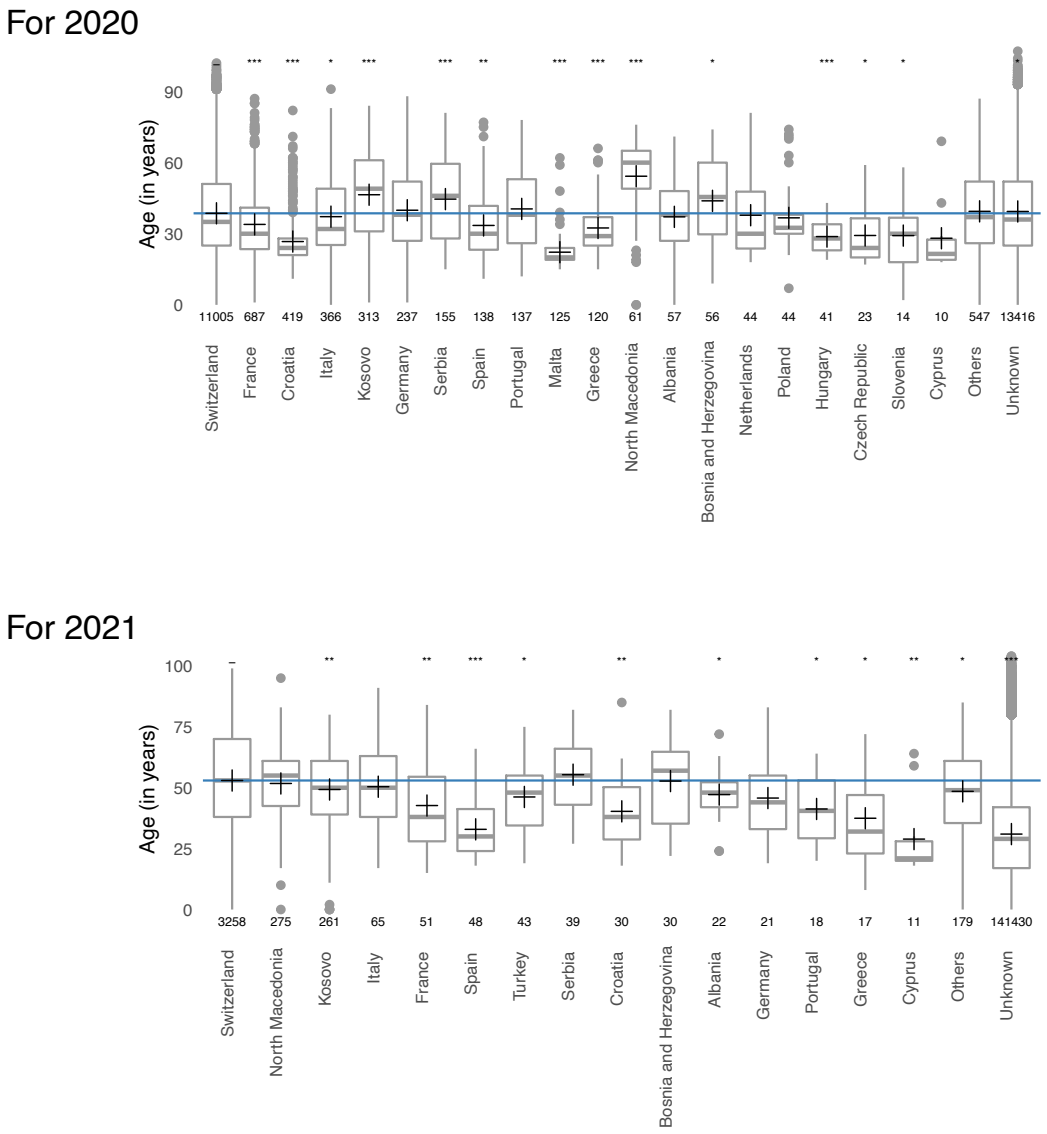

FIGURE A.3: Daily incidence of confirmed SARS-CoV-2 cases in various European countries. The yellow areas indicate the time periods of mandatory quarantine for travelers from the countries to Switzerland. Regional differences existed in France, Austria, and Spain. Incidence (per million, 7-day moving average) in individual countries and Switzerland are represented as black and blue lines, respectively. Countries of exposure are ordered by the reported number of cases.

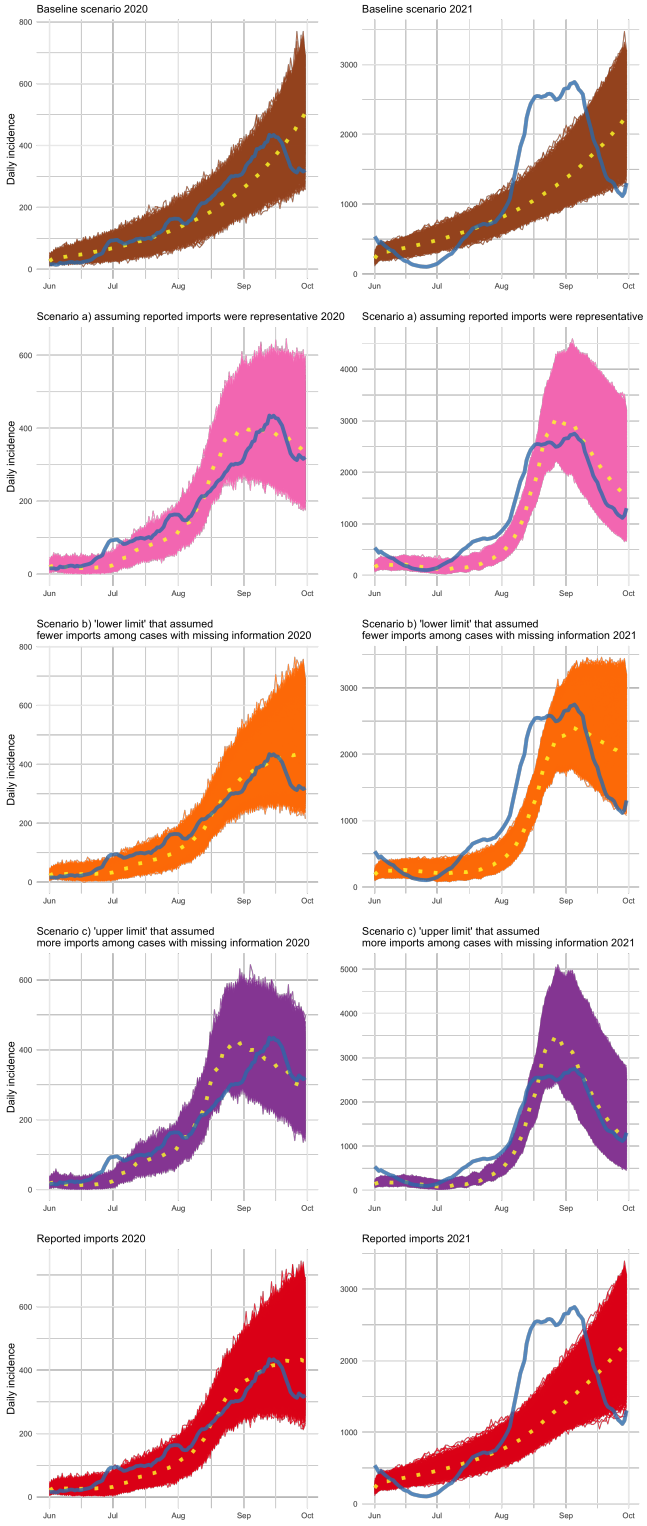

FIGURE A.4: Simulated epidemic trajectories of the SARS-CoV-2 epidemic in Switzerland during summer 2020 and 2021 for all scenarios. Colored areas represent all calibrated epidemic trajectories. The median of the epidemic trajectories and the reported incidence of confirmed cases (7-day moving average) are given as yellow and blue lines, respectively.

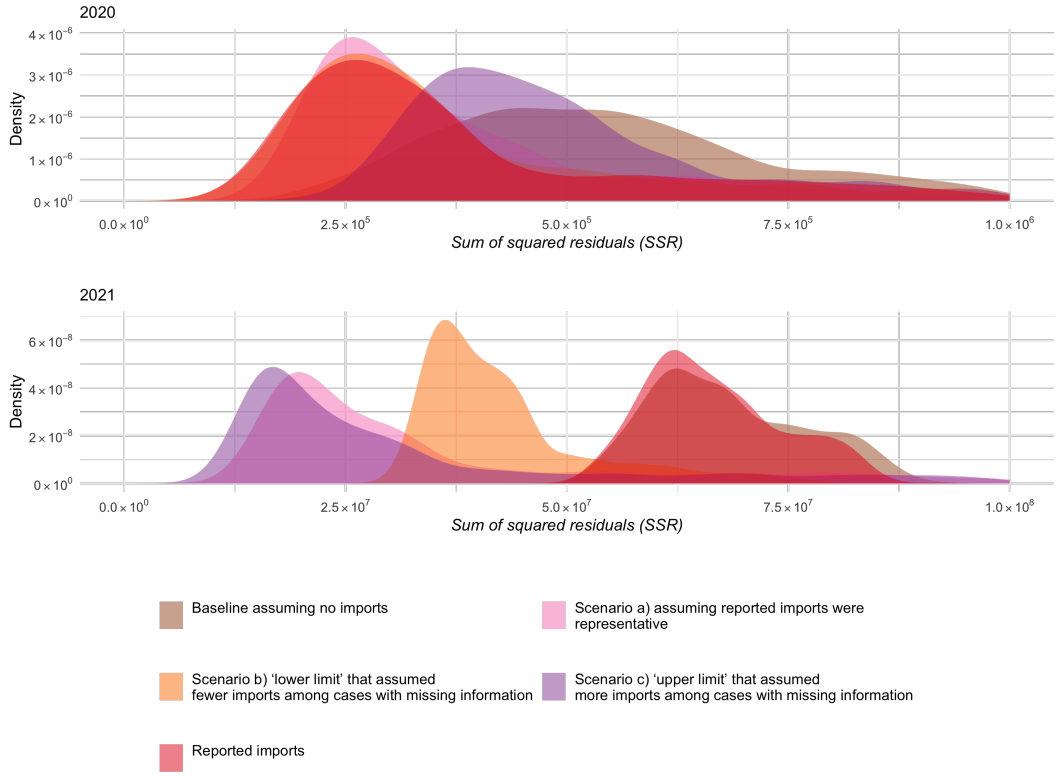

FIGURE A.5: Comparing the quality of simulations for during summer 2020 and 2021: Estimates of sum of squared residuals (SSR) to compare the quality of simulations in describing the observed number of confirmed cases for each scenario in summer 2020 and 2021. The SSR between 1,000 randomly selected trajectories and the daily incidence of confirmed cases (7-day moving average) in each scenario.

TABLE A.1: Confirmed cases of SARS-CoV-2 in Switzerland from 1 June to 30 September by country of exposure. Some countries had quarantine restrictions for high-incidence regions, e.g., Austria, France, and Spain in 2020, and France and Italy in 2021. Abbreviation: IQR, interquartile range. Incidence is shown as 7-day moving average.

[lt] Year	Country	Incidence per 10^6 Median (range)	Confirmed cases	Known exposure (%)	Exposure abroad (%)	Age in years Median (IQR)	p-value (t-test)	Mandatory quarantine
2020	All reported cases							
2020	Switzerland	86.7 (11.9 - 465.9)	8812	72.90	-	35 (24-50)	-	-
2020	Cross-border-associated	-	3276	27.10	100.00	31 (23-47)		-
2020	France	121.9 (27.0 - 363.5)	648	5.36	19.78	29 (23-40)	<.001	2020-09-14 - *
2020	Croatia	45.3 (16.7 - 291.2)	419	3.47	12.79	24 (21-28)	<.001	2020-09-07 - *
2020	Kosovo	39.1 (1.8 - 1118.7)	309	2.56	9.43	49 (31-61)	<.001	2020-07-06 - 2020-09-14
2020	Italy	64.6 (10.6 - 109.4)	299	2.47	9.13	32 (24-46)	0.02	2020-09-28 - *
2020	Germany	33.4 (6.4 - 127.6)	181	1.50	5.53	37 (26-51)	0.335	-
2020	Serbia	42.8 (11.3 - 1018.0)	153	1.27	4.67	46 (28-60)	<.001	2020-07-06 - 2020-08-15
2020	Spain	152.4 (46.6 - 582.9)	136	1.13	4.15	30 (23-42)	<.001	2020-08-08 - *
2020	Malta	85.1 (1.9 - 398.3)	125	1.03	3.82	20 (19-24)	<.001	2020-08-20 - *
2020	Portugal	193.4 (52.0 - 327.2)	114	0.94	3.48	36 (25-49)	0.924	2020-09-28 - *
2020	Greece	219.0 (35.3 - 318.8)	113	0.93	3.45	29 (25-37)	<.001	-
2020	Albania	11.8 (0.9 - 307.9)	57	0.47	1.74	38 (27-48)	0.679	2020-08-20 - *
2020	Bosnia and Herzegovina	19.7 (0.0 - 237.2)	56	0.46	1.71	46 (30-60)	0.022	2020-07-23 - *
2020	North Macedonia	24.0 (2.3 - 483.4)	56	0.46	1.71	60 (49-65)	<.001	2020-07-06 - *
2020	Hungary	8.5 (3.1 - 46.8)	38	0.31	1.16	28 (23-34)	<.001	2020-09-28 - *
2020	Netherlands	140.6 (34.5 - 587.2)	33	0.27	1.01	30 (23-45)	0.547	2020-09-28 - *
2020	Czech Republic	18.4 (10.6 - 46.8)	22	0.18	0.67	24 (20-33)	0.001	2020-09-14 - *
2020	Poland	5.0 (2.0 - 23.5)	20	0.17	0.61	32 (31-44)	0.749	-
2020	Cyprus	307.0 (61.1 - 1139.7)	10	0.08	0.31	22 (19-28)	0.085	-
2020	Slovenia	76.9 (11.9 - 503.1)	10	0.08	0.31	30 (17-35)	0.019	2020-09-28 - *
2020	Others	-	477	3.95	14.56	37 (26-52)	0.229	-
2020	Unknown	-	10831	-	-	35 (25-51)	0.008	-
2021	All reported cases							
2021	Switzerland	86.7 (11.9 - 465.9)	3258	74.59	-	53 (38-70)	-	-
2021	Cross-border-associated	-	1110	25.41	100.00	49 (36-60)		-
2021	North Macedonia	24.0 (2.3 - 483.4)	275	6.30	24.77	55 (42-61)	0.178	-
2021	Kosovo	39.1 (1.8 - 1118.7)	261	5.98	23.51	50 (39-61)	<.001	-
2021	Italy	64.6 (10.6 - 109.4)	65	1.49	5.86	50 (38-63)	0.251	2021-06-01 - 2021-06-03
2021	France	121.9 (27.0 - 363.5)	51	1.17	4.59	38 (28-54)	<.001	2021-06-01 - 2021-06-26
2021	Spain	152.4 (46.6 - 582.9)	48	1.10	4.32	30 (24-41)	<.001	-
2021	Turkey	221.0 (57.4 - 325.5)	43	0.98	3.87	48 (34-55)	0.005	-
2021	Serbia	42.8 (11.3 - 1018.0)	39	0.89	3.51	55 (43-66)	0.322	-
2021	Bosnia and Herzegovina	19.7 (0.0 - 237.2)	30	0.69	2.70	57 (35-65)	0.942	-
2021	Croatia	45.3 (16.7 - 291.2)	30	0.69	2.70	38 (29-50)	<.001	-
2021	Albania	11.8 (0.9 - 307.9)	22	0.50	1.98	48 (42-52)	0.029	-
2021	Germany	33.4 (6.4 - 127.6)	21	0.48	1.89	44 (33-55)	0.089	-
2021	Portugal	193.4 (52.0 - 327.2)	18	0.41	1.62	40 (29-53)	0.003	-
2021	Greece	219.0 (35.3 - 318.8)	17	0.39	1.53	32 (23-47)	0.003	-
2021	Cyprus	307.0 (61.1 - 1139.7)	11	0.25	0.99	21 (20-28)	<.001	-
2021	Others	-	179	4.10	16.13	49 (36-61)	0.001	-
2021	Unknown	-	141430	-	-	29 (17-42)	<.001	-

TABLE A.2: R_e estimates of simulated epidemic trajectories for the SARS-CoV-2 epidemic in Switzerland during summer 2020 and 2021 for all scenarios including sensitivity analyses (overdispersion parameter = 0.1 and 1).

[!ht] Year	Overdispersion parameters	Import scenario	R_e (95%-CrI)
2020	0.5 (range: 0.49-0.52)	Baseline scenario	1.12 (1.08-1.16)
2020	0.5 (range: 0.49-0.52)	Confirmed cases exposed abroad	0.95 (0.9-1)
2020	0.5 (range: 0.49-0.52)	Scenario a)	0.84 (0.78-0.9)
2020	0.5 (range: 0.49-0.52)	Scenario b)	0.96 (0.91-1.01)
2020	0.5 (range: 0.49-0.52)	Scenario c)	0.75 (0.68-0.81)
2021	0.5 (range: 0.49-0.52)	Baseline scenario	1.09 (1.06-1.12)
2021	0.5 (range: 0.49-0.52)	Confirmed cases exposed abroad	1.08 (1.05-1.11)
2021	0.5 (range: 0.49-0.52)	Scenario a)	0.82 (0.74-0.9)
2021	0.5 (range: 0.49-0.52)	Scenario b)	0.93 (0.88-0.98)
2021	0.5 (range: 0.49-0.52)	Scenario c)	0.74 (0.64-0.83)
2020	0.1	Baseline scenario	1.12 (1.04-1.2)
2020	0.1	Confirmed cases exposed abroad	0.95 (0.9-1.01)
2020	0.1	Scenario a)	0.84 (0.78-0.9)
2020	0.1	Scenario b)	0.96 (0.91-1.02)
2020	0.1	Scenario c)	0.75 (0.68-0.81)
2020	1	Baseline scenario	1.12 (1.08-1.16)
2020	1	Confirmed cases exposed abroad	0.95 (0.9-1)
2020	1	Scenario a)	0.84 (0.78-0.9)
2020	1	Scenario b)	0.96 (0.91-1.01)
2020	1	Scenario c)	0.75 (0.68-0.81)
2021	0.1	Baseline scenario	1.09 (1.05-1.13)
2021	0.1	Confirmed cases exposed abroad	1.08 (1.05-1.12)
2021	0.1	Scenario a)	0.82 (0.74-0.9)
2021	0.1	Scenario b)	0.93 (0.88-0.98)
2021	0.1	Scenario c)	0.74 (0.64-0.83)
2021	1	Baseline scenario	1.09 (1.07-1.12)
2021	1	Confirmed cases exposed abroad	1.08 (1.06-1.11)
2021	1	Scenario a)	0.82 (0.74-0.9)
2021	1	Scenario b)	0.93 (0.88-0.98)
2021	1	Scenario c)	0.74 (0.64-0.83)

Supplementary material for chapter 3

Creating the phylogenies

Selecting Swiss sequences

All Swiss Alpha and Delta SARS-CoV-2 sequences prior to 31 March 2021 and 31 July 2021, respectively, were selected using code from CoVariants.org and in-house scripts available at https://github.com/emmahodcroft/Intros-CH-AlphaDelta. These cut-off dates reflect when the variants reached 90% of all sequenced SARS-CoV-2 cases prevalence in Switzerland. These sequences were our 'focal set' and all were included in the analysis, though some were excluded in the phylogenetic pipeline for not passing quality control (QC) metrics. We started with 8,083 Alpha and 5,232 Delta sequences and 7,988 and 5,210 passed QC and were included in the final analysis.

Selecting contextual sequences

In order to detect introductions, we aimed to look at transitions on the phylogeny from 'non-Swiss' to 'Swiss' SARS-CoV-2 sequences; thus, we wanted to include 'context sequences' that were as closely related to our focal set as possible to maximize the probability of correctly separating Swiss sequences that could be separate introductions.
The Nextstrain ncov pipeline has built-in functionality that allows for the selection of background sequences by their 'proximity' (genetic distance) to the focal set. The relevant scripts can be seen at https://github.com/emmahodcroft/ncov_2021/tree/random_context_reduce in the 'scripts' folder. The 'get_distance_to_focal_set.py' script (the 'proximity_score' rule in ncov) generates a matrix of genetic distances between every sequence in the focal set and all of the potential context sequences (here, the rest of the data-set). Every potential context sequence is assigned to its closest focal set sequence, resulting in every focal sequence having a set of context sequences associated with it.
The 'priorities.py' script builds on this by going through every focal sequence and its associated set, and assigning a score to each associated sequence, based on the genetic distance, but lowered by the count of ambiguous and 'N' bases. The associated sequence list is first put in random order and then sorted by scores, highest (closest genetic distance and highest quality sequences; around -1) to lowest (for example -100). Scores are then further fractionally lowered by their position in the resulting list. This fractional lowering, or 'crowding penalty,' ensures that a focal sequence with many, close matches does not have all their associated sequences chosen at the expense of other focal sequences. For example, to ensure the algorithm later selects the top best-scoring sequence match for sequence X overtaking the 10th best-scoring sequence match for sequence Y, all else being equal.
These scores are passed into the 'filter' step of ncov which uses the priority scores to select the specified number of sequences requested (here 10,000) and generate a set of non-Swiss sequences closely related to the focal (Swiss) set. As the context set may include sequences later excluded for QC reasons such as over/under divergence due to

wrong date, the final context set is usually slightly smaller than 10,000. For our builds, we initially selected 10,010 sequences each for Alpha and Delta.

Selecting random background

All ncov-based phylogenies are rooted by Wuhan/Hu-1/2019, and from experience the phylogenetic algorithms resolve more readily when there are a minimal number of sequences from January 2020 through the cutoff date of the run to provide a 'backbone' to the phylogeny. Thus, for each build 200 sequences were randomly selected, and equally distributed by month between January 2020 and the cutoff date. Since the number of months may not evenly divide into 200, sequences may be selected both as random background and as contextual background, and sequences may be later excluded for QC reasons (as above), the final number of sequences is usually slightly lower. In our builds 187 random background sequences for Alpha and 171 for Delta were initially selected.
For the Alpha and Delta builds the total number of both contextual and random background sequences in the final analysis build was 10,063 for Alpha and 10,120 for Delta.
Modifying Sequence Selection for the Reruns We can only detect introductions by looking at transitions from non-Swiss to Swiss sequences in our phylogenies, meaning our inference is dependent on non-Swiss sequences. We wanted to investigate how the level of sequencing outside of Switzerland may have impacted our analysis, alongside exploring variation in phylogenetic reconstruction. Thus, we created 10 reruns of the Alpha & Delta analyses, with each rerun excluding 50% of the available non-Swiss sequences.
For computational efficiency, the proximity genetic distances between all background sequences and the focal set were calculated only once (for Alpha and Delta each) and used for each re-run (since this never changes). However, during the priority step to convert these proximities into priorities, 50% of the sequences were randomly scored down by -10,000 (well below the lowest possible score normally), ensuring they are never selected for inclusion in the context set. Thus, only 50% of the possible context sequences were available for inclusion, simulating a situation where there was approximately 50% less sequencing outside of Switzerland.

Collapsing phylogenies & inferring introductions

Collapsing phylogenies

Since we are primarily interested in the transitions from non-Swiss to Swiss sequences on the phylogeny and never interested in further diversification within a single country, we aimed to simplify the phylogeny to highlight only these transitions, as described previously in Hodcroft et al., 2021.
This was done by recursively collapsing subtrees with sequences only from one country until a mixed-country polytomy was reached, after which collapsing stopped. In Supplementary Methods Figure B.1 below, a simple scenario is shown with steps from left to right. Red represents a node with only sequences from country X, pink sequences are from country Y, and blue are sequences from Switzerland. As shown, all nodes that contain children from just one country are collapsed into polytomies recursively until a polytomy with mixed countries is reached. This can then be represented as a 'pie' (last step) showing the fraction of sequences from each country that make up this polytomy.
In a more complicated example in Supplementary Methods Figure B.2, one subtree is already a polytomy of mixed countries, and thus cannot be collapsed further. Thus, this can be represented by two 'pies,' with the second being descended from the first.

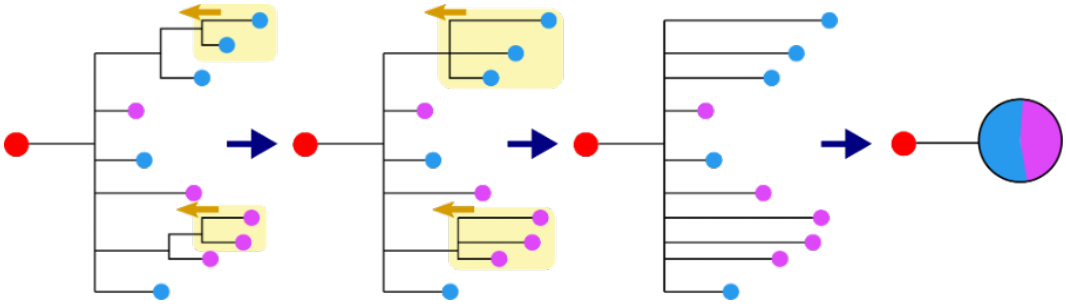

FIGURE B.1: Collapsing a phylogeny to estimate imports |: Steps go from left to right as indicated by blue arrows. Collapsing a phylogeny recursively so that sub-trees with sequences from only one country are collapsed into a multi-country polytomy, and can be represented as 'pies' showing the fraction of sequences from each country. Here red is country X, pink is country Y, and blue is Switzerland.

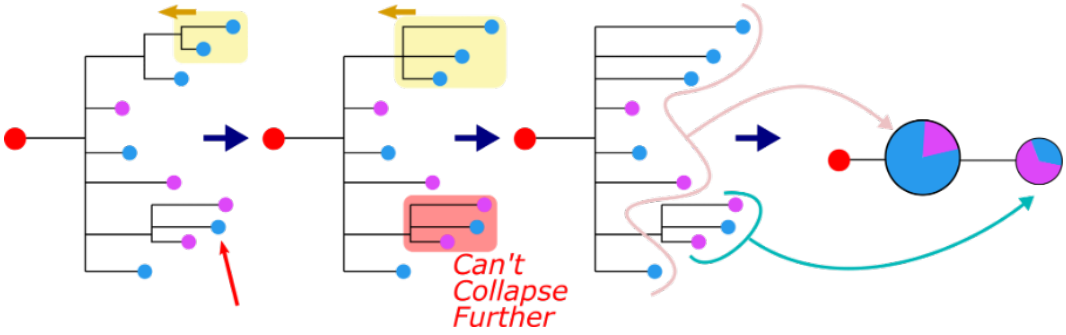

FIGURE B.2: Collapsing a phylogeny to estimate imports ||: Steps go from left to right as indicated by blue arrows. This phylogeny collapses like Supplementary Methods Figure B.1, but now has a sub-tree with sequences from mixed countries (indicated by the red arrow) which can't be collapsed further, leading to two 'pies'. As before, red is country X, pink is country Y, and blue is Switzerland.

Inferring introductions

After collapsing we can traverse the phylogeny to identify 'pies' that contain a mix of Swiss and non-Swiss sequences and consider these as putative introductions. In a simple case, a node with no Swiss sequences (a mix of non-Swiss countries) leads to a node with Swiss sequences; this would always be classified as an introduction (Supplementary Methods Figure B.3 - A, B, & C). However, one can also find nodes containing Swiss sequences descending from nodes containing Swiss sequences (Supplementary Methods Figure B.3 - B, B1, B2). This could represent three scenarios: multiple separate introductions, parallel diversification in Switzerland and elsewhere (no introduction), and export from Switzerland to elsewhere (no introduction). Thus, we considered a liberal scenario where we consider each of these pies an introduction and a conservative scenario where only the first node is considered an introduction, and all subsequent nodes are considered either parallel diversification or export from Switzerland.

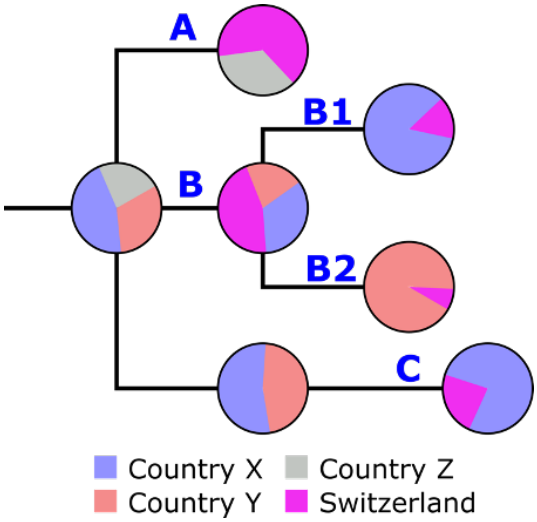

FIGURE B.3: Collapsing a phylogeny to estimate imports |||: A collapsed phylogeny represented as 'pies' of sequences from different countries. Swiss sequences are in pink. A, B, and C show straightforward scenarios where nodes with Swiss sequences descend from non-Swiss nodes; these are always counted as an introduction. B, B1, and B2 show one node that descends from non-Swiss nodes (always one introduction) but has two more nodes descending from it with Swiss sequences. In the 'liberal scenario' B, B1, and B2 would be considered 3 introductions. In the 'conservative scenario', B, B1, and B2 would be considered one introduction.

TABLE B.1: Estimated importation of VoCs and simulated impact on the SARS-CoV-2 epidemic in Switzerland. Abbreviation: VoCs, variants of concern

	Alpha		Delta	
	Liberal	Conservative	Liberal	Conservative
Estimated imports from the phylogeny	1,038	383	1,347	455
Simulation period	1 Oct 2020 - 1 May 2021		1 Feb 2021 - 1 Sep 2021	
Total simulated reported cases	593,418	592,768	288,397	271,702
Number of simulated variant cases	97,116 (16%)	70,898 (12%)	110,596 (38%)	87,861 (32%)
Date by which 50% of cases are the variant (dominance)	05 Mar 2021	22 Mar 2021	30 Jun 2021	09 Jul 2021

TABLE B.2: Data availability statement to use data from GISAID. Separate pdf file available at https://doi.org/10.1371/journal.ppat.1011553.s002.

TABLE B.3: Accession number for SARS-CoV-2 genomes sequenced in Switzerland. Separate machine-readable file available at https://doi.org/10.1371/journal.ppat.1011553.s003.

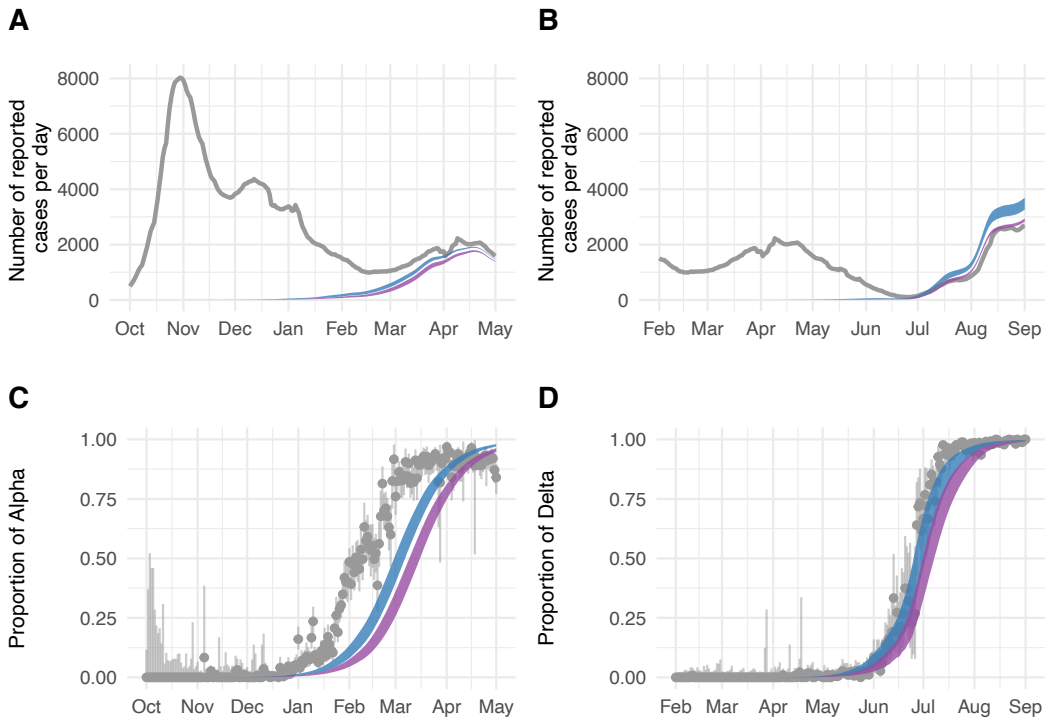

FIGURE B.4: Dynamics of Alpha and Delta importation to Switzerland. This figure is similar to 3.4, but the range was received from eleven simulations using different times of detection lags, namely 3-13 days in 1 day steps. This range was derived from du Plessis et al., 2021 A-B) Number of laboratory-confirmed SARS-CoV-2 cases per day (gray). The blue and purple area show the range of simulated number of VoC cases. C-D) The range of proportion of reported Alpha and Delta among all SARS-CoV-2 infections. Gray: Genomic surveillance data. Blue: Liberal approach. Purple: Conservative approach.

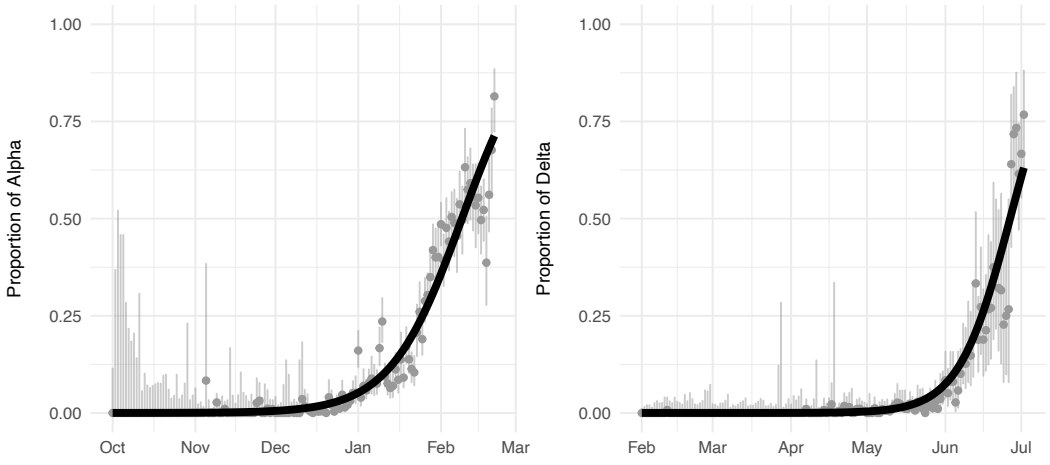

FIGURE B.5: Fit of the logistic growth model to the proportion of SARS-CoV-2 VoCs. Gray dots: Genomic surveillance data with 95% binomial confidence interval. Black line: Model fit.

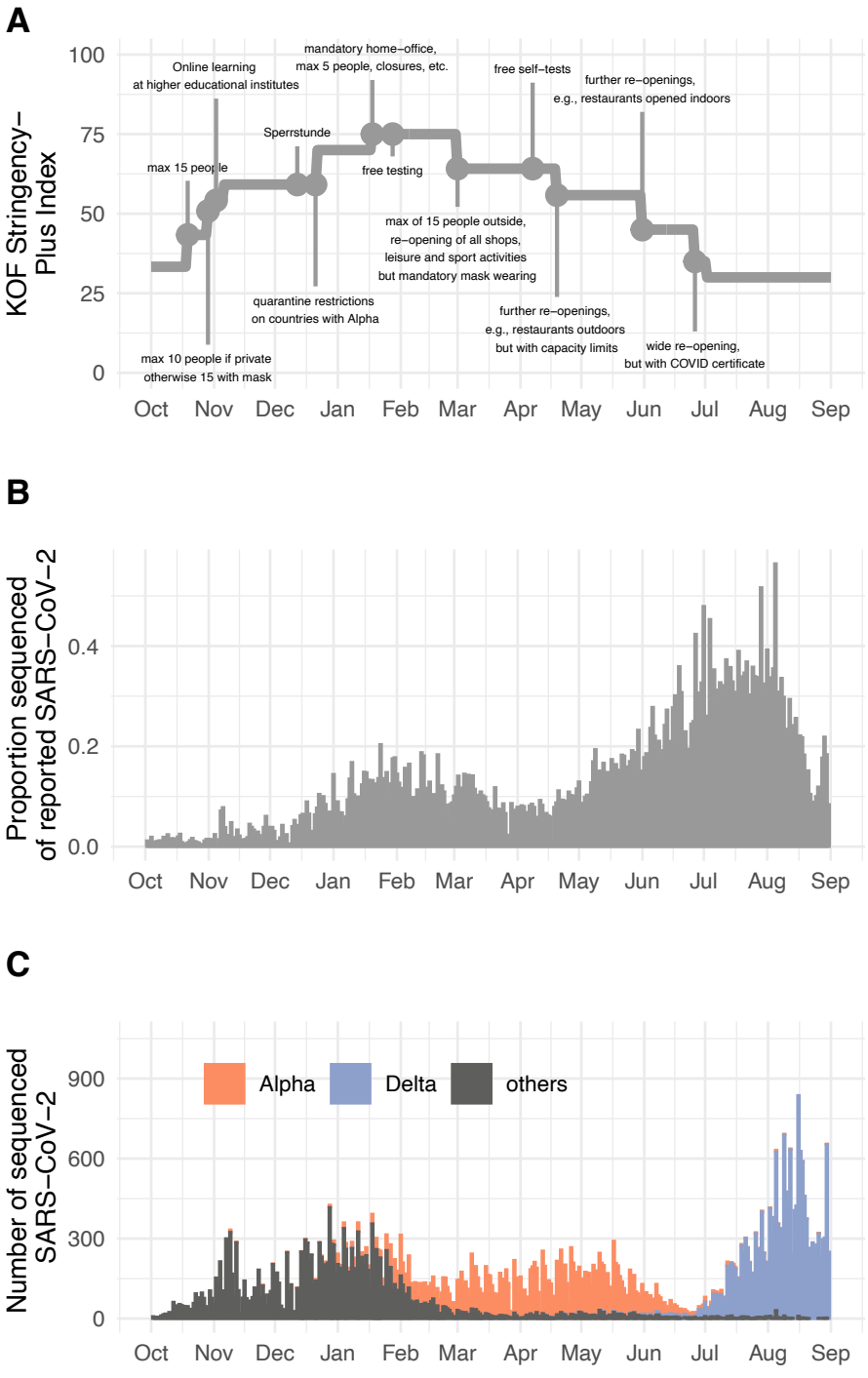

FIGURE B.6: Measures and genomic sequencing during the SARS-CoV-2 epidemic in Switzerland from October 2020 to September 2021. A) The KOF stringency plus index recorded the stringency of SARS-CoV-2 policy measured in Switzerland over time. KOF stands for 'Konjunktur-Forschungsstelle' in German which is an economic research center. The values range from 0 (= no measures) to 100 (= full lockdown). B) Proportion of reported SARS-CoV-2 cases that were sequenced. C) Number of sequenced SARS-CoV-2 cases.

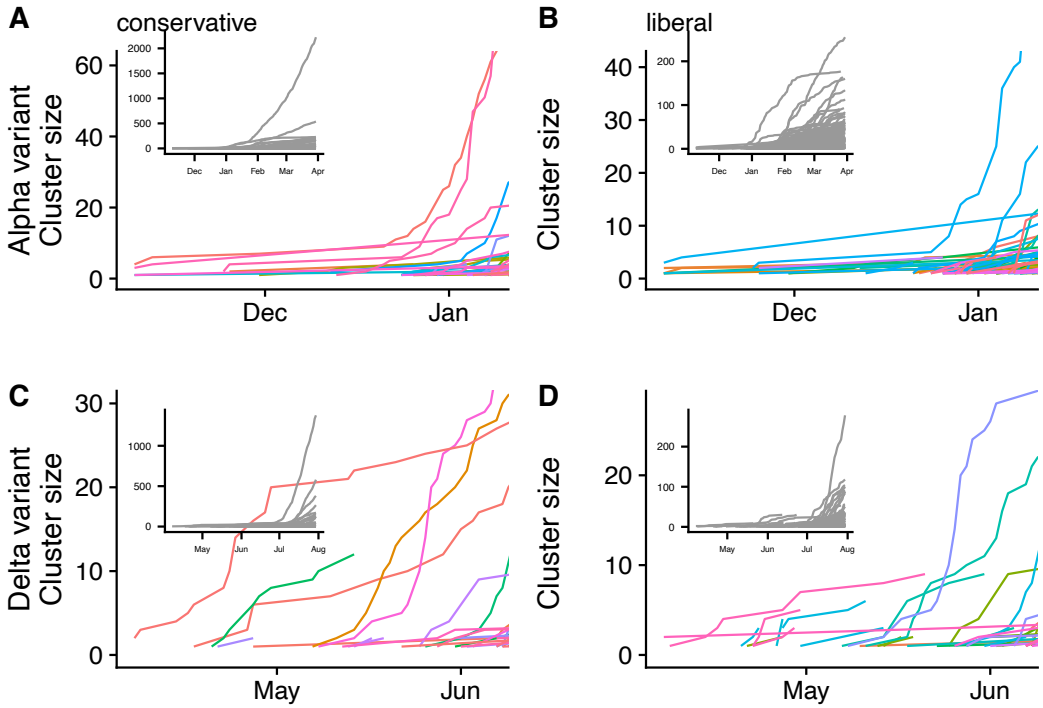

FIGURE B.7: The growth in Swiss sequences of the cluster that led to an import of a VoC. The plots show each cluster for the first two months as a line. The small zoomed plot shows the clusters over a longer time period. A) Alpha variant and conservative approach. B) Alpha variant and liberal approach. C) Delta variant and the conservative approach. D) Delta variant and liberal approach.

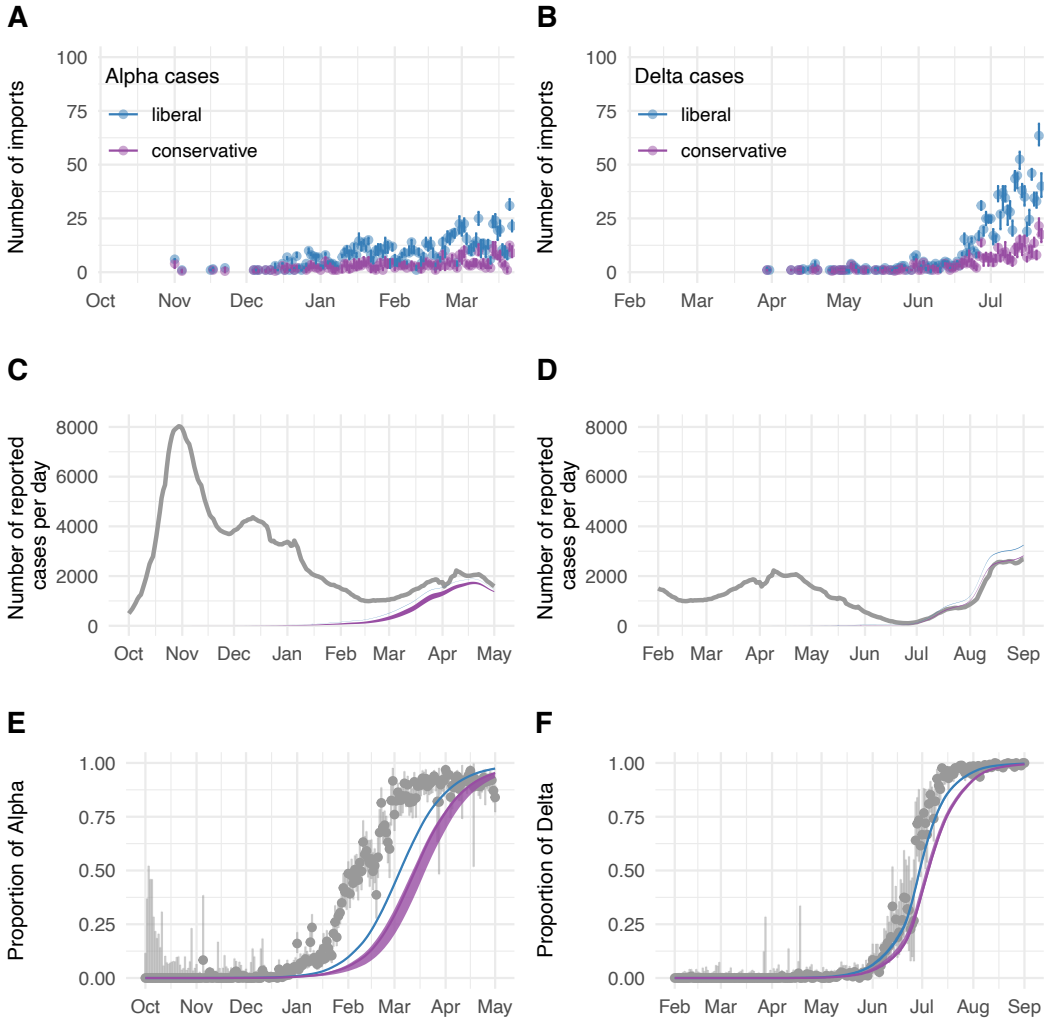

FIGURE B.8: Dynamics of Alpha and Delta importation to Switzerland. Range of the estimated number of imports and resulting model for ten reruns of the Alpha and Delta analysis, where the number of possible context sequences was randomly downsampled by half, simulating a scenario where non-Swiss countries only sequenced half as much. A-B) Range and mean of the number of imports estimated with the phylogenetic analysis. C-D) Number of laboratory-confirmed SARS-CoV-2 cases per day (gray). The blue and purple area show the range of the simulated number of VoC cases using imports from the ten reruns. E-F) The area represents the range of the proportion of reported Alpha and Delta among all SARS-CoV-2 infections, whereas the line represents our estimates from the baseline (Figure 3.4). In general, we found that using fewer context sequences only slightly reduced the number of imports estimated with the liberal approach to 975 (range: 954-995) and 1,064 (range: 1,046-1,078) compared to 1,038 and 1,347 imports of Alpha and Delta into Switzerland, respectively (Figure 3.4). For the conservative approach, we also estimated slightly fewer imports, namely 331 (range: 313-360) and 362 (range: 342-380) compared to 383 and 455 imports of Alpha and Delta into Switzerland, respectively. These findings indicate that the actual number of imports is likely to be between the liberal and conservative estimates but also indicates that the estimates are not deeply dependent on high sequencing coverage around the world. Gray: Genomic surveillance data with a 95% compatibility interval (CI). Blue: Liberal approach. Purple: Conservative approach.

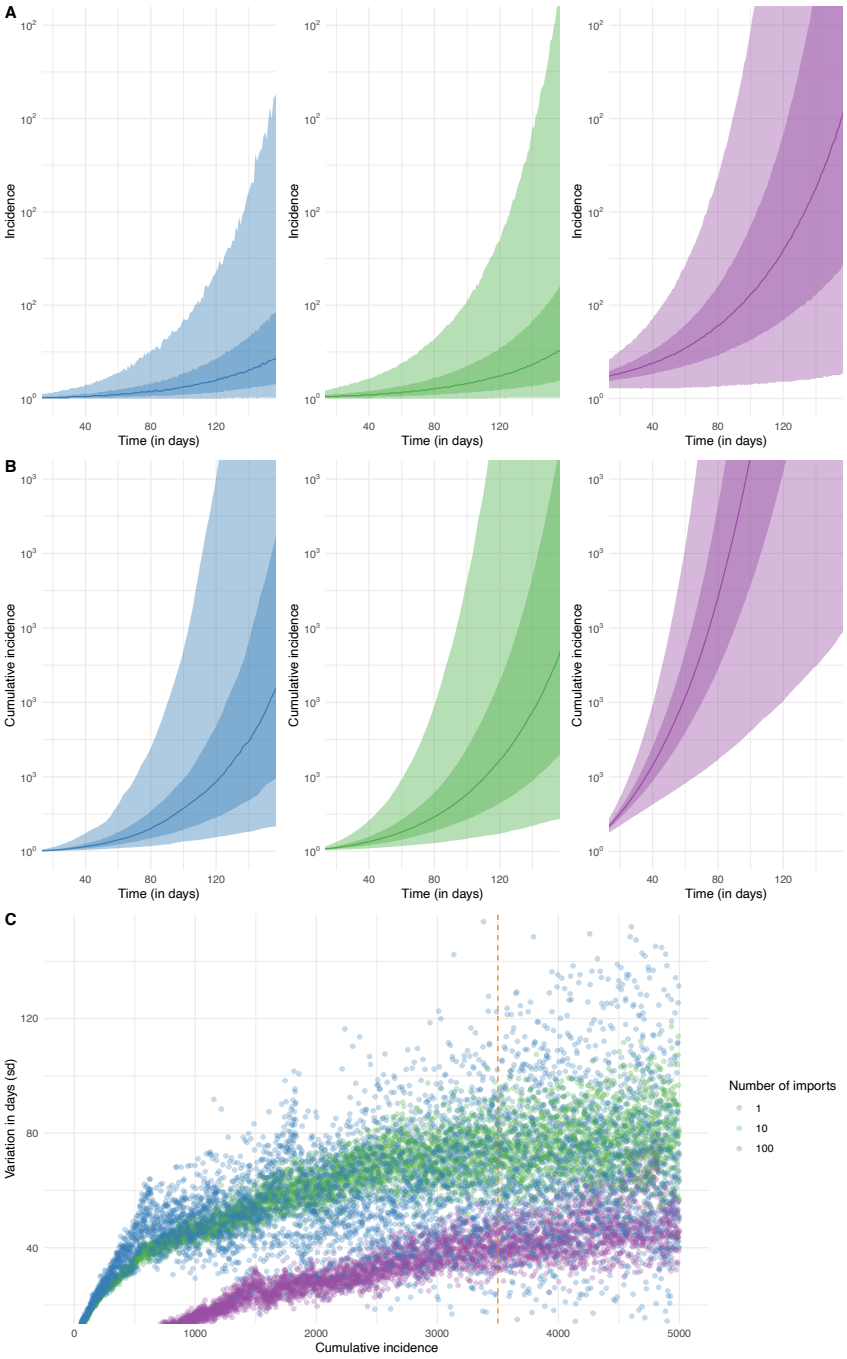

FIGURE B.9: Stochastic effects during the early growth phase of SARS-CoV-2 variants. A-B) Time to reach a certain (cumulative) incidence. Shaded regions correspond to the 50% and 95% interval of all simulations. C: Variation in the time to reach a certain cumulative incidence expressed as standard deviation.

Supplementary material for chapter 4

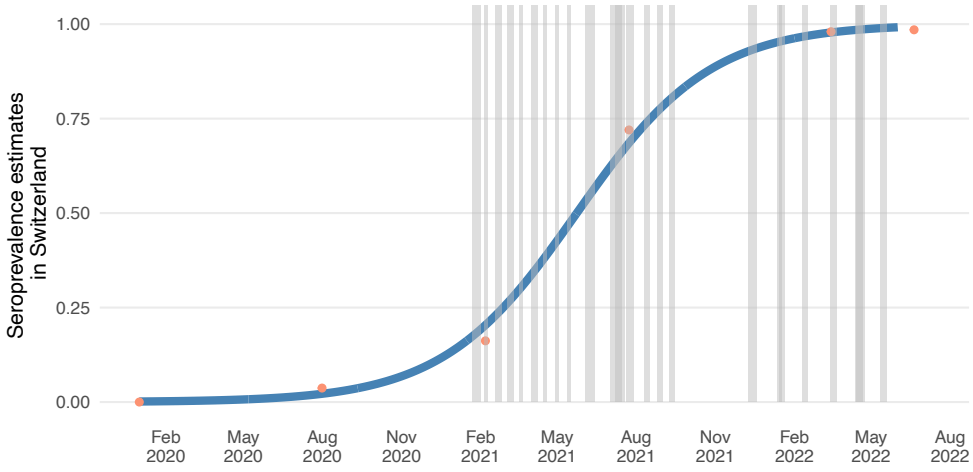

FIGURE C.1: Estimated seroprevalence in Switzerland. The blue line represents the predicted seroprevalence from results by Amati et al. (2022), Frei et al. (2023), and Tancredi et al. (2023). Their estimates are represented as red dots. Gray areas represent the period of the CoMix survey wave.

TABLE C.1: Description of social and transmission contact matrices. *Level of susceptibility changed over time by one minus the seroprevalence. The seroprevalence was predicted with a logistic regression model and results from seroprevalence studies. The growth advantages were estimated with results from Campbell et al. (2021) and Suzuki et al. (2022). Ancestral and other strains not mentioned are included in 'other'.

Figure	Adult data	Children data	Relative growth rate	Susceptibility of adults*	Susceptibility of children*	Level of protection
fig. C.4A	Per survey wave	Closest children wave	Alpha: 100%; Delta: 100%; Omicron: 100%; other:100%	-	-	-
fig. 4.4 & fig. C.4B	Per survey wave	Pooled survey waves	Alpha: 100%; Delta: 100%; Omicron: 100%; other:100%	-	-	-
fig. C.4C	Per survey wave	Closest children wave	Alpha: 100%; Delta: 100%; Omicron: 100%; other:100%	100%	50%	100%
fig. C.4D	Per survey wave	Pooled survey waves	Alpha: 100%; Delta: 100%; Omicron: 100%; other:100%	100%	50%	100%
fig. C.4E	Per survey wave	Closest children wave	Alpha: 100%; Delta: 100%; Omicron: 100%; other:100%	100%	50%	50%
fig. C.4F	Per survey wave	Pooled survey waves	Alpha: 100%; Delta: 100%; Omicron: 100%; other:100%	100%	50%	50%
fig. C.4G	Per survey wave	Closest children wave	Alpha: 129%; Delta: 197%; Omicron: 652%; other:100%	-	-	-
fig. C.4H	Per survey wave	Pooled survey waves	Alpha: 129%; Delta: 197%; Omicron: 652%; other:100%	-	-	-
fig. C.4I	Per survey wave	Closest children wave	Alpha: 129%; Delta: 197%; Omicron: 652%; other:100%	100%	50%	100%
fig. C.4J	Per survey wave	Pooled survey waves	Alpha: 129%; Delta: 197%; Omicron: 652%; other:100%	100%	50%	100%
fig. C.4K	Per survey wave	Closest children wave	Alpha: 129%; Delta: 197%; Omicron: 652%; other:100%	100%	50%	50%
fig. C.4L	Per survey wave	Pooled survey waves	Alpha: 129%; Delta: 197%; Omicron: 652%; other:100%	100%	50%	50%
fig. C.4M	Per survey wave	Closest children wave	Alpha: 129%; Delta: 197%; Omicron: 652%; other:100%	100%	50%	90%
fig. 4.5 & fig. C.4N	Per survey wave	Pooled survey waves	Alpha: 129%; Delta: 197%; Omicron: 652%; other:100%	100%	50%	90%

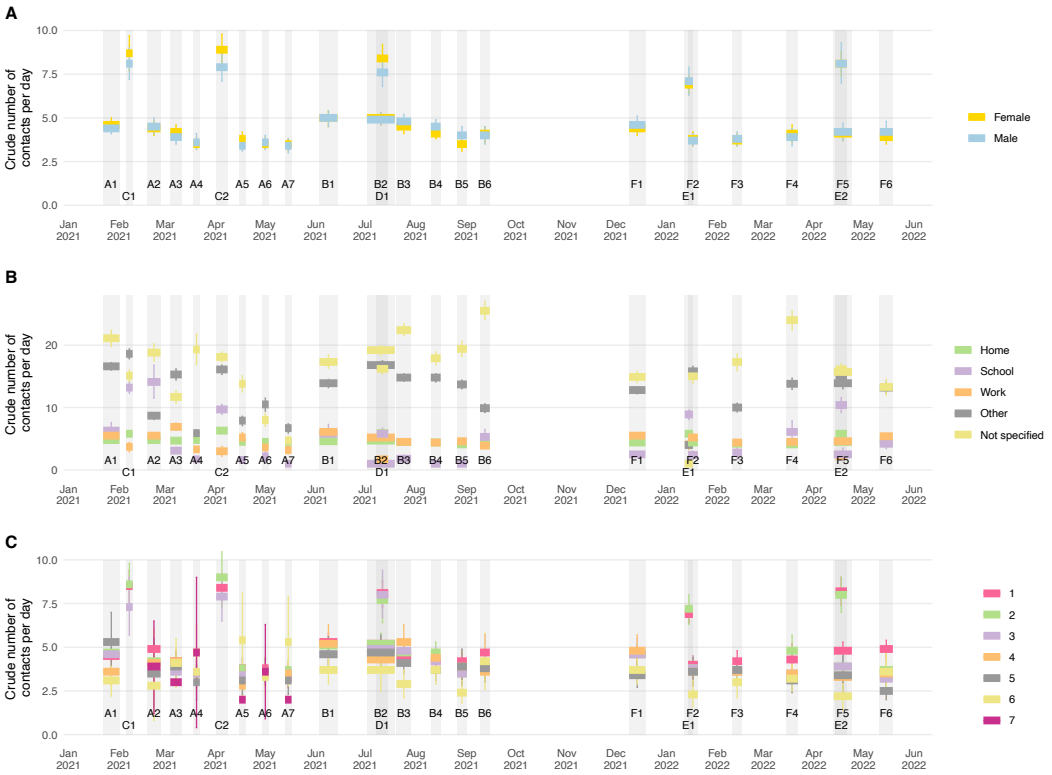

FIGURE C.2: Mean number and 95% compatibility interval of social contacts by A) gender, B) the location of contact, and C) the number of participation. Gray bars and digits represent the CoMix survey wave.

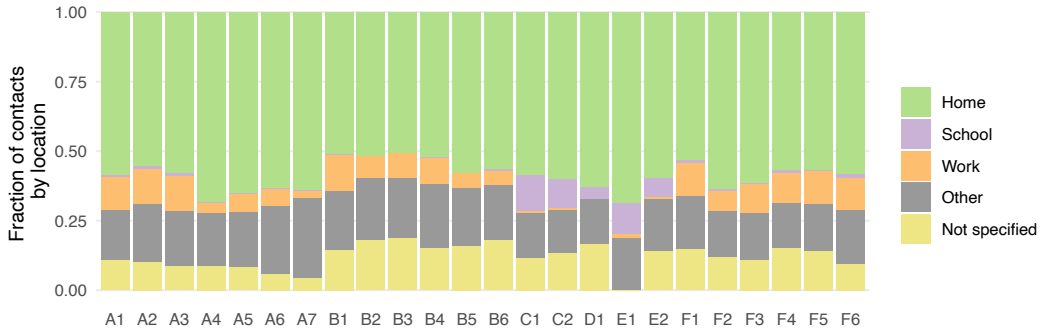

FIGURE C.3: Fraction of contacts by location and survey wave.

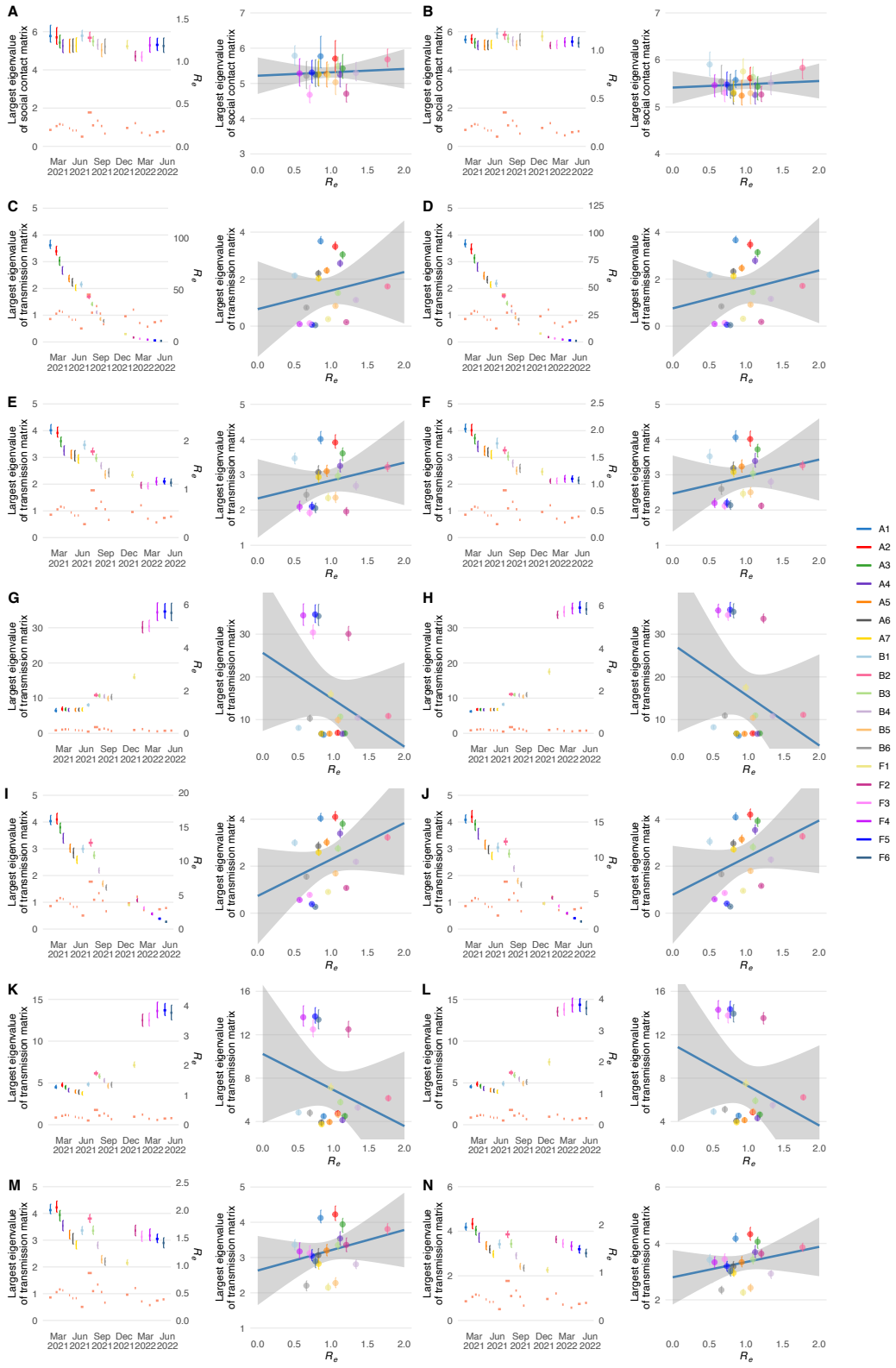

FIGURE C.4: Largest eigenvalue of transmission matrices. Left plots show the largest eigenvalue colored by survey wave (more detail in table C.1) and the median effective reproduction number R_e in red. Right plots show linear association of the largest eigenvalue of transmission matrix with the median effective reproduction number R_e for corresponding survey period. A, C, E, G, I, K, M) closest children wave, B, D, F, H, J, L, N) all children waves pooled.

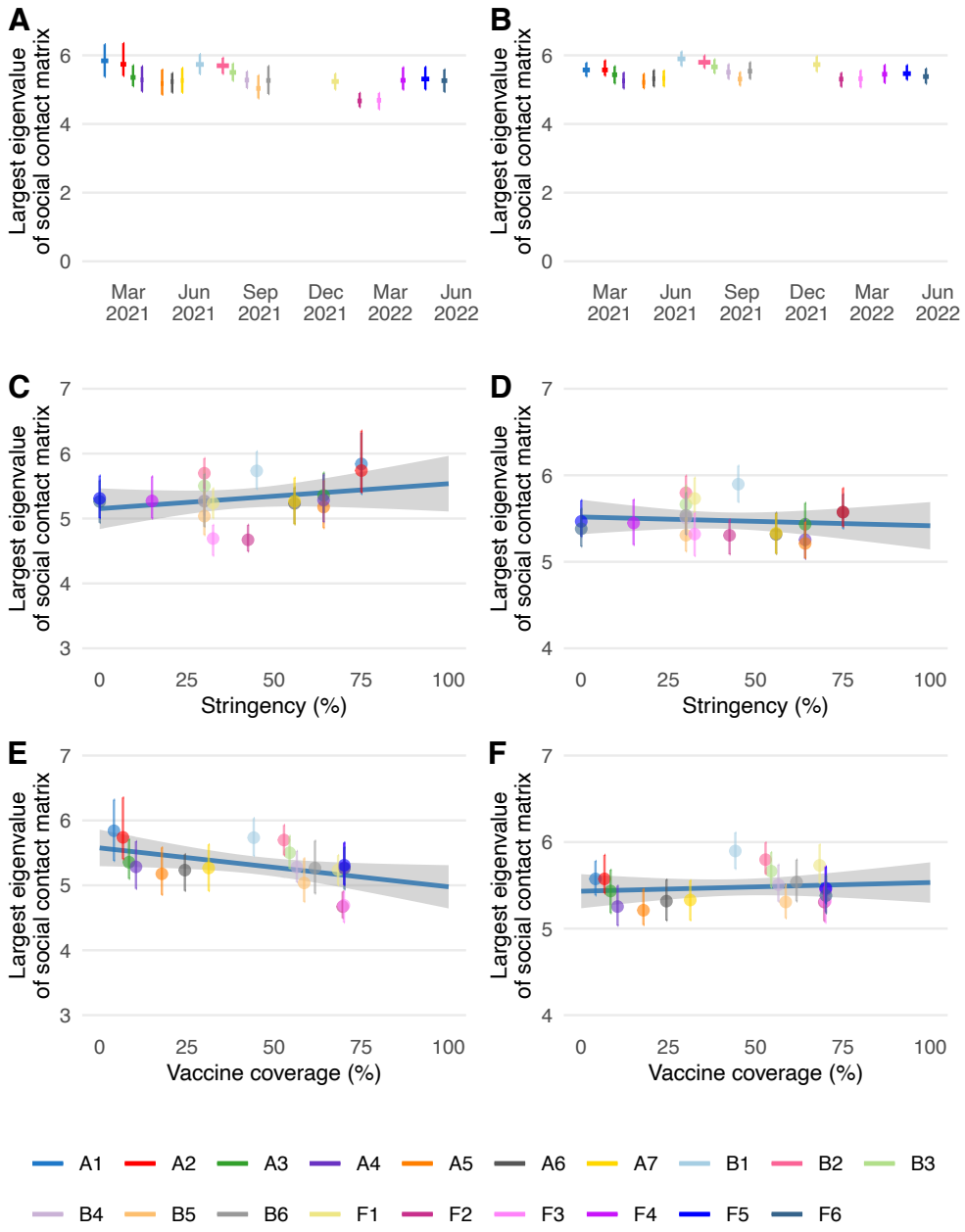

FIGURE C.5: Visually comparing the largest eigenvalue of social matrices when using one or all children waves. A-B) Largest eigenvalue of the social contact matrix by adult survey wave. C-D) Linear association of stringency of measures with largest eigenvalue of social contact matrix for corresponding survey period. E-F) Linear association of vaccine coverage with largest eigenvalue of social contact matrix for corresponding survey period. Shaded areas of the linear association correspond to the 95% confidence interval. A, C, E) closest children wave, B, D, F) all children waves pooled.

Supplementary material for chapter 5

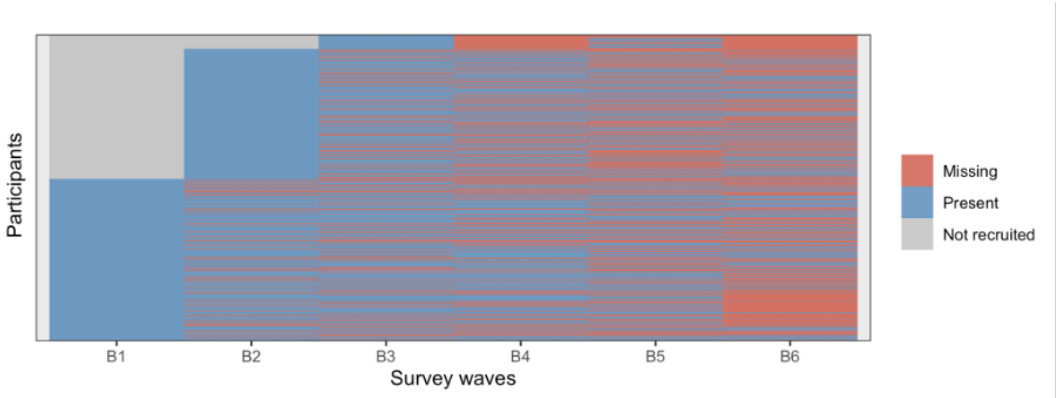

FIGURE D.1: Participants in the six survey waves of the CoMix study in Switzerland.

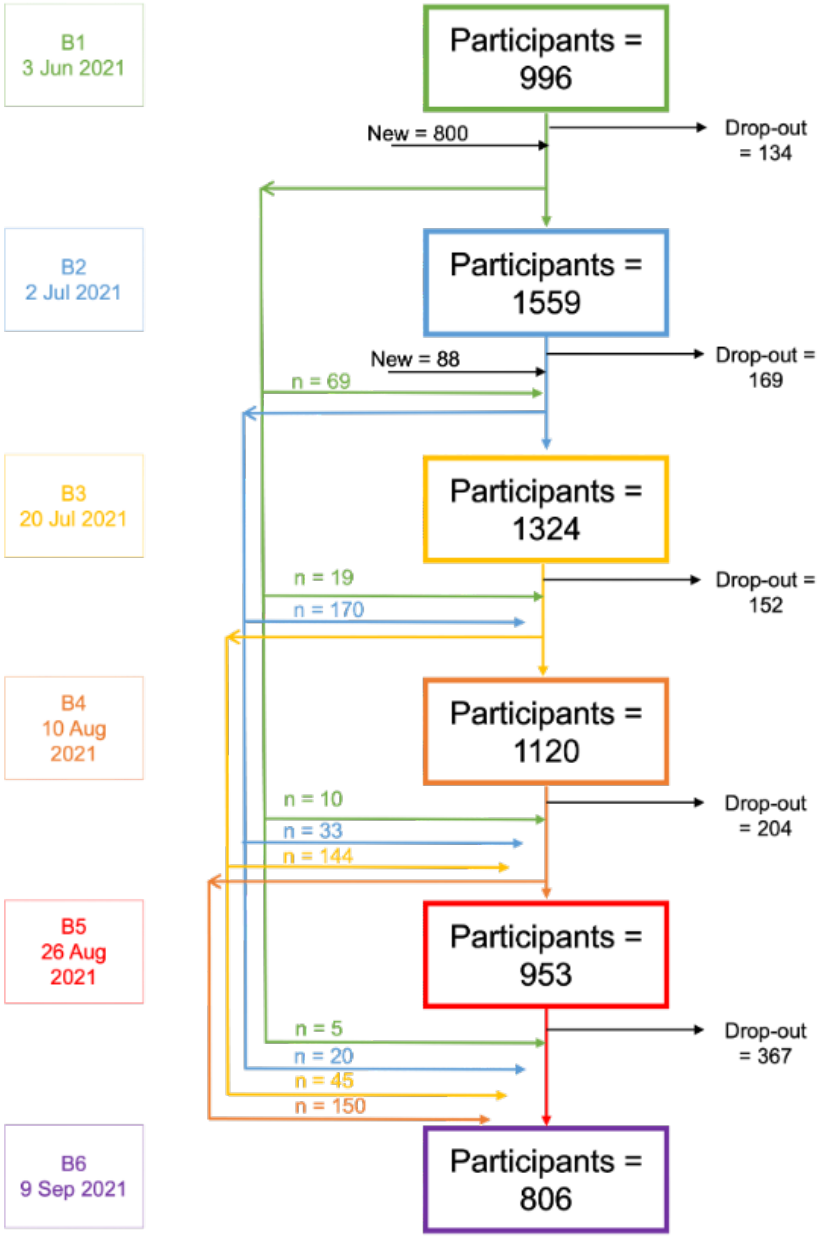

FIGURE D.2: Flow chart of participants in six survey waves of the CoMix study that was conducted in Switzerland.

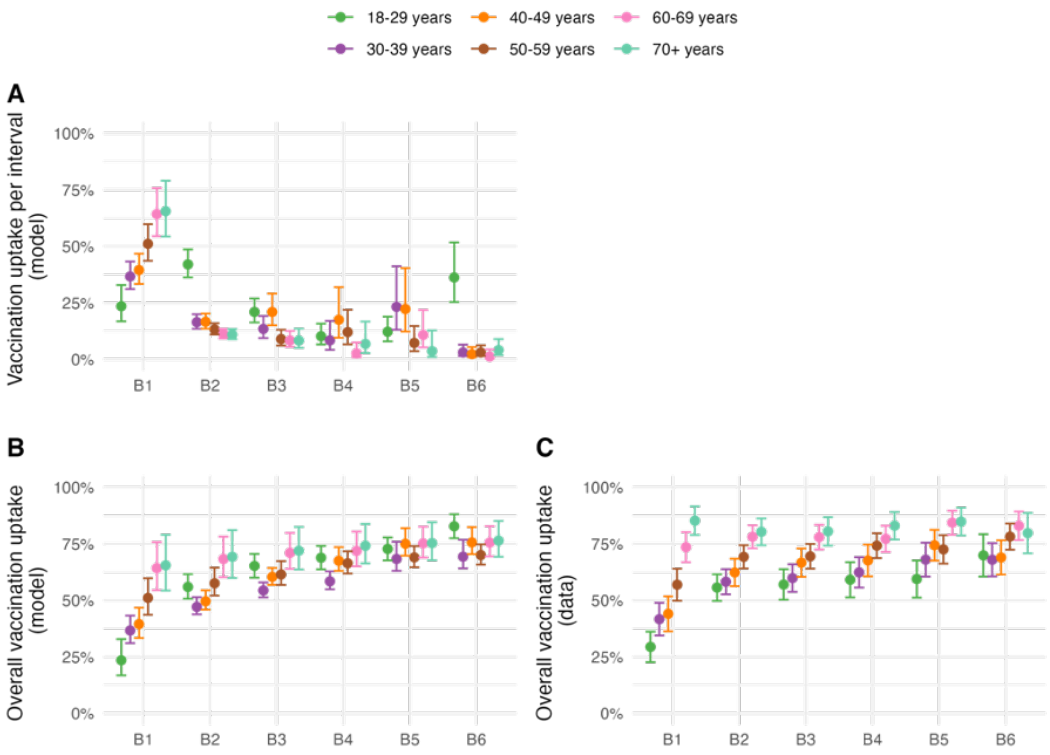

FIGURE D.3: Vaccination uptake per interval and age group. A) Vaccination uptake corresponds to the percentage receiving the first vaccine dose amongst those who have not already received it. Point estimates and confidence intervals (CIs) as predicted by the Poisson regression model. The estimates were adjusted for gender, region, Swiss region of residence, country of birth, education level, employment level, net household income, household size, household with a medically vulnerable individual, testing for SARS-CoV-2, number of contacts per day, and attitude towards COVID-19 measures, with an interaction between age and survey wave. B) Cumulative (overall) vaccination uptake corresponds to the percentage of having received vaccination as predicted by the Poisson regression model. CIs were derived from multivariate parameter samples using the covariance matrix of model estimates C) Overall vaccination uptake of the study population per interval. Point estimates and binomial CIs were calculated separately for each survey wave from the raw data. The error bars indicate the 95% CIs.

TABLE D.1: Milestones of the vaccination program in Switzerland. * Varied across cantons.

Dates	Description (eligible subpopulation)	
19 Dec 2020	Swissmedic, the Swiss agency for the authorisation and supervision of therapeutic products, authorised the mRNA vaccine from Pfizer/BioNTech.	https://www.bag.admin.ch/bag/de/home/das-bag/aktuell/medienmitteilungen.msg-id-81667.html
23 Dec 2020	First person officially received the first vaccine dose in Switzerland.	https://www.srf.ch/news/schweiz/impfstart-in-der-schweiz-luzernerin-erhaelt-erste-impfung-auch-weitere-kantone-gestartet
24 Dec 2020	Switzerland started the COVID-19 vaccination campaign. Priority was given to the elderly (>75 and then 65-75 years) and the chronically ill, and, secondly*, to healthcare workers and those living with people at risk.	
12 Jan 2021	Swissmedic authorized the mRNA vaccine from Moderna.	https://www.bag.admin.ch/bag/de/home/das-bag/aktuell/medienmitteilungen.msg-id-81926.html
May 2021*	General population (>16 years) was able to get vaccinated.	
31 Mai 2021	Vaccinated people were exempt from quarantine, including quarantine after returning from abroad.	https://www.bag.admin.ch/bag/de/home/das-bag/aktuell/medienmitteilungen.msg-id-83531.html
June 2021	Children (>12 years) were able to get vaccinated.	https://www.bag.admin.ch/bag/de/home/das-bag/aktuell/medienmitteilungen.msg-id-84095.html
13 Sep 2021	COVID-19 certificate introduced in September 2021: proof of vaccination, recovery or a negative test result were declared mandatory to access indoor hospitality venues, cultural, sporting and leisure activities indoors, and large-scale outdoor events.	https://www.bag.admin.ch/bag/de/home/das-bag/aktuell/medienmitteilungen.msg-id-85035.html
1 Jan 2022	Children (>5 years) were able to get vaccinated.	https://www.bag.admin.ch/bag/de/home/das-bag/aktuell/medienmitteilungen.msg-id-86451.html

TABLE D.2: Comparison of participants with the Swiss population. The income of study participants is the household income, whereas the income for the Swiss population corresponds to the individual income from full and part-time employees. *No absolute values available for net income of the Swiss population. n represents the number individuals in the corresponding group.

Category	Name	Swiss population, n (%)	Study participants, n (%)	Survey wave, n (%)					
				B1	B2	B3	B4	B5	B6
				497 (49.9%)	761 (48.8%)	645 (48.7%)	556 (49.6%)	452 (47.4%)	386 (47.9%)
Gender	Female	4,367,701 (50.4%)	3,297 (48.8%)	495 (49.7%)	792 (50.8%)	673 (50.8%)	560 (50%)	498 (52.3%)	418 (51.9%)
	Male	4,302,599 (49.6%)	3,436 (50.8%)	4 (0.4%)	6 (0.4%)	6 (0.5%)	4 (0.4%)	3 (0.3%)	2 (0.2%)
	Other	-	25 (0.4%)	177 (17.8%)	275 (17.6%)	207 (15.6%)	154 (13.8%)	138 (14.5%)	93 (11.5%)
Age group	18-29	1,170,597 (16.3%)	1,044 (15.4%)	180 (18.1%)	304 (19.5%)	249 (18.8%)	202 (18%)	150 (15.7%)	156 (19.4%)
	30-39	1,239,355 (17.2%)	1,241 (18.4%)	159 (16%)	247 (15.8%)	219 (16.5%)	170 (15.2%)	160 (16.8%)	145 (18%)
	40-49	1,200,424 (16.7%)	1,100 (16.3%)	188 (18.9%)	309 (19.8%)	273 (20.6%)	245 (21.9%)	194 (20.4%)	198 (24.6%)
	50-59	1,304,794 (18.1%)	1,407 (20.8%)	170 (17.1%)	251 (16.1%)	222 (16.8%)	202 (18%)	179 (18.8%)	135 (16.7%)
	60-69	1,005,687 (14%)	1,159 (17.2%)	122 (12.2%)	173 (11.1%)	154 (11.6%)	147 (13.1%)	132 (13.9%)	79 (9.8%)
	70+	1,276,149 (17.7%)	807 (11.9%)	328 (32.9%)	493 (31.6%)	425 (32.1%)	359 (32.1%)	309 (32.4%)	236 (29.3%)
Household income*	0-5,000	49.4%	2,150 (31.8%)	396 (39.8%)	634 (40.7%)	533 (40.3%)	445 (39.7%)	384 (40.3%)	341 (42.3%)
	5,001-10,000	42.2%	2,733 (40.4%)	124 (12.4%)	203 (13%)	171 (12.9%)	139 (12.4%)	122 (12.8%)	102 (12.7%)
	10,000+	7.6%	861 (12.7%)	148 (14.9%)	229 (14.7%)	195 (14.7%)	177 (15.8%)	138 (14.5%)	127 (15.8%)
	Preferred not to answer	-	1,014 (15%)	216 (21.7%)	344 (22.1%)	286 (21.6%)	241 (21.5%)	226 (23.7%)	176 (21.8%)
Residence	Espace Mittelland	1,895,693 (21.9%)	1,489 (22%)	188 (18.9%)	291 (18.7%)	244 (18.4%)	209 (18.7%)	190 (19.9%)	165 (20.5%)
	Zurich	1,553,423 (17.9%)	1,287 (19%)	168 (16.9%)	273 (17.5%)	225 (17%)	191 (17.1%)	165 (17.3%)	104 (12.9%)
	Lake Geneva region	1,669,608 (19.3%)	1,126 (16.7%)	141 (14.2%)	219 (14%)	192 (14.5%)	161 (14.4%)	138 (14.5%)	112 (13.9%)
	Eastern Switzerland	1,193,069 (13.8%)	963 (14.2%)	143 (14.4%)	219 (14%)	186 (14%)	155 (13.8%)	132 (13.9%)	114 (14.1%)
	Northwestern Switzerland	1,181,776 (13.6%)	949 (14%)	96 (9.6%)	148 (9.5%)	137 (10.3%)	108 (9.6%)	97 (10.2%)	92 (11.4%)

TABLE D.3: Comparison of different models to study the association of socio-demographic and other factors with COVID-19 vaccination uptake in Switzerland. Abbreviations: CI, compatibility interval; HR, hazard ratio; RR, rate ratio.

Name	Categories	Number of participants	Number of answers	Cox proportional hazard model				Poisson regression model				
				Unadjusted HR (95% CI)	Unadjusted weighted HR (95% CI)	Adjusted HR (95% CI)	Adjusted weighted HR (95% CI)	Unadjusted RR (95% CI)	Unadjusted RR (95% CI) with age as interaction	Adjusted RR (95% CI)	Adjusted RR (95% CI) with age as interaction	Adjusted RR (95% CI) with age as interaction (1 June)
Survey wave	B2	1,143	-	-	-	-	-	1.07 (1.01-1.13)	-	-	-	-
Reference: B1	B3	511	-	-	-	-	-	0.43 (0.39-0.48)	-	-	-	-
	B4	356	-	-	-	-	-	0.15 (0.13-0.19)	-	-	-	-
	B5	277	-	-	-	-	-	0.23 (0.19-0.28)	-	-	-	-
	B6	230	-	-	-	-	-	0.20 (0.16-0.25)	-	-	-	-
Age groups, years	30-39	737	359	1.05 (0.87-1.26)	1.15 (0.98-1.36)	-	-	1.07 (0.98-1.16)	-	-	-	-
Reference: 18-29	40-49	606	314	1.09 (0.90-1.32)	1.15 (0.97-1.36)	-	-	1.17 (1.07-1.27)	-	-	-	-
	50-59	676	355	1.26 (1.05-1.51)	1.29 (1.10-1.52)	-	-	1.30 (1.20-1.42)	-	-	-	-
	60-69	474	289	1.67 (1.39-2.01)	1.81 (1.51-2.18)	-	-	1.62 (1.49-1.77)	-	-	-	-
	70+	318	202	2.10 (1.72-2.56)	2.18 (1.79-2.66)	-	-	1.85 (1.69-2.03)	-	-	-	-
Gender	Male	1,708	955	1.17 (1.05-1.30)	1.05 (0.95-1.16)	1.07 (0.95-1.20)	0.96 (0.86-1.07)	1.17 (1.11-1.23)	1.12 (1.06-1.17)	1.09 (1.04-1.15)	1.09 (1.04-1.15)	1.11 (1.04-1.19)
Reference: Female	Others	15	10	1.24 (0.64-2.39)	0.95 (0.68-1.33)	0.86 (0.44-1.69)	0.99 (0.56-1.75)	1.62 (1.20-2.17)	1.76 (1.31-2.38)	1.51 (1.12-2.04)	1.62 (1.20-2.20)	1.78 (1.23-2.57)
Region	Rural	961	456	0.75 (0.66-0.86)	0.80 (0.71-0.90)	0.89 (0.77-1.02)	0.86 (0.76-0.97)	0.75 (0.71-0.80)	0.79 (0.74-0.84)	0.84 (0.79-0.90)	0.85 (0.80-0.90)	0.85 (0.78-0.92)
Reference: Urban												
Swiss regions of residence	Zurich	615	351	1.22 (1.03-1.44)	1.14 (0.99-1.33)	1.23 (1.03-1.47)	1.11 (0.94-1.30)	1.23 (1.14-1.33)	1.19 (1.10-1.29)	1.10 (1.02-1.20)	1.11 (1.02-1.20)	1.12 (1.01-1.25)
Reference: Espace Mittelland	Lake Geneva region	590	337	1.12 (0.94-1.33)	1.06 (0.92-1.23)	1.02 (0.86-1.22)	1.02 (0.88-1.19)	1.17 (1.08-1.27)	1.13 (1.05-1.23)	1.06 (0.98-1.15)	1.06 (0.98-1.15)	1.05 (0.95-1.16)
	Eastern Switzerland	501	263	1.09 (0.91-1.32)	1.03 (0.88-1.21)	1.14 (0.95-1.38)	1.10 (0.93-1.30)	1.10 (1.01-1.20)	1.09 (1.00-1.19)	1.10 (1.01-1.20)	1.09 (1.00-1.18)	1.09 (0.98-1.22)
	Northwestern Switzerland	262	262	1.11 (0.92-1.34)	1.07 (0.91-1.26)	1.28 (1.05-1.55)	1.17 (0.99-1.39)	1.07 (0.98-1.16)	1.08 (0.99-1.17)	1.08 (0.99-1.18)	1.07 (0.98-1.17)	1.09 (0.97-1.22)
	Central Switzerland	352	182	1.07 (0.87-1.32)	0.97 (0.80-1.17)	1.23 (0.99-1.52)	1.06 (0.86-1.31)	1.05 (0.95-1.16)	1.11 (1.01-1.23)	1.18 (1.07-1.30)	1.16 (1.05-1.28)	1.20 (1.06-1.36)
	Ticino	140	82	1.29 (0.97-1.72)	1.59 (1.11-2.27)	1.50 (1.12-2.02)	1.74 (1.20-2.53)	1.16 (1.02-1.32)	1.16 (1.02-1.33)	1.14 (1.00-1.30)	1.15 (1.01-1.31)	1.18 (1.00-1.40)
Country of birth	EU	450	249	1.10 (0.93-1.29)	1.06 (0.93-1.22)	1.09 (0.92-1.29)	1.09 (0.94-1.27)	1.05 (0.98-1.13)	1.02 (0.94-1.10)	0.97 (0.90-1.04)	0.96 (0.89-1.04)	0.97 (0.88-1.07)
Reference: Switzerland	Non-EU	283	156	1.11 (0.91-1.35)	1.13 (0.96-1.33)	1.03 (0.84-1.25)	1.08 (0.89-1.30)	1.06 (0.97-1.16)	1.01 (0.93-1.11)	0.96 (0.88-1.05)	0.98 (0.89-1.07)	1.01 (0.90-1.13)
	Unknown	235	147	1.18 (0.97-1.45)	1.11 (0.86-1.44)	1.10 (0.89-1.36)	1.07 (0.83-1.38)	1.18 (1.08-1.29)	1.03 (0.94-1.13)	1.06 (0.97-1.16)	1.06 (0.97-1.17)	1.10 (0.97-1.24)
Education level	Middle level of education	1,225	639	1.08 (0.95-1.22)	1.11 (0.99-1.25)	1.00 (0.88-1.14)	1.04 (0.92-1.17)	1.06 (1.00-1.12)	1.06 (1.00-1.13)	1.01 (0.95-1.08)	1.01 (0.95-1.07)	0.99 (0.92-1.07)
Reference: Lowest level	Highest level of education	714	439	1.41 (1.23-1.61)	1.23 (1.10-1.37)	1.26 (1.08-1.46)	1.17 (1.02-1.33)	1.39 (1.31-1.48)	1.35 (1.27-1.43)	1.18 (1.10-1.26)	1.18 (1.10-1.27)	1.19 (1.09-1.30)
Employment status	Unemployed	214	110	0.88 (0.69-1.13)	1.04 (0.77-1.40)	0.89 (0.69-1.15)	1.04 (0.77-1.42)	0.86 (0.77-0.96)	0.83 (0.74-0.93)	0.86 (0.77-0.97)	0.86 (0.76-0.97)	0.88 (0.76-1.03)
Reference: Employed	Student	192	116	1.23 (0.98-1.54)	1.04 (0.86-1.25)	1.55 (1.17-2.05)	1.27 (0.98-1.64)	1.13 (1.02-1.26)	1.38 (1.22-1.56)	1.26 (1.11-1.43)	1.33 (1.17-1.51)	1.35 (1.15-1.58)
	Homemaker	164	75	0.73 (0.54-0.99)	0.75 (0.58-0.97)	0.95 (0.69-1.32)	0.81 (0.63-1.05)	0.77 (0.67-0.89)	0.80 (0.70-0.92)	0.96 (0.83-1.10)	0.95 (0.82-1.10)	0.97 (0.81-1.16)
	Retired	607	377	1.66 (1.45-1.89)	1.63 (1.44-1.85)	1.20 (0.95-1.51)	1.11 (0.89-1.38)	1.46 (1.38-1.55)	1.01 (0.91-1.12)	1.05 (0.95-1.17)	1.05 (0.94-1.16)	1.08 (0.94-1.24)
	Other unemployed situation	92	44	0.85 (0.58-1.26)	1.07 (0.78-1.47)	0.96 (0.64-1.44)	1.30 (0.91-1.85)	0.85 (0.71-1.01)	0.82 (0.69-0.98)	0.92 (0.77-1.10)	0.90 (0.75-1.07)	0.80 (0.63-1.03)
Household income, net	5,001-10,000 CHF	1,403	762	1.19 (1.04-1.36)	1.14 (1.01-1.28)	1.25 (1.08-1.44)	1.24 (1.08-1.42)	1.18 (1.11-1.25)	1.21 (1.14-1.28)	1.15 (1.08-1.23)	1.15 (1.08-1.23)	1.14 (1.04-1.24)
Reference: 0-5,000 CHF	10,000+ CHF	387	248	1.49 (1.26-1.77)	1.25 (1.08-1.45)	1.42 (1.17-1.73)	1.29 (1.09-1.54)	1.50 (1.39-1.62)	1.47 (1.36-1.59)	1.33 (1.21-1.45)	1.34 (1.23-1.46)	1.36 (1.22-1.53)
	Preferred not to answer	529	281	1.16 (0.98-1.38)	1.17 (1.00-1.37)	1.14 (0.95-1.36)	1.15 (0.98-1.36)	1.17 (1.08-1.27)	1.16 (1.07-1.25)	1.14 (1.06-1.24)	1.13 (1.04-1.23)	1.15 (1.03-1.27)
Household size	Mean (range)	2 (1 - 10)	2 (1 - 10)	0.96 (0.92-1.00)	0.95 (0.91-0.98)	0.95 (0.89-1.01)	0.97 (0.92-1.02)	0.97 (0.95-0.98)	1.02 (0.99-1.04)	0.96 (0.94-0.99)	0.96 (0.94-0.99)	0.97 (0.94-1.01)
Household with medically vulnerability Reference: No person in a risk group	One or more person in a risk group	944	578	1.33 (1.19-1.49)	1.23 (1.11-1.37)	1.21 (1.07-1.36)	1.18 (1.05-1.33)	1.36 (1.30-1.44)	1.20 (1.13-1.26)	1.18 (1.11-1.24)	1.16 (1.10-1.23)	1.16 (1.08-1.25)
Testing for SARS-CoV-2	Tested	872	-	0.85 (0.46-1.55)	1.11 (0.73-1.70)	0.98 (0.53-1.82)	1.23 (0.77-1.95)	0.73 (0.55-0.98)	0.75 (0.56-1.00)	0.85 (0.63-1.13)	0.87 (0.65-1.17)	0.76 (0.55-1.06)
Reference: Tested positive	Never tested	2,557	-	1.72 (0.95-3.11)	1.72 (1.14-2.58)	1.96 (1.07-3.59)	1.84 (1.17-2.90)	1.09 (0.82-1.44)	0.87 (0.65-1.15)	1.02 (0.77-1.37)	1.06 (0.80-1.42)	0.96 (0.69-1.32)
	Preferred not to answer	56	-	0.96 (0.43-2.15)	1.13 (0.55-2.31)	1.59 (0.70-3.61)	1.53 (0.70-3.35)	0.58 (0.40-0.85)	0.55 (0.38-0.81)	0.74 (0.50-1.09)	0.76 (0.51-1.12)	0.61 (0.38-0.98)
Number of contacts per day	3-5	937	-	1.13 (0.98-1.30)	1.08 (0.95-1.22)	1.23 (1.07-1.43)	1.13 (0.99-1.29)	1.03 (0.97-1.09)	1.02 (0.96-1.09)	1.02 (0.95-1.09)	1.02 (0.95-1.09)	1.01 (0.92-1.10)
Reference: 0-2	6+	1,282	-	1.16 (1.02-1.31)	1.01 (0.90-1.13)	1.28 (1.10-1.49)	1.13 (0.98-1.30)	1.06 (1.00-1.12)	1.09 (1.03-1.16)	1.08 (1.01-1.16)	1.08 (1.01-1.16)	1.10 (1.01-1.20)
Attitudes towards COVID-19 measures	Too lenient	663	-	0.88 (0.77-1.01)	0.81 (0.73-0.90)	0.85 (0.74-0.97)	0.79 (0.70-0.88)	1.02 (0.96-1.08)	1.05 (0.99-1.12)	1.01 (0.95-1.07)	1.02 (0.96-1.08)	1.03 (0.95-1.11)
	Too strict	1,157	-	0.32 (0.28-0.37)	0.49 (0.41-0.58)	0.33 (0.28-0.39)	0.51 (0.42-0.60)	0.44 (0.41-0.47)	0.55 (0.52-0.59)	0.56 (0.52-0.60)	0.56 (0.53-0.61)	0.52 (0.48-0.57)
Reference: About right	Don't know	111	-	0.43 (0.29-0.63)	0.53 (0.38-0.74)	0.45 (0.31-0.68)	0.56 (0.39-0.80)	0.51 (0.43-0.61)	0.61 (0.51-0.72)	0.63 (0.53-0.76)	0.64 (0.53-0.77)	0.70 (0.56-0.88)

TABLE D.4: Results from the Cox proportional hazard model to study the association of socio-demographic and other factors with COVID-19 vaccination uptake in Switzerland. Compared to Supplementary Table 3, Supplementary Table 4 shows participants that either got not vaccinated during our study or had an exact date of vaccination. Abbreviations: CI, confidence interval; HR, hazard ratio.

Name	Categories	Number of answers	Unadjusted HR (95% CI)	Adjusted weighted HR (95% CI)
Age groups, years	30-39	336	1.31 (1.07-1.61)	
Reference: 18-29	40-49	282	1.31 (1.06-1.62)	
	50-59	334	1.89 (1.55-2.31)	
	60-69	266	2.98 (2.42-3.66)	
	70+	186	4.78 (3.83-5.97)	
Gender	Male	869	1.05 (0.93-1.17)	0.95 (0.84-1.07)
Reference: Female	Others	7	2.29 (0.95-5.53)	2.23 (0.90-5.56)
Region	Rural	430	0.89 (0.78-1.03)	0.98 (0.85-1.15)
Reference: Urban				
Swiss regions of residence	Zurich	323	1.12 (0.93-1.34)	0.98 (0.82-1.18)
Reference: Espace Mittelland	Lake Geneva region	316	1.12 (0.93-1.35)	1.09 (0.90-1.32)
	Eastern Switzerland	247	1.10 (0.90-1.34)	1.05 (0.86-1.27)
	Northwestern Switzerland	231	1.08 (0.87-1.33)	1.13 (0.91-1.39)
	Central Switzerland	161	0.87 (0.69-1.09)	0.95 (0.76-1.20)
	Ticino	77	1.01 (0.74-1.36)	1.24 (0.83-1.85)
Country of birth	EU	237	0.99 (0.84-1.17)	0.95 (0.80-1.12)
Reference: Switzerland	Non-EU	150	0.95 (0.77-1.17)	0.93 (0.76-1.14)
	Unknown	117	1.10 (0.87-1.40)	1.08 (0.82-1.41)
Education level	Middle level of education	584	1.01 (0.88-1.16)	1.17 (1.01-1.35)
Reference: Lowest level	Highest level of education	397	1.02 (0.89-1.19)	1.26 (1.08-1.47)
Employment status	Unemployed	104	1.01 (0.77-1.31)	1.03 (0.76-1.39)
Reference: Employed	Student	97	0.71 (0.55-0.92)	0.95 (0.70-1.27)
	Homemaker	68	0.99 (0.70-1.40)	1.00 (0.72-1.38)
	Retired	348	2.47 (2.15-2.85)	1.24 (0.98-1.57)
	Other unemployed situation	41	1.83 (1.21-2.78)	1.56 (1.06-2.29)
Household income, net	5,001-10,000 CHF	704	0.95 (0.83-1.10)	1.36 (1.16-1.60)
Reference: 0-5,000 CHF	10,000+ CHF	231	0.90 (0.75-1.08)	1.26 (1.01-1.56)
	Preferred not to answer	238	0.91 (0.75-1.11)	1.02 (0.84-1.24)
Household size	Mean (range)	2 (1 - 9)	0.85 (0.81-0.90)	0.88 (0.82-0.94)
Household with medically vulnerability	One or more person in a risk group	529	1.46 (1.29-1.65)	1.50 (1.31-1.72)
Reference: Nonvulnerable population				
Testing for SARS-CoV-2	Tested	316	0.81 (0.40-1.63)	0.75 (0.33-1.73)
Reference: Tested positive	Never Tested	1376	1.37 (0.68-2.75)	1.06 (0.46-2.41)
	Preferred not to answer	25	0.56 (0.21-1.49)	0.56 (0.19-1.64)
Number of contacts per day	3-May	462	1.01 (0.87-1.17)	1.17 (1.01-1.37)
Reference: 0-2	6+	692	0.87 (0.76-0.99)	1.11 (0.94-1.30)
Attitudes towards COVID-19 measures	Too lenient	368	0.94 (0.82-1.08)	0.84 (0.73-0.96)
Reference: About right	Too strict	420	0.74 (0.62-0.87)	0.82 (0.69-0.97)
	Don't know	46	0.39 (0.24-0.62)	0.72 (0.36-1.44)

TABLE D.5: Results from the logistic regression model to study the association of study participants' characteristics with missed survey participation. Abbreviations: CI, confidence interval; OR, odds ratio; adjusted OR, aOR.

Category	Variables	Number of participants	Number of observations	Univariable OR (95% CI)	aOR (95% CI) without time varying variables	aOR (95% CI) with time varying variables
Age groups, years	30-39	358	358	0.54 (0.36-0.81)	0.94 (0.88-1.00)	0.93 (0.87-1.00)
Reference: 18-29	40-49	308	308	0.41 (0.27-0.61)	0.90 (0.83-0.96)	0.89 (0.83-0.95)
	50-59	363	363	0.28 (0.19-0.41)	0.84 (0.78-0.90)	0.84 (0.78-0.90)
	60-69	289	289	0.35 (0.23-0.52)	0.90 (0.82-0.98)	0.90 (0.82-0.98)
	70+	207	207	0.37 (0.24-0.57)	0.91 (0.82-1.02)	0.92 (0.82-1.03)
Gender	Male	955	955	0.91 (0.74-1.13)	0.98 (0.94-1.02)	0.98 (0.95-1.02)
Reference: Female	Others	10	10	1.17 (0.25-5.56)	1.03 (0.79-1.34)	1.04 (0.80-1.34)
Region	Rural	457	457	0.86 (0.67-1.09)	0.99 (0.94-1.04)	0.99 (0.94-1.03)
Reference: Urban						
Swiss region of residence	Zurich	351	351	0.97 (0.70-1.34)	0.99 (0.93-1.05)	0.99 (0.93-1.05)
Reference: Espace Mittelland	Lake Geneva region	337	337	1.66 (1.16-2.38)	1.08 (1.01-1.14)	1.07 (1.01-1.13)
	Eastern Switzerland	263	263	1.08 (0.75-1.54)	1.01 (0.94-1.07)	1.01 (0.94-1.07)
	Northwestern Switzerland	262	262	1.16 (0.81-1.67)	1.02 (0.95-1.09)	1.02 (0.95-1.09)
	Central Switzerland	182	182	0.88 (0.60-1.31)	0.98 (0.91-1.06)	0.99 (0.92-1.06)
	Ticino	82	82	5.44 (2.14-13.81)	1.22 (1.10-1.35)	1.21 (1.10-1.34)
Country of birth	EU	249	249	1.61 (1.13-2.30)	1.09 (1.03-1.16)	1.10 (1.03-1.16)
Reference: Switzerland	Non-EU	156	156	1.32 (0.87-1.99)	1.05 (0.98-1.12)	1.05 (0.98-1.12)
	Unknown	147	147	0.85 (0.58-1.24)	0.99 (0.92-1.06)	0.98 (0.91-1.06)
Education level	Middle level of education	639	639	1.03 (0.81-1.31)	0.98 (0.94-1.03)	0.97 (0.93-1.02)
Reference: Lowest level	Highest level of education	439	439	1.18 (0.89-1.56)	0.99 (0.93-1.04)	0.99 (0.94-1.04)
Employment status	Unemployed	110	110	1.05 (0.66-1.67)	1.01 (0.92-1.09)	1.00 (0.92-1.09)
Reference: Employed	Student	116	116	5.64 (2.45-12.96)	1.08 (0.99-1.19)	1.09 (0.99-1.20)
	Homemaker	75	75	0.70 (0.42-1.16)	0.92 (0.83-1.02)	0.92 (0.83-1.02)
	Retired	377	377	0.83 (0.64-1.08)	1.00 (0.92-1.08)	1.00 (0.92-1.09)
	Other unemployed situation	44	44	0.73 (0.38-1.42)	0.98 (0.86-1.12)	0.97 (0.86-1.11)
Household income, net	5,001-10,000 CHF	762	762	0.98 (0.76-1.27)	0.98 (0.93-1.03)	0.98 (0.93-1.02)
Reference: 0-5,000 CHF	10,000+ CHF	248	248	1.07 (0.75-1.52)	0.98 (0.91-1.05)	0.99 (0.93-1.06)
	Preferred not to answer	281	281	0.93 (0.67-1.30)	0.97 (0.91-1.03)	0.98 (0.92-1.04)
Household size	Mean (range)	2 (1 - 10)	2 (1 - 10)	1.20 (1.09-1.32)	1.02 (1.01-1.04)	0.99 (0.98-1.01)
Household with medically vulnerability	One or more person in a risk group	578	578	0.84 (0.67-1.06)	0.97 (0.93-1.02)	0.97 (0.93-1.02)
Reference: Nonvulnerable population						
Vaccination status	Vaccinated	-	1,321	0.74 (0.58-0.94)	-	0.95 (0.91-0.99)
Reference: Not vaccinated						
Testing for SARS-CoV-2	Tested	-	543	0.66 (0.25-1.76)	-	0.94 (0.81-1.09)
Reference: Tested positive	Never tested	-	1,277	0.60 (0.23-1.58)	-	0.95 (0.81-1.10)
	Preferred not to answer	-	32	0.83 (0.23-3.07)	-	0.98 (0.79-1.21)
Number of contacts per day	3-5	-	527	1.12 (0.87-1.43)	-	1.02 (0.98-1.07)
Reference: 0-2	6+	-	589	2.54 (1.92-3.36)	-	1.16 (1.10-1.23)
Attitudes towards COVID-19 measures	Too lenient	-	423	1.07 (0.81-1.41)	-	1.03 (0.98-1.08)
	Too strict	-	501	0.90 (0.70-1.16)	-	0.97 (0.92-1.01)
Reference: About right	Don't know	-	46	1.71 (0.75-3.87)	-	1.08 (0.94-1.23)

Bibliography

Aalen, O. O., Borgan, Ø., & Gjessing, H. K. (2008). *Survival and Event History Analysis* (M. Gail, K. Krickeberg, J. Samet, A. Tsiatis, & W. Wong, Eds.). Springer New York. https://doi.org/10.1007/978-0-387-68560-1

Abbott, S., Hellewell, J., Thompson, R. N., Sherratt, K., Gibbs, H. P., Bosse, N. I., Munday, J. D., Meakin, S., Doughty, E. L., Chun, J. Y., Chan, Y.-W. D., Finger, F., Campbell, P., Endo, A., Pearson, C. A. B., Gimma, A., Russell, T., CMMID COVID modelling group, Flasche, S., … Funk, S. (2020). Estimating the time-varying reproduction number of SARS-CoV-2 using national and subnational case counts. *Wellcome Open Res*, *5*, 112. https://doi.org/10.12688/wellcomeopenres.16006.1

Abbott, S., Hickson, J., Funk, S., Hamada S. Badr, Monticone, P., Ellis, P., Munday, J., Allen, J., Pearson, C. A. B., Chapman, L., DeWitt, M., Bosse, N., & Meakin, S. (2023). *Epiforecasts/EpiNow2: 1.3.4 release*. https://doi.org/10.5281/ZENODO.7611804

Al-Amer, R., Maneze, D., Everett, B., Montayre, J., Villarosa, A. R., Dwekat, E., & Salamonson, Y. (2022). COVID-19 vaccination intention in the first year of the pandemic: A systematic review. *J Clin Nurs*, *31*(1-2), 62–86. https://doi.org/10.1111/jocn.15951

Albrecht, D. (2022). Vaccination, politics and COVID-19 impacts. *BMC Public Health*, *22*(1), 96. https://doi.org/10.1186/s12889-021-12432-x

Alm, E., Broberg, E. K., Connor, T., Hodcroft, E. B., Komissarov, A. B., Maurer-Stroh, S., Melidou, A., Neher, R. A., O'Toole, Á., Pereyaslov, D., & The WHO European Region sequencing laboratories and GISAID EpiCoV group. (2020). Geographical and temporal distribution of SARS-CoV-2 clades in the WHO European Region, January to June 2020. *Eurosurveillance*, *25*(32). https://doi.org/10.2807/1560-7917.ES.2020.25.32.2001410

Alpert, T., Brito, A. F., Lasek-Nesselquist, E., Rothman, J., Valesano, A. L., MacKay, M. J., Petrone, M. E., Breban, M. I., Watkins, A. E., Vogels, C. B., Kalinich, C. C., Dellicour, S., Russell, A., Kelly, J. P., Shudt, M., Plitnick, J., Schneider, E., Fitzsimmons, W. J., Khullar, G., … Grubaugh, N. D. (2021). Early introductions and transmission of SARS-CoV-2 variant B.1.1.7 in the United States. *Cell*, *184*(10), 2595–2604.e13. https://doi.org/10.1016/j.cell.2021.03.061

Althaus, C. L. (2015). Ebola superspreading. *The Lancet Infectious Diseases*, *15*(5), 507–508. https://doi.org/10.1016/S1473-3099(15)70135-0

Althaus, C. L., Baggio, S., Reichmuth, M. L., Hodcroft, E. B., Riou, J., Neher, R. A., Jacquerioz, F., Spechbach, H., Salamun, J., Vetter, P., Williamson, C., Hsiao, N.-y., Preiser, W., Davies, M.-A., Lessells, R. J., de Olivera, T., Kaiser, L., & Eckerle, I. (2021). A tale of two variants: Spread of SARS-CoV-2 variants Alpha in Geneva, Switzerland, and Beta in South Africa. https://doi.org/10.1101/2021.06.10.21258468

Althaus, C. L., Schlaufer, C., Frahsa, A., Hadorn, S., Sager, F., & Zwahlen,

M. (2022). *Thesenpapier im Auftrag des Bundesamtes für Gesundheit (BAG) im Rahmen der Revision des Epidemiengesetzes (EpG)* (tech. rep.).

Amati, R., Frei, A., Kaufmann, M., Sabatini, S., Pellaton, C., Fehr, J., Albanese, E., Puhan, M. A., & on behalf of the Corona Immunitas Research Group. (2022). Functional immunity against SARS-CoV-2 in the general population after a booster campaign and the Delta and Omicron waves, Switzerland, March 2022. *Eurosurveillance*, *27*(31). https://doi.org/10.2807/1560-7917.ES.2022.27.31.2200561

Amicone, M., Borges, V., Alves, M. J., Isidro, J., Zé-Zé, L., Duarte, S., Vieira, L., Guiomar, R., Gomes, J. P., & Gordo, I. (2022). Mutation rate of SARS-CoV-2 and emergence of mutators during experimental evolution. *Evolution, Medicine, and Public Health*, *10*(1), 142–155. https://doi.org/10.1093/emph/eoac010

Ashcroft, P., Lehtinen, S., Angst, D. C., Low, N., & Bonhoeffer, S. (2021). Quantifying the impact of quarantine duration on COVID-19 transmission. *eLife*, *10*, e63704. https://doi.org/10.7554/eLife.63704

Backer, J. A., Mollema, L., Vos, E. R., Klinkenberg, D., Van Der Klis, F. R., De Melker, H. E., Van Den Hof, S., & Wallinga, J. (2021). Impact of physical distancing measures against COVID-19 on contacts and mixing patterns: Repeated cross-sectional surveys, the Netherlands, 2016–17, April 2020 and June 2020. *Eurosurveillance*, *26*(8). https://doi.org/10.2807/1560-7917.ES.2021.26.8.2000994

Baker, S. C., Baric, R. S., De Groot, R. J., Drosten, C., Gulyaeva, A. A., Haagmans, B. L., Lauber, C., Leontovich, A. M., Neuman, B. W., Penzar, D., Perlman, S., Poon, L. L. M., Samborskiy, D. V., Sidorov, I. A., Sola, I., Ziebuhr, J., & Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. (2020). The species Severe acute respiratory syndrome-related coronavirus: Classifying 2019-nCoV and naming it SARS-CoV-2. *Nat Microbiol*, *5*(4), 536–544. https://doi.org/10.1038/s41564-020-0695-z

Belshaw, R., Sanjuán, R., & Pybus, O. G. (2011). Viral mutation and substitution: Units and levels. *Current Opinion in Virology*, *1*(5), 430–435. https://doi.org/10.1016/j.coviro.2011.08.004

Bendall, E. E., Callear, A. P., Getz, A., Goforth, K., Edwards, D., Monto, A. S., Martin, E. T., & Lauring, A. S. (2023). Rapid transmission and tight bottlenecks constrain the evolution of highly transmissible SARS-CoV-2 variants. *Nat Commun*, *14*(1), 272. https://doi.org/10.1038/s41467-023-36001-5

BFS. (2021). *Specific causes of death* [Federal Statistical Office]. Retrieved August 6, 2023, from https://www.bfs.admin.ch/bfs/en/home/statistics/health/state-health/mortality-causes-death/specific.html

BFS. (2022). *Bevoelkerung - Stand and Entwicklung*. Retrieved May 8, 2023, from https://dam-api.bfs.admin.ch/hub/api/dam/assets/23064766/master

BFS. (2023). *Population* [Federal Statistical Office (BFS)]. Retrieved January 26, 2023, from https://www.bfs.admin.ch/bfs/en/home/statistics/population.html

Bi, Q., Wu, Y., Mei, S., Ye, C., Zou, X., Zhang, Z., Liu, X., Wei, L., Truelove, S. A., Zhang, T., Gao, W., Cheng, C., Tang, X., Wu, X., Wu, Y., Sun, B., Huang, S., Sun, Y., Zhang,

J., ... Feng, T. (2020). Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: A retrospective cohort study. *The Lancet Infectious Diseases*, *20*(8), 911–919. https://doi.org/10.1016/S1473-3099(20)30287-5

Biggerstaff, M., Cauchemez, S., Reed, C., Gambhir, M., & Finelli, L. (2014). Estimates of the reproduction number for seasonal, pandemic, and zoonotic influenza: A systematic review of the literature. *BMC Infect Dis*, *14*(1), 480. https://doi.org/10.1186/1471-2334-14-480

Black, S., & Rappuoli, R. (2010). A Crisis of Public Confidence in Vaccines. *Sci. Transl. Med.*, *2*(61). https://doi.org/10.1126/scitranslmed.3001738

Bosshardt, L., Bühler, G., Bütikofer, S., Craviolini, J., Hermann, M., David, K., Müller, E., & Bruno, W. (2020). *Die Schweiz und die Corona-Krise* (tech. rep.). Forschungsstelle sotomo.

Brito, A. F., Semenova, E., Dudas, G., Hassler, G. W., Kalinich, C. C., Kraemer, M. U. G., Ho, J., Tegally, H., Githinji, G., Agoti, C. N., Matkin, L. E., Whittaker, C., Bulgarian SARS-CoV-2 sequencing group, Kantardjiev, T., Korsun, N., Stoitsova, S., Dimitrova, R., Trifonova, I., Dobrinov, V., ... Faria, N. R. (2022). Global disparities in SARS-CoV-2 genomic surveillance. *Nat Commun*, *13*(1), 7003. https://doi.org/10.1038/s41467-022-33713-y

Bromham, L., & Penny, D. (2003). The modern molecular clock. *Nat Rev Genet*, *4*(3), 216–224. https://doi.org/10.1038/nrg1020

Brownson, R. C., Chriqui, J. F., & Stamatakis, K. A. (2009). Understanding Evidence-Based Public Health Policy. *Am J Public Health*, *99*(9), 1576–1583. https://doi.org/10.2105/AJPH.2008.156224

Brugger, J., & Althaus, C. L. (2020). Transmission of and susceptibility to seasonal influenza in Switzerland from 2003 to 2015. *Epidemics*, *30*, 100373. https://doi.org/10.1016/j.epidem.2019.100373

Buitrago-Garcia, D., Egli-Gany, D., Counotte, M. J., Hossmann, S., Imeri, H., Ipekci, A. M., Salanti, G., & Low, N. (2020). Occurrence and transmission potential of asymptomatic and presymptomatic SARS-CoV-2 infections: A living systematic review and meta-analysis (N. Ford, Ed.). *PLoS Med*, *17*(9), e1003346. https://doi.org/10.1371/journal.pmed.1003346

Campbell, F., Archer, B., Laurenson-Schafer, H., Jinnai, Y., Konings, F., Batra, N., Pavlin, B., Vandemaele, K., Van Kerkhove, M. D., Jombart, T., Morgan, O., & le Polain de Waroux, O. (2021). Increased transmissibility and global spread of SARS-CoV-2 variants of concern as at June 2021. *Eurosurveillance*, *26*(24). https://doi.org/10.2807/1560-7917.ES.2021.26.24.2100509

Carabelli, A. M., Peacock, T. P., Thorne, L. G., Harvey, W. T., Hughes, J., COVID-19 Genomics UK Consortium, De Silva, T. I., Peacock, S. J., Barclay, W. S., De Silva, T. I., Towers, G. J., & Robertson, D. L. (2023). SARS-CoV-2 variant biology: Immune escape, transmission and fitness. *Nat Rev Microbiol*. https://doi.org/10.1038/s41579-022-00841-7

CDC. (2022). *Nonpharmaceutical Interventions (NPIs)* [Centers for Disease Control and Prevention (CDC)]. Retrieved August 9, 2023, from https://www.cdc.gov/nonpharmaceutical-interventions/index.html

Chen, C., Nadeau, S., Yared, M., Voinov, P., Xie, N., Roemer, C., & Stadler,

T. (2022a). CoV-Spectrum: Analysis of globally shared SARS-CoV-2 data to identify and characterize new variants (C. Alkan, Ed.). *Bioinformatics*, *38*(6), 1735–1737. https://doi.org/10.1093/bioinformatics/btab856

Chen, C., Nadeau, S. A., Topolsky, I., Manceau, M., Huisman, J. S., Jablonski, K. P., Fuhrmann, L., Dreifuss, D., Jahn, K., Beckmann, C., Redondo, M., Noppen, C., Risch, L., Risch, M., Wohlwend, N., Kas, S., Bodmer, T., Roloff, T., Stange, M., … Stadler, T. (2021). Quantification of the spread of SARS-CoV-2 variant B.1.1.7 in Switzerland. *Epidemics*, *37*, 100480. https://doi.org/10.1016/j.epidem.2021.100480

Chen, Z., Azman, A. S., Chen, X., Zou, J., Tian, Y., Sun, R., Xu, X., Wu, Y., Lu, W., Ge, S., Zhao, Z., Yang, J., Leung, D. T., Domman, D. B., & Yu, H. (2022b). Global landscape of SARS-CoV-2 genomic surveillance and data sharing. *Nat Genet*, *54*(4), 499–507. https://doi.org/10.1038/s41588-022-01033-y

Chinazzi, M., Davis, J. T., Ajelli, M., Gioannini, C., Litvinova, M., Merler, S., Pastore Y Piontti, A., Mu, K., Rossi, L., Sun, K., Viboud, C., Xiong, X., Yu, H., Halloran, M. E., Longini, I. M., & Vespignani, A. (2020). The effect of travel restrictions on the spread of the 2019 novel coronavirus (COVID-19) outbreak. *Science*, *368*(6489), 395–400. https://doi.org/10.1126/science.aba9757

Choi, B. C. K., & Pak, A. W. P. (2006). Multidisciplinarity, interdisciplinarity and transdisciplinarity in health research, services, education and policy: 1. Definitions, objectives, and evidence of effectiveness. *Clin Invest Med*, *29*(6), 351–364.

Clifford, S., Pearson, C. A. B., Klepac, P., Van Zandvoort, K., Quilty, B. J., CMMID COVID-19 working group, Eggo, R. M., & Flasche, S. (2020). Effectiveness of interventions targeting air travellers for delaying local outbreaks of SARS-CoV-2. *Journal of Travel Medicine*, *27*(5), taaa068. https://doi.org/10.1093/jtm/taaa068

Clifford, S., Quilty, B. J., Russell, T. W., Liu, Y., Chan, Y.-W. D., Pearson, C. A. B., Eggo, R. M., Endo, A., CMMID COVID-19 Working Group, Flasche, S., & Edmunds, W. J. (2021). Strategies to reduce the risk of SARS-CoV-2 importation from international travellers: Modelling estimations for the United Kingdom, July 2020. *Eurosurveillance*, *26*(39). https://doi.org/10.2807/1560-7917.ES.2021.26.39.2001440

Cohen, M. L. (2000). Changing patterns of infectious disease. *Nature*, *406*(6797), 762–767. https://doi.org/10.1038/35021206

Coletti, P., Libin, P., Petrof, O., Willem, L., Abrams, S., Herzog, S. A., Faes, C., Kuylen, E., Wambua, J., Beutels, P., & Hens, N. (2021). A data-driven metapopulation model for the Belgian COVID-19 epidemic: Assessing the impact of lockdown and exit strategies. *BMC Infect Dis*, *21*(1), 503. https://doi.org/10.1186/s12879-021-06092-w

Coletti, P., Wambua, J., Gimma, A., Willem, L., Vercruysse, S., Vanhoutte, B., Jarvis, C. I., Van Zandvoort, K., Edmunds, J., Beutels, P., & Hens, N. (2020). CoMix: Comparing mixing patterns in the Belgian population during and after lockdown. *Sci Rep*, *10*(1), 21885. https://doi.org/10.1038/s41598-020-78540-7

Committee on the Science of Science Communication: A Research Agenda, Division of Behavioral and Social Sciences and Education, & National Academies of Sciences, Engineering, and Medicine. (2017).

Communicating Science Effectively: A Research Agenda [Pages: 23674]. National Academies Press. https://doi.org/10.17226/23674

Corey, L., Corbett-Detig, R., & Beyrer, C. (2022). Expanding Efforts and Support to Respond to the HIV and COVID-19 Intersecting Pandemics. *JAMA*, *327*(13), 1227. https://doi.org/10.1001/jama.2022.3517

Crawshaw, A. F., Farah, Y., Deal, A., Rustage, K., Hayward, S. E., Carter, J., Knights, F., Goldsmith, L. P., Campos-Matos, I., Wurie, F., Majeed, A., Bedford, H., Forster, A. S., & Hargreaves, S. (2022). Defining the determinants of vaccine uptake and undervaccination in migrant populations in Europe to improve routine and COVID-19 vaccine uptake: A systematic review. *The Lancet Infectious Diseases*, *22*(9), e254–e266. https://doi.org/10.1016/S1473-3099(22)00066-4

Danwang, C., Noubiap, J. J., Robert, A., & Yombi, J. C. (2022). Outcomes of patients with HIV and COVID-19 co-infection: A systematic review and meta-analysis. *AIDS Res Ther*, *19*(1), 3. https://doi.org/10.1186/s12981-021-00427-y

Davies, N. G., Abbott, S., Barnard, R. C., Jarvis, C. I., Kucharski, A. J., Munday, J. D., Pearson, C. A. B., Russell, T. W., Tully, D. C., Washburne, A. D., Wenseleers, T., Gimma, A., Waites, W., Wong, K. L. M., van Zandvoort, K., Silverman, J. D., CMMID COVID-19 Working Group1‡, COVID-19 Genomics UK (COG-UK) Consortium‡, Diaz-Ordaz, K., … Edmunds, W. J. (2021). Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England. *Science*, eabg3055. https://doi.org/10.1126/science.abg3055

Davies, N. G., Klepac, P., Liu, Y., Prem, K., Jit, M., CMMID COVID-19 working group, Pearson, C. A. B., Quilty, B. J., Kucharski, A. J., Gibbs, H., Clifford, S., Gimma, A., Van Zandvoort, K., Munday, J. D., Diamond, C., Edmunds, W. J., Houben, R. M. G. J., Hellewell, J., Russell, T. W., … Eggo, R. M. (2020). Age-dependent effects in the transmission and control of COVID-19 epidemics. *Nat Med*, *26*(8), 1205–1211. https://doi.org/10.1038/s41591-020-0962-9

Davis, H. E., McCorkell, L., Vogel, J. M., & Topol, E. J. (2023). Long COVID: Major findings, mechanisms and recommendations. *Nat Rev Microbiol*, *21*(3), 133–146. https://doi.org/10.1038/s41579-022-00846-2

De Maio, N., Walker, C., Borges, R., Weilguny, L., Slodkowicz, G., & Goldman, N. (2020). *Issues with SARS-CoV-2 sequencing data* (tech. rep.).

de Figueiredo, A., & Larson, H. J. (2021). Exploratory study of the global intent to accept COVID-19 vaccinations. *Commun Med*, *1*(1), 30. https://doi.org/10.1038/s43856-021-00027-x

Delamater, P. L., Street, E. J., Leslie, T. F., Yang, Y. T., & Jacobsen, K. H. (2019). Complexity of the Basic Reproduction Number (R_0). *Emerg. Infect. Dis.*, *25*(1), 1–4. https://doi.org/10.3201/eid2501.171901

Detoc, M., Bruel, S., Frappe, P., Tardy, B., Botelho-Nevers, E., & Gagneux-Brunon, A. (2020). Intention to participate in a COVID-19 vaccine clinical trial and to get vaccinated against COVID-19 in France during the pandemic. *Vaccine*, *38*(45), 7002–7006. https://doi.org/10.1016/j.vaccine.2020.09.041

Dickerman, B. A., Madenci, A. L., Gerlovin, H., Kurgansky, K. E., Wise, J. K., Figueroa Muñiz, M. J., Ferolito, B. R., Gagnon, D. R., Gaziano,

J. M., Cho, K., Casas, J. P., & Hernán, M. A. (2022). Comparative Safety of BNT162b2 and mRNA-1273 Vaccines in a Nationwide Cohort of US Veterans. *JAMA Intern Med*, *182*(7), 739. https://doi.org/10.1001/jamainternmed.2022.2109

Diekmann, O., Heesterbeek, J., & Metz, J. (1990). On the definition and the computation of the basic reproduction ratio R 0 in models for infectious diseases in heterogeneous populations. *J. Math. Biol.*, *28*(4). https://doi.org/10.1007/BF00178324

Dietz, K., & Heesterbeek, J. (2002). Daniel Bernoulli's epidemiological model revisited. *Mathematical Biosciences*, *180*(1-2), 1–21. https://doi.org/10.1016/S0025-5564(02)00122-0

Dong, E., Du, H., & Gardner, L. (2020). An interactive web-based dashboard to track COVID-19 in real time. *The Lancet Infectious Diseases*, *20*(5), 533–534. https://doi.org/10.1016/S1473-3099(20)30120-1

Drummond, A. J., & Rambaut, A. (2007). BEAST: Bayesian evolutionary analysis by sampling trees. *BMC Evol Biol*, *7*(1), 214. https://doi.org/10.1186/1471-2148-7-214

Dubé, E., Gagnon, D., Nickels, E., Jeram, S., & Schuster, M. (2014). Mapping vaccine hesitancy—Country-specific characteristics of a global phenomenon. *Vaccine*, *32*(49), 6649–6654. https://doi.org/10.1016/j.vaccine.2014.09.039

Dubé, E., & MacDonald, N. E. (2022). COVID-19 vaccine hesitancy. *Nat Rev Nephrol*, *18*(7), 409–410. https://doi.org/10.1038/s41581-022-00571-2

du Plessis, L., McCrone, J. T., Zarebski, A. E., Hill, V., Ruis, C., Gutierrez, B., Raghwani, J., Ashworth, J., Colquhoun, R., Connor, T. R., Faria, N. R., Jackson, B., Loman, N. J., O'Toole, Á., Nicholls, S. M., Parag, K. V., Scher, E., Vasylyeva, T. I., Volz, E. M., ... Pybus, O. G. (2021). Establishment and lineage dynamics of the SARS-CoV-2 epidemic in the UK. *Science*, *371*(6530), 708–712. https://doi.org/10.1126/science.abf2946

Earnest, R., Uddin, R., Matluk, N., Renzette, N., Turbett, S. E., Siddle, K. J., Loreth, C., Adams, G., Tomkins-Tinch, C. H., Petrone, M. E., Rothman, J. E., Breban, M. I., Koch, R. T., Billig, K., Fauver, J. R., Vogels, C. B., Bilguvar, K., De Kumar, B., Landry, M. L., ... Mandese, Z. M. (2022). Comparative transmissibility of SARS-CoV-2 variants Delta and Alpha in New England, USA. *Cell Reports Medicine*, *3*(4), 100583. https://doi.org/10.1016/j.xcrm.2022.100583

Eaton, J. W., & Hallett, T. B. (2014). Why the proportion of transmission during early-stage HIV infection does not predict the long-term impact of treatment on HIV incidence. *Proc. Natl. Acad. Sci. U.S.A.*, *111*(45), 16202–16207. https://doi.org/10.1073/pnas.1323007111

ECDC. (2021a). *Disaster Preparedness Guidance Note* (tech. rep.) [European Centre for Disease Prevention and Control (ECDC)].

ECDC. (2021b). *Threat Assessment Brief: Emergence of SARS-CoV-2 B.1.617 variants in India and situation in the EU/EEA* [European Centre for Disease Prevention and Control (ECDC)]. Retrieved July 15, 2022, from https://www.ecdc.europa.eu/en/publications-data/threat-assessment-emergence-sars-cov-2-b1617-variants

Elbe, S., & Buckland-Merrett, G. (2017). Data, disease and diplomacy: GISAID's innovative contribution to global health: Data, Disease and Diplomacy. *Global Challenges*,

1(1), 33–46. https://doi.org/10.1002/gch2.1018

Fang, E., Liu, X., Li, M., Zhang, Z., Song, L., Zhu, B., Wu, X., Liu, J., Zhao, D., & Li, Y. (2022). Advances in COVID-19 mRNA vaccine development. *Sig Transduct Target Ther*, *7*(1), 94. https://doi.org/10.1038/s41392-022-00950-y

Featherstone, J. D., Bell, R. A., & Ruiz, J. B. (2019). Relationship of people's sources of health information and political ideology with acceptance of conspiratorial beliefs about vaccines. *Vaccine*, *37*(23), 2993–2997. https://doi.org/10.1016/j.vaccine.2019.04.063

Federal Council. (2020a). *COVID-19: Switzerland can start vaccinating vulnerable groups already in December*. Retrieved August 6, 2023, from https://www.admin.ch/gov/en/start/documentation/media-releases.msg-id-81762.html

Federal Council. (2020b). *New Coronavirus 2019-nCoV: First confirmed case in Switzerland*. Retrieved August 6, 2023, from https://www.admin.ch/gov/en/start/documentation/media-releases.msg-id-78233.html

Federal Council. (2020c). *Press release by Federal Council: Coronavirus* [Bern, Switzerland]. Retrieved May 18, 2021, from https://www.admin.ch/gov/en/start/documentation/media-releases/media-releases-federal-council.html?dyn_startDate=01.05.2020

Federal Council. (2021). *Ordinance on Measures to Combat the Coronavirus (COVID-19) in International Passenger Transport*. Retrieved April 26, 2022, from https://www.fedlex.admin.ch/eli/cc/2021/61/en

Feehan, D. M., & Mahmud, A. S. (2021). Quantifying population contact patterns in the United States during the COVID-19 pandemic. *Nat Commun*, *12*(1), 893. https://doi.org/10.1038/s41467-021-20990-2

Fewell, Z., Hernán, M. A., Wolfe, F., Tilling, K., Choi, H., & Sterne, J. A. C. (2004). Controlling for Time-dependent Confounding using Marginal Structural Models. *The Stata Journal*, *4*(4), 402–420. https://doi.org/10.1177/1536867X0400400403

FOPH. (2020). *Media releases* [Federal Office of Public Health (FOPH)]. Retrieved August 9, 2023, from https://www.bag.admin.ch/bag/en/home/das-bag/aktuell/medienmitteilungen.html

FOPH. (2023a). *Coronavirus* [Federal Office of Public Health (FOPH)]. Retrieved August 9, 2023, from https://www.bag.admin.ch/bag/en/home/krankheiten/ausbrueche-epidemien-pandemien/aktuelle-ausbrueche-epidemien/novel-cov.html

FOPH. (2023b). *Infectious diseases requiring notification – key facts* [Federal Office of Public Health (FOPH)]. Retrieved August 9, 2023, from https://www.bag.admin.ch/bag/en/home/krankheiten/infektionskrankheiten-bekaempfen/meldesysteme-infektionskrankheiten/meldepflichtige-ik.html

FOPH. (2023c). *Zahlen zu Infektionskrankheiten* [Federal Office of Public Health (FOPH)]. Retrieved August 9, 2023, from https://www.bag.admin.ch/bag/de/home/zahlen-und-statistiken/zahlen-zu-infektionskrankheiten.html

Frei, A., Kaufmann, M., Amati, R., Butty Dettwiler, A., Von Wyl, V., Annoni, A. M., Vincentini, J., Pellaton, C., Pantaleo, G., Fehr, J. S., D'Acremont, V., Bochud, M., Albanese, E., Puhan, M. A., Corona Immunitas Research Group, Albanese, E., Amati, R., Amendola,

A., Anagnostopoulos, A., ... Zuppinger, C. (2023). Development of hybrid immunity during a period of high incidence of Omicron infections. *International Journal of Epidemiology*, dyad098. https://doi.org/10.1093/ije/dyad098

Funk, S., & Willem, L. (2022). *Socialmixr: Social Mixing Matrices for Infectious Disease Modelling. R package version 0.2.0* (tech. rep.).

Ganyani, T., Kremer, C., Chen, D., Torneri, A., Faes, C., Wallinga, J., & Hens, N. (2020). Estimating the generation interval for coronavirus disease (COVID-19) based on symptom onset data, March 2020. *Eurosurveillance*, *25*(17). https://doi.org/10.2807/1560-7917.ES.2020.25.17.2000257

Gesetzgebung übertragbare Krankheiten – Epidemiengesetz (EpG). (2010). https://www.bag.admin.ch/bag/en/home/gesetze-und-bewilligungen/gesetzgebung/gesetzgebung-mensch-gesundheit/epidemiengesetz.html

Ghafari, M., Hall, M., Golubchik, T., Ayoubkhani, D., House, T., MacIntyre-Cockett, G., Fryer, H., Thomson, L., Nurtay, A., Buck, D., Green, A., Trebes, A., Piazza, P., Lonie, L. J., Studley, R., Rourke, E., Smith, D., Bashton, M., Nelson, A., ... Lythgoe, K. (2023). *High number of SARS-CoV-2 persistent infections uncovered through genetic analysis of samples from a large community-based surveillance study* (preprint). Epidemiology. https://doi.org/10.1101/2023.01.29.23285160

Gimma, A., Munday, J. D., Wong, K. L. M., Coletti, P., Van Zandvoort, K., Prem, K., CMMID COVID-19 working group, Klepac, P., Rubin, G. J., Funk, S., Edmunds, W. J., & Jarvis, C. I. (2022). Changes in social contacts in England during the COVID-19 pandemic between March 2020 and March 2021 as measured by the CoMix survey: A repeated cross-sectional study. *PLoS Med*, *19*(3), e1003907. https://doi.org/10.1371/journal.pmed.1003907

Gómez-Carballa, A., Bello, X., Pardo-Seco, J., Martinón-Torres, F., & Salas, A. (2020). Mapping genome variation of SARS-CoV-2 worldwide highlights the impact of COVID-19 super-spreaders. *Genome Res.*, *30*(10), 1434–1448. https://doi.org/10.1101/gr.266221.120

Goncalves Cabecinhas, A. R., Roloff, T., Stange, M., Bertelli, C., Huber, M., Ramette, A., Chen, C., Nadeau, S., Gerth, Y., Yerly, S., Opota, O., Pillonel, T., Schuster, T., Metzger, C. M. J. A., Sieber, J., Bel, M., Wohlwend, N., Baumann, C., Koch, M. C., ... Egli, A. (2021). SARS-CoV-2 N501Y Introductions and Transmissions in Switzerland from Beginning of October 2020 to February 2021—Implementation of Swiss-Wide Diagnostic Screening and Whole Genome Sequencing. *Microorganisms*, *9*(4), 677. https://doi.org/10.3390/microorganisms9040677

Gostic, K. M., McGough, L., Baskerville, E. B., Abbott, S., Joshi, K., Tedijanto, C., Kahn, R., Niehus, R., Hay, J. A., De Salazar, P. M., Hellewell, J., Meakin, S., Munday, J. D., Bosse, N. I., Sherrat, K., Thompson, R. N., White, L. F., Huisman, J. S., Scire, J., ... Cobey, S. (2020). Practical considerations for measuring the effective reproductive number, Rt (V. E. Pitzer, Ed.). *PLoS Comput Biol*, *16*(12), e1008409. https://doi.org/10.1371/journal.pcbi.1008409

Grasselli, G., Pesenti, A., & Cecconi, M. (2020). Critical Care Utilization for the COVID-19 Outbreak in Lombardy, Italy: Early Experience and Forecast During an Emergency Response. *JAMA*, *323*(16), 1545.

https://doi.org/10.1001/jama.2020.4031

Grassly, N. C., & Fraser, C. (2008). Mathematical models of infectious disease transmission. *Nat Rev Microbiol*, *6*(6), 477–487. https://doi.org/10.1038/nrmicro1845

Green, W. D., Ferguson, N. M., & Cori, A. (2022). Inferring the reproduction number using the renewal equation in heterogeneous epidemics. *J. R. Soc. Interface.*, *19*(188), 20210429. https://doi.org/10.1098/rsif.2021.0429

Grenfell, B. T., Pybus, O. G., Gog, J. R., Wood, J. L. N., Daly, J. M., Mumford, J. A., & Holmes, E. C. (2004). Unifying the Epidemiological and Evolutionary Dynamics of Pathogens. *Science*, *303*(5656), 327–332. https://doi.org/10.1126/science.1090727

Grubaugh, N. D., Ladner, J. T., Lemey, P., Pybus, O. G., Rambaut, A., Holmes, E. C., & Andersen, K. G. (2018). Tracking virus outbreaks in the twenty-first century. *Nat Microbiol*, *4*(1), 10–19. https://doi.org/10.1038/s41564-018-0296-2

Hadfield, J., Megill, C., Bell, S. M., Huddleston, J., Potter, B., Callender, C., Sagulenko, P., Bedford, T., & Neher, R. A. (2018). Nextstrain: Real-time tracking of pathogen evolution (J. Kelso, Ed.). *Bioinformatics*, *34*(23), 4121–4123. https://doi.org/10.1093/bioinformatics/bty407

Hale, T., Angrist, N., Goldszmidt, R., Kira, B., Petherick, A., Phillips, T., Webster, S., Cameron-Blake, E., Hallas, L., Majumdar, S., & Tatlow, H. (2021). A global panel database of pandemic policies (Oxford COVID-19 Government Response Tracker). *Nat Hum Behav*, *5*(4), 529–538. https://doi.org/10.1038/s41562-021-01079-8

Harari, S., Tahor, M., Rutsinsky, N., Meijer, S., Miller, D., Henig, O., Halutz, O., Levytskyi, K., Ben-Ami, R., Adler, A., Paran, Y., & Stern, A. (2022). Drivers of adaptive evolution during chronic SARS-CoV-2 infections. *Nat Med*, *28*(7), 1501–1508. https://doi.org/10.1038/s41591-022-01882-4

Harris, R. J., Hall, J. A., Zaidi, A., Andrews, N. J., Dunbar, J. K., & Dabrera, G. (2021). Effect of Vaccination on Household Transmission of SARS-CoV-2 in England. *N Engl J Med*, *385*(8), 759–760. https://doi.org/10.1056/NEJMc2107717

Hart, W. S., Miller, E., Andrews, N. J., Waight, P., Maini, P. K., Funk, S., & Thompson, R. N. (2022). Generation time of the alpha and delta SARS-CoV-2 variants: An epidemiological analysis. *The Lancet Infectious Diseases*, *22*(5), 603–610. https://doi.org/10.1016/S1473-3099(22)00001-9

Hasell, J., Mathieu, E., Beltekian, D., Macdonald, B., Giattino, C., Ortiz-Ospina, E., Roser, M., & Ritchie, H. (2020). A cross-country database of COVID-19 testing. *Sci Data*, *7*(1), 345. https://doi.org/10.1038/s41597-020-00688-8

Haydon, D. T., Cleaveland, S., Taylor, L. H., & Laurenson, M. K. (2002). Identifying reservoirs of infection: A conceptual and practical challenge. *Emerg Infect Dis*, *8*(12), 1468–1473. https://doi.org/10.3201/eid0812.010317

Heim, N., & Müller, S. (2020). *Corona und Reiseverhalten Ergebnisse einer Studie zur Untersuchung der Konsumentenpräferenzen*. Retrieved June 4, 2021, from https://www.zhaw.ch/de/sml/institute-zentren/imm/newsdetail/event-news/drei-von-vier-reisen-werden-storniert/

Heiniger, S., Schliek, M., Moser, A., von Wyl, V., & Höglinger, M. (2022). Differences in COVID-19 vaccination uptake in the first 12 months of vaccine availability in Switzerland – a prospective cohort study. *Swiss*

Med Wkly, *152*(13-14). https://doi.org/10.4414/smw.2022.w30162

Hens, N., Ayele, G. M., Goeyvaerts, N., Aerts, M., Mossong, J., Edmunds, J. W., & Beutels, P. (2009). Estimating the impact of school closure on social mixing behaviour and the transmission of close contact infections in eight European countries. *BMC Infect Dis*, *9*(1), 187. https://doi.org/10.1186/1471-2334-9-187

Hethcote, H. W. (1989). *Three Basic Epidemiological Models. In: Levin S.A., Hallam T.G., Gross L.J. (eds)* (S. A. Levin, Ed.; Softcover reprint of the original 1st ed. 1989). Springer-Verl.

Hodcroft, E. B., Zuber, M., Nadeau, S., Vaughan, T. G., Crawford, K. H. D., Althaus, C. L., Reichmuth, M. L., Bowen, J. E., Walls, A. C., Corti, D., Bloom, J. D., Veesler, D., Mateo, D., Hernando, A., Comas, I., Candelas, F. G., SeqCOVID-SPAIN consortium, Comas, I., González-Candelas, F., … Neher, R. A. (2021). Spread of a SARS-CoV-2 variant through Europe in the summer of 2020. *Nature*. https://doi.org/10.1038/s41586-021-03677-y

Horne, Z., Powell, D., Hummel, J. E., & Holyoak, K. J. (2015). Countering antivaccination attitudes. *Proc. Natl. Acad. Sci. U.S.A.*, *112*(33), 10321–10324. https://doi.org/10.1073/pnas.1504019112

Huecker, M. R., Shreffler, J., McKeny, P. T., & Davis, D. (2023). Imposter Phenomenon. *StatPearls*. StatPearls Publishing.

Huisman, J. S., Scire, J., Angst, D. C., Li, J., Neher, R. A., Maathuis, M. H., Bonhoeffer, S., & Stadler, T. (2022). Estimation and worldwide monitoring of the effective reproductive number of SARS-CoV-2. *eLife*, *11*, e71345. https://doi.org/10.7554/eLife.71345

Ito, M., Yamada, K.-I., Takasaki, T., Pandey, B., Nerome, R., Tajima, S., Morita, K., & Kurane, I. (2007). Phylogenetic Analysis of Dengue Viruses Isolated From Imported Dengue Patients: Possible Aid for Determining the Countries Where Infections Occurred. *J Travel Med*, *14*(4), 233–244. https://doi.org/10.1111/j.1708-8305.2007.00130.x

Jackson, C. B., Farzan, M., Chen, B., & Choe, H. (2022). Mechanisms of SARS-CoV-2 entry into cells. *Nat Rev Mol Cell Biol*, *23*(1), 3–20. https://doi.org/10.1038/s41580-021-00418-x

Jahn, K., Dreifuss, D., Topolsky, I., Kull, A., Ganesanandamoorthy, P., Fernandez-Cassi, X., Bänziger, C., Devaux, A. J., Stachler, E., Caduff, L., Cariti, F., Corzón, A. T., Fuhrmann, L., Chen, C., Jablonski, K. P., Nadeau, S., Feldkamp, M., Beisel, C., Aquino, C., … Beerenwinkel, N. (2022). Early detection and surveillance of SARS-CoV-2 genomic variants in wastewater using COJAC. *Nat Microbiol*, *7*(8), 1151–1160. https://doi.org/10.1038/s41564-022-01185-x

Jarvis, C. I., CMMID COVID-19 working group, Van Zandvoort, K., Gimma, A., Prem, K., Klepac, P., Rubin, G. J., & Edmunds, W. J. (2020). Quantifying the impact of physical distance measures on the transmission of COVID-19 in the UK. *BMC Med*, *18*(1), 124. https://doi.org/10.1186/s12916-020-01597-8

Jarvis, C. I., Coletti, P., Backer, J. A., Munday, J. D., Faes, C., Beutels, P., Althaus, C. L., Low, N., Wallinga, J., Hens, N., & Edmunds, W. J. (2023). *Social contact patterns following the COVID-19 pandemic: A snapshot of post-pandemic behaviour from the CoMix study*. https://doi.org/10.1101/2023.08.29.23294767

Jarvis, C. I., Gimma, A., Van Zandvoort, K., Wong, K. L. M., Edmunds, W. J., & CMMID COVID-19 working group. (2021). The impact of local and

national restrictions in response to COVID-19 on social contacts in England: A longitudinal natural experiment. *BMC Med*, *19*(1), 52. https://doi.org/10.1186/s12916-021-01924-7

Jassat, W., Cohen, C., Tempia, S., Masha, M., Goldstein, S., Kufa, T., Murangandi, P., Savulescu, D., Walaza, S., Bam, J.-L., Davies, M.-A., Prozesky, H. W., Naude, J., Mnguni, A. T., Lawrence, C. A., Mathema, H. T., Zamparini, J., Black, J., Mehta, R., … Zwane, N. (2021). Risk factors for COVID-19-related in-hospital mortality in a high HIV and tuberculosis prevalence setting in South Africa: A cohort study. *The Lancet HIV*, *8*(9), e554–e567. https://doi.org/10.1016/S2352-3018(21)00151-X

Jones, T. C., Biele, G., Mühlemann, B., Veith, T., Schneider, J., Beheim-Schwarzbach, J., Bleicker, T., Tesch, J., Schmidt, M. L., Sander, L. E., Kurth, F., Menzel, P., Schwarzer, R., Zuchowski, M., Hofmann, J., Krumbholz, A., Stein, A., Edelmann, A., Corman, V. M., & Drosten, C. (2021). Estimating infectiousness throughout SARS-CoV-2 infection course. *Science*, *373*(6551), eabi5273. https://doi.org/10.1126/science.abi5273

Karthikeyan, S., Levy, J. I., De Hoff, P., Humphrey, G., Birmingham, A., Jepsen, K., Farmer, S., Tubb, H. M., Valles, T., Tribelhorn, C. E., Tsai, R., Aigner, S., Sathe, S., Moshiri, N., Henson, B., Mark, A. M., Hakim, A., Baer, N. A., Barber, T., … Knight, R. (2022). Wastewater sequencing reveals early cryptic SARS-CoV-2 variant transmission. *Nature*, *609*(7925), 101–108. https://doi.org/10.1038/s41586-022-05049-6

Keeling, M. J., & Rohani, P. (2008). *Modeling infectious diseases in humans and animals* [OCLC: ocn163616681]. Princeton University Press.

Kermack, W. O., & McKendrick, A. G. (1991a). Contributions to the mathematical theory of epidemics—I. *Bltn Mathcal Biology*, *53*(1-2), 33–55. https://doi.org/10.1007/BF02464423

Kermack, W. O., & McKendrick, A. G. (1991b). Contributions to the mathematical theory of epidemics—II. The problem of endemicity. *Bltn Mathcal Biology*, *53*(1-2), 57–87. https://doi.org/10.1007/BF02464424

Kermack, W. O., & McKendrick, A. G. (1991c). Contributions to the mathematical theory of epidemics—III. Further studies of the problem of endemicity. *Bltn Mathcal Biology*, *53*(1-2), 89–118. https://doi.org/10.1007/BF02464425

Keyes, K. M., Rutherford, C., Popham, F., Martins, S. S., & Gray, L. (2018). How Healthy Are Survey Respondents Compared with the General Population?: Using Survey-linked Death Records to Compare Mortality Outcomes. *Epidemiology*, *29*(2), 299–307. https://doi.org/10.1097/EDE.0000000000000775

Kirkwood, B. R., & Sterne, J. A. C. (2003). *Essential medical statistics* (2nd ed). Blackwell Science.

Kiti, M. C., Aguolu, O. G., Zelaya, A., Chen, H. Y., Ahmed, N., Batross, J., Liu, C. Y., Nelson, K. N., Jenness, S. M., Melegaro, A., Ahmed, F., Malik, F., Omer, S. B., & Lopman, B. A. (2023). Changing social contact patterns among US workers during the COVID-19 pandemic: April 2020 to December 2021. *Epidemics*, *45*, 100727. https://doi.org/10.1016/j.epidem.2023.100727

Klymak, M., & Vlandas, T. (2022). Partisanship and Covid-19 vaccination in the UK. *Sci Rep*, *12*(1), 19785. https://doi.org/10.1038/s41598-022-23035-w

Ko, A. I., Karim, S. S. A., Morel, C., Swaminathan, S., Daszak, P., & Keusch, G. T. (2023). Threatening the Future of Global Health — NIH Policy Changes on International Research Collaborations. *N Engl J Med*, *389*(10), 869–871. https://doi.org/10.1056/NEJMp2307543

Kremer, C., Torneri, A., Boesmans, S., Meuwissen, H., Verdonschot, S., Vanden Driessche, K., Althaus, C. L., Faes, C., & Hens, N. (2021). Quantifying superspreading for COVID-19 using Poisson mixture distributions. *Sci Rep*, *11*(1), 14107. https://doi.org/10.1038/s41598-021-93578-x

Kucharski, A. J., & Althaus, C. L. (2015). The role of superspreading in Middle East respiratory syndrome coronavirus (MERS-CoV) transmission. *Eurosurveillance*, *20*(25). https://doi.org/10.2807/1560-7917.ES2015.20.25.21167

Kucharski, A. J., Jit, M., Logan, J. G., Cotten, M., Clifford, S., Quilty, B. J., Russell, T. W., Peeling, R. W., Antonio, M., & Heymann, D. L. (2022). Travel measures in the SARS-CoV-2 variant era need clear objectives. *The Lancet*, *399*(10333), 1367–1369. https://doi.org/10.1016/S0140-6736(22)00366-X

Kuchipudi, S. V., Tan, C., Van Dorp, L., Lichtveld, M., Pickering, B., Bowman, J., Mubareka, S., & Balloux, F. (2023). Coordinated surveillance is essential to monitor and mitigate the evolutionary impacts of SARS-CoV-2 spillover and circulation in animal hosts. *Nat Ecol Evol*, *7*(7), 956–959. https://doi.org/10.1038/s41559-023-02082-0

Kutter, J. S., Spronken, M. I., Fraaij, P. L., Fouchier, R. A., & Herfst, S. (2018). Transmission routes of respiratory viruses among humans. *Current Opinion in Virology*, *28*, 142–151. https://doi.org/10.1016/j.coviro.2018.01.001

Larson, H. J., Gakidou, E., & Murray, C. J. (2022). The Vaccine-Hesitant Moment. *N Engl J Med*, *387*(1), 58–65. https://doi.org/10.1056/NEJMra2106441

Larson, H. J., Jarrett, C., Eckersberger, E., Smith, D. M., & Paterson, P. (2014). Understanding vaccine hesitancy around vaccines and vaccination from a global perspective: A systematic review of published literature, 2007–2012. *Vaccine*, *32*(19), 2150–2159. https://doi.org/10.1016/j.vaccine.2014.01.081

Laxminarayan, R., Wahl, B., Dudala, S. R., Gopal, K., Mohan B, C., Neelima, S., Jawahar Reddy, K. S., Radhakrishnan, J., & Lewnard, J. A. (2020). Epidemiology and transmission dynamics of COVID-19 in two Indian states. *Science*, *370*(6517), 691–697. https://doi.org/10.1126/science.abd7672

Lazarus, J. V., Ratzan, S. C., Palayew, A., Gostin, L. O., Larson, H. J., Rabin, K., Kimball, S., & El-Mohandes, A. (2021). A global survey of potential acceptance of a COVID-19 vaccine. *Nat Med*, *27*(2), 225–228. https://doi.org/10.1038/s41591-020-1124-9

Lemaitre, J. C., Perez-Saez, J., Azman, A. S., Rinaldo, A., & Fellay, J. (2020). Assessing the impact of non-pharmaceutical interventions on SARS-CoV-2 transmission in Switzerland. *Swiss Med Wkly*. https://doi.org/10.4414/smw.2020.20295

Lemey, P., Hong, S. L., Hill, V., Baele, G., Poletto, C., Colizza, V., O'Toole, Á., McCrone, J. T., Andersen, K. G., Worobey, M., Nelson, M. I., Rambaut, A., & Suchard, M. A. (2020). Accommodating individual travel history and unsampled diversity in Bayesian phylogeographic inference of SARS-CoV-2. *Nat Commun*, *11*(1), 5110. https://doi.org/10.1038/s41467-020-18877-9

Lemey, P., Ruktanonchai, N., Hong, S. L., Colizza, V., Poletto, C., Van den Broeck, F., Gill, M. S., Ji, X., Levasseur, A., Oude Munnink, B. B., Koopmans, M., Sadilek, A., Lai, S., Tatem, A. J., Baele, G., Suchard, M. A., & Dellicour, S. (2021). Untangling introductions and persistence in COVID-19 resurgence in Europe. *Nature*. https://doi.org/10.1038/s41586-021-03754-2

Lemieux, J. E., Siddle, K. J., Shaw, B. M., Loreth, C., Schaffner, S. F., Gladden-Young, A., Adams, G., Fink, T., Tomkins-Tinch, C. H., Krasilnikova, L. A., DeRuff, K. C., Rudy, M., Bauer, M. R., Lagerborg, K. A., Normandin, E., Chapman, S. B., Reilly, S. K., Anahtar, M. N., Lin, A. E., ... MacInnis, B. L. (2021). Phylogenetic analysis of SARS-CoV-2 in Boston highlights the impact of superspreading events. *Science*, *371*(6529), eabe3261. https://doi.org/10.1126/science.abe3261

Leos-Toro, C., Ribeaud, D., Bechtiger, L., Steinhoff, A., Nivette, A., Murray, A. L., Hepp, U., Quednow, B. B., Eisner, M. P., & Shanahan, L. (2021). Attitudes Toward COVID-19 Vaccination Among Young Adults in Zurich, Switzerland, September 2020. *Int J Public Health*, *66*, 643486. https://doi.org/10.3389/ijph.2021.643486

Leung, N. H. L. (2021). Transmissibility and transmission of respiratory viruses. *Nat Rev Microbiol*. https://doi.org/10.1038/s41579-021-00535-6

Li, R., Shen, M., Yang, Q., Fairley, C. K., Chai, Z., McIntyre, R., Ong, J. J., Liu, H., Lu, P., Hu, W., Zou, Z., Li, Z., He, S., Zhuang, G., & Zhang, L. (2023). Global Diabetes Prevalence in COVID-19 Patients and Contribution to COVID-19– Related Severity and Mortality: A Systematic Review and Meta-analysis. *Diabetes Care*, *46*(4), 890–897. https://doi.org/10.2337/dc22-1943

Lipsitch, M. (2020). Good science is good science: We need specialists, not sects. *Eur J Epidemiol*, *35*(6), 519–522. https://doi.org/10.1007/s10654-020-00651-2

Liu, T., Hu, J., Kang, M., Lin, L., Zhong, H., Xiao, J., He, G., Song, T., Huang, Q., Rong, Z., Deng, A., Zeng, W., Tan, X., Zeng, S., Zhu, Z., Li, J., Wan, D., Lu, J., Deng, H., ... Ma, W. (2020a). Transmission Dynamics of 2019 Novel Coronavirus (2019-nCoV). *SSRN Journal*. https://doi.org/10.2139/ssrn.3526307

Liu, Y.-C., Kuo, R.-L., & Shih, S.-R. (2020b). COVID-19: The first documented coronavirus pandemic in history. *Biomedical Journal*, *43*(4), 328–333. https://doi.org/10.1016/j.bj.2020.04.007

Lloyd-Smith, J. O., Schreiber, S. J., Kopp, P. E., & Getz, W. M. (2005). Superspreading and the effect of individual variation on disease emergence. *Nature*, *438*(7066), 355–359. https://doi.org/10.1038/nature04153

Loedy, N., Coletti, P., Wambua, J., Hermans, L., Willem, L., Jarvis, C. I., Wong, K. L. M., Edmunds, W. J., Robert, A., Leclerc, Q. J., Gimma, A., Molenberghs, G., Beutels, P., Faes, C., & Hens, N. (2023). Longitudinal social contact data analysis: Insights from 2 years of data collection in Belgium during the COVID-19 pandemic. *BMC Public Health*, *23*(1), 1298. https://doi.org/10.1186/s12889-023-16193-7

Lu, L., Sikkema, R. S., Velkers, F. C., Nieuwenhuijse, D. F., Fischer, E. A. J., Meijer, P. A., Bouwmeester-Vincken, N., Rietveld, A., Wegdam-Blans, M. C. A., Tolsma, P., Koppelman, M., Smit, L. A. M., Hakze-van Der Honing, R. W., Van Der Poel, W. H. M., Van Der Spek, A. N.,

Spierenburg, M. A. H., Molenaar, R. J., Rond, J. D., Augustijn, M., … Koopmans, M. P. G. (2021). Adaptation, spread and transmission of SARS-CoV-2 in farmed minks and associated humans in the Netherlands. *Nat Commun*, *12*(1), 6802. https://doi.org/10.1038/s41467-021-27096-9

Ma, Y., Horsburgh, C. R., White, L. F., & Jenkins, H. E. (2018). Quantifying TB transmission: A systematic review of reproduction number and serial interval estimates for tuberculosis. *Epidemiol. Infect.*, *146*(12), 1478–1494. https://doi.org/10.1017/S0950268818001760

MacDonald, N. E. (2015). Vaccine hesitancy: Definition, scope and determinants. *Vaccine*, *33*(34), 4161–4164. https://doi.org/10.1016/j.vaccine.2015.04.036

Madewell, Z. J., Yang, Y., Longini, I. M., Halloran, M. E., & Dean, N. E. (2022). Household Secondary Attack Rates of SARS-CoV-2 by Variant and Vaccination Status: An Updated Systematic Review and Meta-analysis. *JAMA Netw Open*, *5*(4), e229317. https://doi.org/10.1001/jamanetworkopen.2022.9317

Magliano, D. J., Boyko, E. J., & Diabetes Atlas 10th edition scientific committee. (2021). *IDF Diabetes Atlas - 2021* (IDF DIABETES ATLAS). International Diabetes Federation. Brussels.

Mallapaty, S. (2021). Omicron-variant border bans ignore the evidence, say scientists. *Nature*, *600*(7888), 199–199. https://doi.org/10.1038/d41586-021-03608-x

Manica, M., De Bellis, A., Guzzetta, G., Mancuso, P., Vicentini, M., Venturelli, F., Zerbini, A., Bisaccia, E., Litvinova, M., Menegale, F., Molina Grané, C., Poletti, P., Marziano, V., Zardini, A., d'Andrea, V., Trentini, F., Bella, A., Riccardo, F., Pezzotti, P., … Merler, S. (2022). Intrinsic generation time of the SARS-CoV-2 Omicron variant: An observational study of household transmission. *The Lancet Regional Health - Europe*, *19*, 100446. https://doi.org/10.1016/j.lanepe.2022.100446

Maponga, T. G., Jeffries, M., Tegally, H., Sutherland, A., Wilkinson, E., Lessells, R. J., Msomi, N., Van Zyl, G., De Oliveira, T., & Preiser, W. (2023). Persistent Severe Acute Respiratory Syndrome Coronavirus 2 Infection With accumulation of mutations in a patient with poorly controlled Human Immunodeficiency Virus infection. *Clinical Infectious Diseases*, *76*(3), e522–e525. https://doi.org/10.1093/cid/ciac548

Markov, P. V., Ghafari, M., Beer, M., Lythgoe, K., Simmonds, P., Stilianakis, N. I., & Katzourakis, A. (2023). The evolution of SARS-CoV-2. *Nat Rev Microbiol*, *21*(6), 361–379. https://doi.org/10.1038/s41579-023-00878-2

Marshall, J. S., Warrington, R., Watson, W., & Kim, H. L. (2018). An introduction to immunology and immunopathology. *Allergy Asthma Clin Immunol*, *14*(S2), 49. https://doi.org/10.1186/s13223-018-0278-1

Martani, A., Egli, P., Widmer, M., & Elger, B. (2020). Data protection and biomedical research in Switzerland: Setting the record straight. *Swiss Med Wkly*, *150*(3536), w20332. https://doi.org/10.4414/smw.2020.20332

McCrone, J. T., Hill, V., Bajaj, S., Pena, R. E., Lambert, B. C., Inward, R., Bhatt, S., Volz, E., Ruis, C., Dellicour, S., Baele, G., Zarebski, A. E., Sadilek, A., Wu, N., Schneider, A., Ji, X., Raghwani, J., Jackson, B., Colquhoun, R., … Kraemer, M. U. G. (2022). Context-specific emergence and growth of

the SARS-CoV-2 Delta variant. *Nature*. https://doi.org/10.1038/s41586-022-05200-3

McIntosh, E. D. G., Janda, J., Ehrich, J. H., Pettoello-Mantovani, M., & Somekh, E. (2016). Vaccine Hesitancy and Refusal. *The Journal of Pediatrics*, *175*, 248–249.e1. https://doi.org/10.1016/j.jpeds.2016.06.006

Mikolajczyk, R. T., & Kretzschmar, M. (2008). Collecting social contact data in the context of disease transmission: Prospective and retrospective study designs. *Social Networks*, *30*(2), 127–135. https://doi.org/10.1016/j.socnet.2007.09.002

Minh, B. Q., Schmidt, H. A., Chernomor, O., Schrempf, D., Woodhams, M. D., Von Haeseler, A., & Lanfear, R. (2020). Corrigendum to: IQ-TREE 2: New Models and Efficient Methods for Phylogenetic Inference in the Genomic Era. *Molecular Biology and Evolution*, *37*(8), 2461–2461. https://doi.org/10.1093/molbev/msaa131

Mora, C., McKenzie, T., Gaw, I. M., Dean, J. M., Von Hammerstein, H., Knudson, T. A., Setter, R. O., Smith, C. Z., Webster, K. M., Patz, J. A., & Franklin, E. C. (2022). Over half of known human pathogenic diseases can be aggravated by climate change. *Nat. Clim. Chang.*, *12*(9), 869–875. https://doi.org/10.1038/s41558-022-01426-1

Morawska, L., & Cao, J. (2020). Airborne transmission of SARS-CoV-2: The world should face the reality. *Environment International*, *139*, 105730. https://doi.org/10.1016/j.envint.2020.105730

Morel, B., Barbera, P., Czech, L., Bettisworth, B., Hübner, L., Lutteropp, S., Serdari, D., Kostaki, E.-G., Mamais, I., Kozlov, A. M., Pavlidis, P., Paraskevis, D., & Stamatakis, A. (2021). Phylogenetic Analysis of SARS-CoV-2 Data Is Difficult (H. Malik, Ed.). *Molecular Biology and Evolution*, *38*(5), 1777–1791. https://doi.org/10.1093/molbev/msaa314

Moser, A., Bopp, M., Zwahlen, M., & Swiss National Cohort study group. (2018). Calibration adjustments to address bias in mortality analyses due to informative sampling—a census-linked survey analysis in Switzerland. *PeerJ*, *6*, e4376. https://doi.org/10.7717/peerj.4376

Mossong, J., Hens, N., Jit, M., Beutels, P., Auranen, K., Mikolajczyk, R., Massari, M., Salmaso, S., Tomba, G. S., Wallinga, J., Heijne, J., Sadkowska-Todys, M., Rosinska, M., & Edmunds, W. J. (2008). Social Contacts and Mixing Patterns Relevant to the Spread of Infectious Diseases (S. Riley, Ed.). *PLoS Med*, *5*(3), e74. https://doi.org/10.1371/journal.pmed.0050074

Mousa, A., Winskill, P., Watson, O. J., Ratmann, O., Monod, M., Ajelli, M., Diallo, A., Dodd, P. J., Grijalva, C. G., Kiti, M. C., Krishnan, A., Kumar, R., Kumar, S., Kwok, K. O., Lanata, C. F., De Waroux, O. L. P., Leung, K., Mahikul, W., Melegaro, A., … Whittaker, C. (2021). Social contact patterns and implications for infectious disease transmission – a systematic review and meta-analysis of contact surveys. *eLife*, *10*, e70294. https://doi.org/10.7554/eLife.70294

Munday, J. D., Abbott, S., Meakin, S., & Funk, S. (2023). Evaluating the use of social contact data to produce age-specific short-term forecasts of SARS-CoV-2 incidence in England. *PLoS Comput Biol*, *19*(9), e1011453. https://doi.org/10.1371/journal.pcbi.1011453

Munday, J. D., Jarvis, C. I., Gimma, A., Wong, K. L. M., van Zandvoort, K., CMMID COVID-19 Working Group, Liu, Y., Hellewell, J.,

Davies, N. G., Villabona-Arenas, C. J., Eggo, R. M., Endo, A., Bosse, N. I., Gibbs, H. P., Pearson, C. A. B., Sun, F. Y., Jit, M., O'Reilly, K., Jafari, Y., ... Edmunds, W. J. (2021). Estimating the impact of reopening schools on the reproduction number of SARS-CoV-2 in England, using weekly contact survey data. *BMC Med*, *19*(1), 233. https://doi.org/10.1186/s12916-021-02107-0

Nadeau, S., Beckmann, C., Topolsky, I., Vaughan, T., Hodcroft, E., Schär, T., Nissen, I., Santacroce, N., Burcklen, E., Ferreira, P., Jablonski, K. P., Posada-Céspedes, S., Capece, V., Seidel, S., de Souza, N. S., Martinez-Gomez, J. M., Cheng, P., Bosshard, P. P., Levesque, M. P., ... Stadler, T. (2020). *Quantifying SARS-CoV-2 spread in Switzerland based on genomic sequencing data* (preprint). Epidemiology. https://doi.org/10.1101/2020.10.14.20212621

Neher, R. A., Dyrdak, R., Druelle, V., Hodcroft, E. B., & Albert, J. (2020). Potential impact of seasonal forcing on a SARS-CoV-2 pandemic. *Swiss Med Wkly*. https://doi.org/10.4414/smw.2020.20224

Nelson, C., Lurie, N., Wasserman, J., & Zakowski, S. (2007). Conceptualizing and Defining Public Health Emergency Preparedness. *Am J Public Health*, *97*(Supplement_1), S9–S11. https://doi.org/10.2105/AJPH.2007.114496

OHHLEP, Adisasmito, W. B., Almuhairi, S., Behravesh, C. B., Bilivogui, P., Bukachi, S. A., Casas, N., Cediel Becerra, N., Charron, D. F., Chaudhary, A., Ciacci Zanella, J. R., Cunningham, A. A., Dar, O., Debnath, N., Dungu, B., Farag, E., Gao, G. F., Hayman, D. T. S., Khaitsa, M., ... Zhou, L. (2022). One Health: A new definition for a sustainable and healthy future (J. D. Dvorin, Ed.) [One Health High-Level Expert Panel (OHHLEP)]. *PLoS Pathog*, *18*(6), e1010537. https://doi.org/10.1371/journal.ppat.1010537

Oliu-Barton, M., Pradelski, B. S. R., Woloszko, N., Guetta-Jeanrenaud, L., Aghion, P., Artus, P., Fontanet, A., Martin, P., & Wolff, G. B. (2022). The effect of COVID certificates on vaccine uptake, health outcomes, and the economy. *Nat Commun*, *13*(1), 3942. https://doi.org/10.1038/s41467-022-31394-1

Pal, R., & Bhadada, S. K. (2020). COVID-19 and diabetes mellitus: An unholy interaction of two pandemics. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*, *14*(4), 513–517. https://doi.org/10.1016/j.dsx.2020.04.049

Park, S. W., Champredon, D., Weitz, J. S., & Dushoff, J. (2019). A practical generation-interval-based approach to inferring the strength of epidemics from their speed. *Epidemics*, *27*, 12–18. https://doi.org/10.1016/j.epidem.2018.12.002

Perez-Guzman, P. N., Knock, E., Imai, N., Rawson, T., Elmaci, Y., Alcada, J., Whittles, L. K., Thekke Kanapram, D., Sonabend, R., Gaythorpe, K. A. M., Hinsley, W., FitzJohn, R. G., Volz, E., Verity, R., Ferguson, N. M., Cori, A., & Baguelin, M. (2023). Epidemiological drivers of transmissibility and severity of SARS-CoV-2 in England. *Nat Commun*, *14*(1), 4279. https://doi.org/10.1038/s41467-023-39661-5

Pickering, B., Lung, O., Maguire, F., Kruczkiewicz, P., Kotwa, J. D., Buchanan, T., Gagnier, M., Guthrie, J. L., Jardine, C. M., Marchand-Austin, A., Massé, A., McClinchey, H., Nirmalarajah, K., Aftanas, P., Blais-Savoie, J., Chee, H.-Y., Chien, E., Yim, W., Banete, A., ... Bowman, J. (2022). Divergent SARS-CoV-2 variant emerges

in white-tailed deer with deer-to-human transmission. *Nat Microbiol*, *7*(12), 2011–2024. https://doi.org/10.1038/s41564-022-01268-9

Pleninger, R., Streicher, S., & Sturm, J.-E. (2021). Do COVID-19 Containment Measures Work? Evidence from Switzerland [Publisher: ETH Zurich]. https://doi.org/10.3929/ETHZ-B-000493408

Polack, F. P., Thomas, S. J., Kitchin, N., Absalon, J., Gurtman, A., Lockhart, S., Perez, J. L., Pérez Marc, G., Moreira, E. D., Zerbini, C., Bailey, R., Swanson, K. A., Roychoudhury, S., Koury, K., Li, P., Kalina, W. V., Cooper, D., Frenck, R. W., Hammitt, L. L., … Gruber, W. C. (2020). Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med*, *383*(27), 2603–2615. https://doi.org/10.1056/NEJMoa2034577

Poongavanan, J., Xavier, J., Dunaiski, M., Tegally, H., Oladejo, S. O., Ayorinde, O., Wilkinson, E., Baxter, C., & De Oliveira, T. (2023). Managing and assembling population-scale data streams, tools and workflows to plan for future pandemics within the INFORM-Africa Consortium. *S. Afr. J. Sci*, *119*(5/6). https://doi.org/10.17159/sajs.2023/14659

Pouwels, K. B., Pritchard, E., Matthews, P. C., Stoesser, N., Eyre, D. W., Vihta, K.-D., House, T., Hay, J., Bell, J. I., Newton, J. N., Farrar, J., Crook, D., Cook, D., Rourke, E., Studley, R., Peto, T. E. A., Diamond, I., & Walker, A. S. (2021). Effect of Delta variant on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK. *Nat Med*, *27*(12), 2127–2135. https://doi.org/10.1038/s41591-021-01548-7

Prem, K., Liu, Y., Russell, T. W., Kucharski, A. J., Eggo, R. M., Davies, N., Jit, M., Klepac, P., Flasche, S., Clifford, S., Pearson, C. A. B., Munday, J. D., Abbott, S., Gibbs, H., Rosello, A., Quilty, B. J., Jombart, T., Sun, F., Diamond, C., … Hellewell, J. (2020). The effect of control strategies to reduce social mixing on outcomes of the COVID-19 epidemic in Wuhan, China: A modelling study. *The Lancet Public Health*, *5*(5), e261–e270. https://doi.org/10.1016/S2468-2667(20)30073-6

Prem, K., Zandvoort, K. V., Klepac, P., Eggo, R. M., Davies, N. G., Centre for the Mathematical Modelling of Infectious Diseases COVID-19 Working Group, Cook, A. R., & Jit, M. (2021). Projecting contact matrices in 177 geographical regions: An update and comparison with empirical data for the COVID-19 era. *PLoS Comput Biol*, *17*(7), e1009098. https://doi.org/10.1371/journal.pcbi.1009098

Egger, M., Razum, O., & Rieder, A. (Eds.). (2021). *Public health kompakt* (4th ed.). De Gruyter.

Pulliam, J. R. C., van Schalkwyk, C., Govender, N., von Gottberg, A., Cohen, C., Groome, M. J., Dushoff, J., Mlisana, K., & Moultrie, H. (2022). Increased risk of SARS-CoV-2 reinfection associated with emergence of Omicron in South Africa. *Science*, *376*(6593), eabn4947. https://doi.org/10.1126/science.abn4947

Pung, R., Clapham, H. E., Russell, T. W., CMMID COVID-19 Working Group, Lee, V. J., & Kucharski, A. J. (2023). Relative role of border restrictions, case finding and contact tracing in controlling SARS-CoV-2 in the presence of undetected transmission: A mathematical modelling study. *BMC Med*, *21*(1), 97. https://doi.org/10.1186/s12916-023-02802-0

R Core Team. (2020). *R: A Language and Environment for Statistical Computing*. https://www.R-project.org/

Reichmuth, M. L., Heron, L., Low, N., & Althaus, C. L. (2022a). *Social contacts and attitudes towards vaccination during the COVID-19 pandemic: Insights from the CoMix study.* (tech. rep.).

Reichmuth, M. L., Heron, L., Low, N., & Althaus, C. L. (2023a). *CoMix social contact data for Switzerland (2021-2022)*. https://doi.org/10.5281/ZENODO.10147647

Reichmuth, M. L., Heron, L., Riou, J., Moser, A., Hauser, A., Low, N., & Althaus, C. L. (2023b). Sociodemographic characteristics associated with COVID-19 vaccination uptake in Switzerland: Longitudinal analysis of the CoMix study. *BMC Public Health*, *23*(1), 1523. https://doi.org/10.1186/s12889-023-16405-0

Reichmuth, M. L., Hodcroft, E. B., Riou, J., Neher, R. A., Hens, N., & Althaus, C. L. (2022b). Impact of cross-border-associated cases on the SARS-CoV-2 epidemic in Switzerland during summer 2020 and 2021. *Epidemics*, *41*, 100654. https://doi.org/10.1016/j.epidem.2022.100654

Richard, M., Kok, A., De Meulder, D., Bestebroer, T. M., Lamers, M. M., Okba, N. M. A., Fentener Van Vlissingen, M., Rockx, B., Haagmans, B. L., Koopmans, M. P. G., Fouchier, R. A. M., & Herfst, S. (2020). SARS-CoV-2 is transmitted via contact and via the air between ferrets. *Nat Commun*, *11*(1), 3496. https://doi.org/10.1038/s41467-020-17367-2

Riesen, M., Konstantinoudis, G., Lang, P., Low, N., Hatz, C., Maeusezahl, M., Spaar, A., Bühlmann, M., Spycher, B. D., & Althaus, C. L. (2018). Exploring variation in human papillomavirus vaccination uptake in Switzerland: A multilevel spatial analysis of a national vaccination coverage survey. *BMJ Open*, *8*(5), e021006. https://doi.org/10.1136/bmjopen-2017-021006

Riou, J., & Althaus, C. L. (2020). Pattern of early human-to-human transmission of Wuhan 2019 novel coronavirus (2019-nCoV), December 2019 to January 2020. *Eurosurveillance*, *25*(4). https://doi.org/10.2807/1560-7917.ES.2020.25.4.2000058

Riou, J., Hauser, A., Fesser, A., Althaus, C. L., Egger, M., & Konstantinoudis, G. (2023). Direct and indirect effects of the COVID-19 pandemic on mortality in Switzerland. *Nat Commun*, *14*(1), 90. https://doi.org/10.1038/s41467-022-35770-9

Ritchie, H., Edouard, M., Lucas, R.-G., Appel, C., Giattino, C., Ortiz-Ospina, E., Hasell, J., Macdonald, B., Beltekian, D., & Roser, M. (2020). Coronavirus Pandemic (COVID-19). *Our World in Data*.

Rockett, R. J., Draper, J., Gall, M., Sim, E. M., Arnott, A., Agius, J. E., Johnson-Mackinnon, J., Fong, W., Martinez, E., Drew, A. P., Lee, C., Ngo, C., Ramsperger, M., Ginn, A. N., Wang, Q., Fennell, M., Ko, D., Hueston, L., Kairaitis, L., … Sintchenko, V. (2022). Co-infection with SARS-CoV-2 Omicron and Delta variants revealed by genomic surveillance. *Nat Commun*, *13*(1), 2745. https://doi.org/10.1038/s41467-022-30518-x

Russell, T. W., Wu, J. T., Clifford, S., Edmunds, W. J., Kucharski, A. J., & Jit, M. (2021). Effect of internationally imported cases on internal spread of COVID-19: A mathematical modelling study. *The Lancet Public Health*, *6*(1), e12–e20. https://doi.org/10.1016/S2468-2667(20)30263-2

Sanjuán, R., Nebot, M. R., Chirico, N., Mansky, L. M., & Belshaw, R.

(2010). Viral Mutation Rates. *J Virol*, *84*(19), 9733–9748. https://doi.org/10.1128/JVI.00694-10

Scalia Tomba, G., & Wallinga, J. (2008). A simple explanation for the low impact of border control as a countermeasure to the spread of an infectious disease. *Mathematical Biosciences*, *214*(1-2), 70–72. https://doi.org/10.1016/j.mbs.2008.02.009

Schaffer DeRoo, S., Pudalov, N. J., & Fu, L. Y. (2020). Planning for a COVID-19 Vaccination Program. *JAMA*, *323*(24), 2458. https://doi.org/10.1001/jama.2020.8711

Schleicher, A. (2019). *PISA 2018: Insights and Interpretations* (tech. rep.).

Shearer, F. M., Walker, J., Tellioglu, N., McCaw, J. M., McVernon, J., Black, A., & Geard, N. (2022). Rapid assessment of the risk of SARS-CoV-2 importation: Case study and lessons learned. *Epidemics*, *38*, 100549. https://doi.org/10.1016/j.epidem.2022.100549

Shu, Y., & McCauley, J. (2017). GISAID: Global initiative on sharing all influenza data – from vision to reality. *Eurosurveillance*, *22*(13). https://doi.org/10.2807/1560-7917.ES.2017.22.13.30494

Skjefte, M., Ngirbabul, M., Akeju, O., Escudero, D., Hernandez-Diaz, S., Wyszynski, D. F., & Wu, J. W. (2021). COVID-19 vaccine acceptance among pregnant women and mothers of young children: Results of a survey in 16 countries. *Eur J Epidemiol*, *36*(2), 197–211. https://doi.org/10.1007/s10654-021-00728-6

Smieszek, T., Burri, E. U., Scherzinger, R., & Scholz, R. W. (2012). Collecting close-contact social mixing data with contact diaries: Reporting errors and biases. *Epidemiol. Infect.*, *140*(4), 744–752. https://doi.org/10.1017/S0950268811001130

Smieszek, T. (2009). A mechanistic model of infection: Why duration and intensity of contacts should be included in models of disease spread. *Theor Biol Med Model*, *6*(1), 25. https://doi.org/10.1186/1742-4682-6-25

Somaini, B., Zimmermann, H. P., & Flückiger, H. (1986). Morbiditätserfassung in der Praxis. *Soz Präventivmed*, *31*(1), 37–39. https://doi.org/10.1007/BF02103746

Stadler, T., Kouyos, R., von Wyl, V., Yerly, S., Böni, J., Bürgisser, P., Klimkait, T., Joos, B., Rieder, P., Xie, D., Günthard, H. F., Drummond, A. J., Bonhoeffer, S., & the Swiss HIV Cohort Study. (2012). Estimating the Basic Reproductive Number from Viral Sequence Data. *Molecular Biology and Evolution*, *29*(1), 347–357. https://doi.org/10.1093/molbev/msr217

Stock, S. J., Carruthers, J., Calvert, C., Denny, C., Donaghy, J., Goulding, A., Hopcroft, L. E. M., Hopkins, L., McLaughlin, T., Pan, J., Shi, T., Taylor, B., Agrawal, U., Auyeung, B., Katikireddi, S. V., McCowan, C., Murray, J., Simpson, C. R., Robertson, C., … Wood, R. (2022). SARS-CoV-2 infection and COVID-19 vaccination rates in pregnant women in Scotland. *Nat Med*, *28*(3), 504–512. https://doi.org/10.1038/s41591-021-01666-2

Stringhini, S., Zaballa, M.-E., Pullen, N., Perez-Saez, J., de Mestral, C., Loizeau, A. J., Lamour, J., Pennacchio, F., Wisniak, A., Dumont, R., Baysson, H., Richard, V., Lorthe, E., Semaani, C., Balavoine, J.-F., Pittet, D., Vuilleumier, N., Chappuis, F., Kherad, O., … on behalf of the Specchio-COVID19 study group. (2021a). Seroprevalence of anti-SARS-CoV-2 antibodies 6 months into the vaccination campaign in Geneva, Switzerland, 1 June to 7 July 2021. *Eurosurveillance*, *26*(43). https://doi.org/10.

2807/1560-7917.ES.2021.26.43.2100830

Stringhini, S., Zaballa, M.-E., Pullen, N., Perez-Saez, J., de Mestral, C., Loizeau, A. J., Lamour, J., Pennacchio, F., Wisniak, A., Dumont, R., Baysson, H., Richard, V., Lorthe, E., Semaani, C., Balavoine, J.-F., Pittet, D., Vuilleumier, N., Chappuis, F., Kherad, O., ... on behalf of the Specchio-COVID19 study group. (2021b). Seroprevalence of anti-SARS-CoV-2 antibodies 6 months into the vaccination campaign in Geneva, Switzerland, 1 June to 7 July 2021. *Eurosurveillance*, *26*(43). https://doi.org/10.2807/1560-7917.ES.2021.26.43.2100830

Suchard, M. A., Lemey, P., Baele, G., Ayres, D. L., Drummond, A. J., & Rambaut, A. (2018). Bayesian phylogenetic and phylodynamic data integration using BEAST 1.10. *Virus Evolution*, *4*(1). https://doi.org/10.1093/ve/vey016

Sun, J., Wu, D., & Ke, C. (2017). Molecular phylogenetic analyses of imported Zika virus genomes in China. *The Lancet*, *390*, S36. https://doi.org/10.1016/S0140-6736(17)33174-4

Sun, K., Tempia, S., Kleynhans, J., Von Gottberg, A., McMorrow, M. L., Wolter, N., Bhiman, J. N., Moyes, J., Carrim, M., Martinson, N. A., Kahn, K., Lebina, L., Du Toit, J. D., Mkhencele, T., Viboud, C., Cohen, C., the PHIRST-C group, Buys, A., De Gouveia, L., ... Wafawanaka, F. (2023). Rapidly shifting immunologic landscape and severity of SARS-CoV-2 in the Omicron era in South Africa. *Nat Commun*, *14*(1), 246. https://doi.org/10.1038/s41467-022-35652-0

Suzuki, R., Yamasoba, D., Kimura, I., Wang, L., Kishimoto, M., Ito, J., Morioka, Y., Nao, N., Nasser, H., Uriu, K., Kosugi, Y., Tsuda, M., Orba, Y., Sasaki, M., Shimizu, R., Kawabata, R., Yoshimatsu, K., Asakura, H., Nagashima, M., ... Sato, K. (2022). Attenuated fusogenicity and pathogenicity of SARS-CoV-2 Omicron variant. *Nature*, *603*(7902), 700–705. https://doi.org/10.1038/s41586-022-04462-1

Tan, S. T., Kwan, A. T., Rodríguez-Barraquer, I., Singer, B. J., Park, H. J., Lewnard, J. A., Sears, D., & Lo, N. C. (2023). Infectiousness of SARS-CoV-2 breakthrough infections and reinfections during the Omicron wave. *Nat Med*, *29*(2), 358–365. https://doi.org/10.1038/s41591-022-02138-x

Tancredi, S., Chiolero, A., Wagner, C., Haller, M. L., Chocano-Bedoya, P., Ortega, N., Rodondi, N., Kaufmann, L., Lorthe, E., Baysson, H., Stringhini, S., Michel, G., Lüdi, C., Harju, E., Frank, I., Imboden, M., Witzig, M., Keidel, D., Probst-Hensch, N., ... Zuppinger, C. (2023). Seroprevalence trends of anti-SARS-CoV-2 antibodies and associated risk factors: A population-based study. *Infection*, *51*(5), 1453–1465. https://doi.org/10.1007/s15010-023-02011-0

Taube, J. C., Miller, P. B., & Drake, J. M. (2021). *An open-access database of infectious disease transmission trees to explore superspreader epidemiology* (preprint). Infectious Diseases (except HIV/AIDS). https://doi.org/10.1101/2021.01.11.21249622

Tayoun, A. A., Loney, T., Khansaheb, H., Ramaswamy, S., Harilal, D., Deesi, Z. O., Varghese, R. M., Al Suwaidi, H., Alkhajeh, A., AlDabal, L. M., Uddin, M., Hamoudi, R., Halwani, R., Senok, A., Hamid, Q., Nowotny, N., & Alsheikh-Ali, A. (2020). Multiple early introductions of SARS-CoV-2 into a global travel hub in the Middle East. *Sci Rep*, *10*(1),

17720. https://doi.org/10.1038/s41598-020-74666-w

Tegally, H., Wilkinson, E., Lessells, R. J., Giandhari, J., Pillay, S., Msomi, N., Mlisana, K., Bhiman, J. N., von Gottberg, A., Walaza, S., Fonseca, V., Allam, M., Ismail, A., Glass, A. J., Engelbrecht, S., Van Zyl, G., Preiser, W., Williamson, C., Petruccione, F., ... de Oliveira, T. (2021). Sixteen novel lineages of SARS-CoV-2 in South Africa. *Nat Med*, *27*(3), 440–446. https://doi.org/10.1038/s41591-021-01255-3

Tegally, H., Wilkinson, E., Tsui, J. L. H., Moir, M., Martin, D., Brito, A. F., Giovanetti, M., Khan, K., Huber, C., Bogoch, I. I., San, J. E., Poongavanan, J., Xavier, J. S., Candido, D. D. S., Romero, F., Baxter, C., Pybus, O. G., Lessells, R. J., Faria, N. R., ... De Oliveira, T. (2023). Dispersal patterns and influence of air travel during the global expansion of SARS-CoV-2 variants of concern. *Cell*, *186*(15), 3277–3290.e16. https://doi.org/10.1016/j.cell.2023.06.001

Terry, E., Cartledge, S., Damery, S., & Greenfield, S. (2022). Factors associated with COVID-19 vaccine intentions during the COVID-19 pandemic; a systematic review and meta-analysis of cross-sectional studies. *BMC Public Health*, *22*(1), 1667. https://doi.org/10.1186/s12889-022-14029-4

The Academy of Medical Sciences. (2016). *Improving the health of the public by 2040: Optimising the Research Environment for a Healthier, Fairer Future* (tech. rep.). London, UK.

Tomori, D. V., Rübsamen, N., Berger, T., Scholz, S., Walde, J., Wittenberg, I., Lange, B., Kuhlmann, A., Horn, J., Mikolajczyk, R., Jaeger, V. K., & Karch, A. (2021). Individual social contact data and population mobility data as early markers of SARS-CoV-2 transmission dynamics during the first wave in Germany—an analysis based on the COVIMOD study. *BMC Med*, *19*(1), 271. https://doi.org/10.1186/s12916-021-02139-6

Tsui, J. L.-H., McCrone, J. T., Lambert, B., Bajaj, S., Inward, R. P. D., Bosetti, P., Pena, R. E., Tegally, H., Hill, V., Zarebski, A. E., Peacock, T. P., Liu, L., Wu, N., Davis, M., Bogoch, I. I., Khan, K., Kall, M., Abdul Aziz, N. I. B., Colquhoun, R., ... Kraemer, M. U. G. (2023). Genomic assessment of invasion dynamics of SARS-CoV-2 Omicron BA.1. *Science*, *381*(6655), 336–343. https://doi.org/10.1126/science.adg6605

Turakhia, Y., De Maio, N., Thornlow, B., Gozashti, L., Lanfear, R., Walker, C. R., Hinrichs, A. S., Fernandes, J. D., Borges, R., Slodkowicz, G., Weilguny, L., Haussler, D., Goldman, N., & Corbett-Detig, R. (2020). Stability of SARS-CoV-2 phylogenies (G. S. Barsh, Ed.). *PLOS Genetics*, *16*(11), e1009175. https://doi.org/10.1371/journal.pgen.1009175

UNAIDS. (2022). *Global HIV & AIDS statistics — Fact sheet* [The Joint United Nations Programme on HIV/AIDS (UNAIDS)]. https://www.unaids.org/en/resources/fact-sheet

Vaidyanathan, G. (2021). Coronavirus variants are spreading in India — what scientists know so far. *Nature*, *593*(7859), 321–322. https://doi.org/10.1038/d41586-021-01274-7

Van Kerkhove, M. D., Ryan, M. J., & Ghebreyesus, T. A. (2021). Preparing for "Disease X". *Science*, *374*(6566), 377–377. https://doi.org/10.1126/science.abm7796

Van Seventer, J. M., & Hochberg, N. S. (2017). Principles of Infectious

Diseases: Transmission, Diagnosis, Prevention, and Control. *International Encyclopedia of Public Health* (pp. 22–39). Elsevier. https://doi.org/10.1016/B978-0-12-803678-5.00516-6

Vandenbroucke, J. P. (2007). Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and Elaboration. *Ann Intern Med*, *147*(8), W. https://doi.org/10.7326/0003-4819-147-8-200710160-00010-w1

Verelst, F., Hermans, L., Vercruysse, S., Gimma, A., Coletti, P., Backer, J. A., Wong, K. L. M., Wambua, J., van Zandvoort, K., Willem, L., Bogaardt, L., Faes, C., Jarvis, C. I., Wallinga, J., Edmunds, W. J., Beutels, P., & Hens, N. (2021). SOCRATES-CoMix: A platform for timely and open-source contact mixing data during and in between COVID-19 surges and interventions in over 20 European countries. *BMC Med*, *19*(1), 254. https://doi.org/10.1186/s12916-021-02133-y

Viana, R., Moyo, S., Amoako, D. G., Tegally, H., Scheepers, C., Althaus, C. L., Anyaneji, U. J., Bester, P. A., Boni, M. F., Chand, M., Choga, W. T., Colquhoun, R., Davids, M., Deforche, K., Doolabh, D., du Plessis, L., Engelbrecht, S., Everatt, J., Giandhari, J., … de Oliveira, T. (2022). Rapid epidemic expansion of the SARS-CoV-2 Omicron variant in southern Africa. *Nature*, *603*(7902), 679–686. https://doi.org/10.1038/s41586-022-04411-y

Villabona-Arenas, C. J., Hanage, W. P., & Tully, D. C. (2020). Phylogenetic interpretation during outbreaks requires caution. *Nat Microbiol*, *5*(7), 876–877. https://doi.org/10.1038/s41564-020-0738-5

Viner, R. M., Mytton, O. T., Bonell, C., Melendez-Torres, G. J., Ward, J., Hudson, L., Waddington, C., Thomas, J., Russell, S., Van Der Klis, F., Koirala, A., Ladhani, S., Panovska-Griffiths, J., Davies, N. G., Booy, R., & Eggo, R. M. (2021). Susceptibility to SARS-CoV-2 Infection Among Children and Adolescents Compared With Adults: A Systematic Review and Meta-analysis. *JAMA Pediatr*, *175*(2), 143. https://doi.org/10.1001/jamapediatrics.2020.4573

Volz, E., Mishra, S., Chand, M., Barrett, J. C., Johnson, R., Geidelberg, L., Hinsley, W. R., Laydon, D. J., Dabrera, G., O'Toole, Á., Amato, R., Ragonnet-Cronin, M., Harrison, I., Jackson, B., Ariani, C. V., Boyd, O., Loman, N. J., McCrone, J. T., Gonçalves, S., … Ferguson, N. M. (2021). Assessing transmissibility of SARS-CoV-2 lineage B.1.1.7 in England. *Nature*, *593*(7858), 266–269. https://doi.org/10.1038/s41586-021-03470-x

Volz, E. M., Koelle, K., & Bedford, T. (2013). Viral Phylodynamics (S. Wodak, Ed.). *PLoS Comput Biol*, *9*(3), e1002947. https://doi.org/10.1371/journal.pcbi.1002947

Volz, E. M., Romero-Severson, E., & Leitner, T. (2017). Phylodynamic Inference across Epidemic Scales. *Molecular Biology and Evolution*, *34*(5), 1276–1288. https://doi.org/10.1093/molbev/msx077

Wallinga, J., & Lipsitch, M. (2007). How generation intervals shape the relationship between growth rates and reproductive numbers. *Proc. R. Soc. B.*, *274*(1609), 599–604. https://doi.org/10.1098/rspb.2006.3754

Wallinga, J., Teunis, P., & Kretzschmar, M. (2006). Using Data on Social Contacts to Estimate Age-specific Transmission Parameters for Respiratory-spread Infectious Agents. *American Journal of Epidemiology*, *164*(10), 936–944. https://doi.org/10.1093/aje/kwj317

Ward, T., & Johnsen, A. (2021). Understanding an evolving pandemic: An analysis of the clinical time delay distributions of COVID-19 in the United Kingdom (P. Mitra, Ed.). *PLoS ONE*, *16*(10), e0257978. https://doi.org/10.1371/journal.pone.0257978

Wegehaupt, O., Endo, A., & Vassall, A. (2023). Superspreading, overdispersion and their implications in the SARS-CoV-2 (COVID-19) pandemic: A systematic review and meta-analysis of the literature. *BMC Public Health*, *23*(1), 1003. https://doi.org/10.1186/s12889-023-15915-1

Weitkunat, R., Junker, C., Caviezel, S., & Fehst, K. (2021). Mortality monitoring in Switzerland. *Swiss Med Wkly*, *151*(3738), w30030. https://doi.org/10.4414/SMW.2021.w30030

WHO. (2003). *Consensus document on the epidemiology of severe acute respiratory syndrome (SARS)* (tech. rep.) [Geneva: World Health Organization].

WHO. (2014). *Strategies for addressing vaccine hesitancy– A systematic review* (tech. rep.) [SAGE working group dealing with vaccine hesitancy].

WHO. (2020a). *10 global health issues to track in 2021*. https://www.who.int/news-room/spotlight/10-global-health-issues-to-track-in-2021

WHO. (2020b). *Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV)* [Geneva: World Health Organization]. Retrieved October 10, 2023, from https://www.who.int/news-room/detail/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov)

WHO. (2023a). *Immunization, Vaccines and Biologicals* [Geneva: World Health Organization]. Retrieved August 6, 2023, from https://www.who.int/teams/immunization-vaccines-and-biologicals

WHO. (2023b). *Tracking SARS-CoV-2 variants* [Geneva: World Health Organization]. Retrieved August 6, 2023, from https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/

WHO. (2023c). *WHO COVID-19 Dashboard* [Geneva: World Health Organization]. Retrieved August 6, 2023, from https://covid19.who.int/

Wiemken, T. L., Khan, F., Puzniak, L., Yang, W., Simmering, J., Polgreen, P., Nguyen, J. L., Jodar, L., & McLaughlin, J. M. (2023). Seasonal trends in COVID-19 cases, hospitalizations, and mortality in the United States and Europe. *Sci Rep*, *13*(1), 3886. https://doi.org/10.1038/s41598-023-31057-1

Wilder-Smith, A. (2022). What is the vaccine effect on reducing transmission in the context of the SARS-CoV-2 delta variant? *The Lancet Infectious Diseases*, *22*(2), 152–153. https://doi.org/10.1016/S1473-3099(21)00690-3

Wilkinson, S. A. J., Richter, A., Casey, A., Osman, H., Mirza, J. D., Stockton, J., Quick, J., Ratcliffe, L., Sparks, N., Cumley, N., Poplawski, R., Nicholls, S. N., Kele, B., Harris, K., Peacock, T. P., & Loman, N. J. (2022). Recurrent SARS-CoV-2 mutations in immunodeficient patients. *Virus Evolution*, *8*(2), veac050. https://doi.org/10.1093/ve/veac050

Wise, J. (2020). Covid-19: New coronavirus variant is identified in UK. *BMJ*, m4857. https://doi.org/10.1136/bmj.m4857

Wong, K. L. M., Gimma, A., Coletti, P., CoMix Europe Working Group, Paolotti, D., Tizzani, M., Cattuto, C., Schmidt, A., Gredinger, G., Stumpfl, S., Baruch, J., Melillo, T., Hudeckova, H., Zibolenova, J., Chladna, Z., Rosinska, M., Niedzwiedzka-Stadnik, M., Fischer, K., Vorobjov, S., … Jarvis, C. I. (2023). Social contact patterns during the COVID-19 pandemic in 21 European countries – evidence from a two-year study. *BMC Infect Dis*, *23*(1), 268. https://doi.org/10.1186/s12879-023-08214-y

Wong, K. L. M., Gimma, A., Paixao, E. S., CoMix Europe Working Group, Paolotti, D., Karch, A., Jäger, V., Baruch, J., Melillo, T., Hudeckova, H., Rosinska, M., Niedzwiedzka-Stadnik, M., Fischer, K., Vorobjov, S., Sõnajalg, H., Althaus, C., Low, N., Reichmuth, M., Auranen, K., … Edmunds, W. J. (2022). Pregnancy during COVID-19: Social contact patterns and vaccine coverage of pregnant women from CoMix in 19 European countries. *BMC Pregnancy Childbirth*, *22*(1), 757. https://doi.org/10.1186/s12884-022-05076-1

Woolhouse, M. E. J., Dye, C., Etard, J.-F., Smith, T., Charlwood, J. D., Garnett, G. P., Hagan, P., Hii, J. L. K., Ndhlovu, P. D., Quinnell, R. J., Watts, C. H., Chandiwana, S. K., & Anderson, R. M. (1997). Heterogeneities in the transmission of infectious agents: Implications for the design of control programs. *Proc. Natl. Acad. Sci. U.S.A.*, *94*(1), 338–342. https://doi.org/10.1073/pnas.94.1.338

Worobey, M., Pekar, J., Larsen, B. B., Nelson, M. I., Hill, V., Joy, J. B., Rambaut, A., Suchard, M. A., Wertheim, J. O., & Lemey, P. (2020). The emergence of SARS-CoV-2 in Europe and North America. *Science*, *370*(6516), 564–570. https://doi.org/10.1126/science.abc8169

Wu, F., Zhao, S., Yu, B., Chen, Y.-M., Wang, W., Song, Z.-G., Hu, Y., Tao, Z.-W., Tian, J.-H., Pei, Y.-Y., Yuan, M.-L., Zhang, Y.-L., Dai, F.-H., Liu, Y., Wang, Q.-M., Zheng, J.-J., Xu, L., Holmes, E. C., & Zhang, Y.-Z. (2020). A new coronavirus associated with human respiratory disease in China. *Nature*, *579*(7798), 265–269. https://doi.org/10.1038/s41586-020-2008-3

Zhang, J., Litvinova, M., Wang, W., Wang, Y., Deng, X., Chen, X., Li, M., Zheng, W., Yi, L., Chen, X., Wu, Q., Liang, Y., Wang, X., Yang, J., Sun, K., Longini, I. M., Halloran, M. E., Wu, P., Cowling, B. J., … Yu, H. (2020). Evolving epidemiology and transmission dynamics of coronavirus disease 2019 outside Hubei province, China: A descriptive and modelling study. *The Lancet Infectious Diseases*, *20*(7), 793–802. https://doi.org/10.1016/S1473-3099(20)30230-9

Zhao, C., Tepekule, B., Criscuolo, N. G., Wendel Garcia, P. D., Hilty, M. P., Risc-19-Icu Investigators For Switzerland, Fumeaux, T., & Van Boeckel, T. P. (2020). Icumonitoring.ch: A platform for short-term forecasting of intensive care unit occupancy during the COVID-19 epidemic in Switzerland. *Swiss Med Wkly*, *150*(1920), w20277. https://doi.org/10.4414/smw.2020.20277

Zuma, K., Simbayi, L., Zungu, N., Moyo, S., Marinda, E., Jooste, S., North, A., Nadol, P., Aynalem, G., Igumbor, E., Dietrich, C., Sigida, S., Chibi, B., Makola, L., Kondlo, L., Porter, S., Ramlagan, S., & on behalf of the SABSSM V Study Group Contributors. (2022). The HIV Epidemic in South Africa: Key Findings from 2017 National Population-Based Survey. *IJERPH*, *19*(13), 8125. https://doi.org/10.3390/ijerph19138125

List of publications

- **Reichmuth, ML.**, Heron, L., Hens, N., Beutels, P., Low, N., Althaus, CL., (2024). Social contacts in Switzerland during the COVID-19 pandemic: insights from the CoMix study. *under review*.
- **Reichmuth, ML.**, Hodcroft, EB., Althaus, CL., 2023. Importation of Alpha and Delta variants during the SARS-CoV-2 epidemic in Switzerland: phylogenetic analysis and intervention scenario. *PLOS Pathogens*.
- **Reichmuth, ML.**, Heron, L., Riou, J., Moser, A., Hauser, A., Low, N., Althaus, CL., (2023). Importation of Alpha and Delta variants during the SARS-CoV-2 epidemic in Switzerland: phylogenetic analysis and intervention scenario. *BMC Public Health*.
- **Reichmuth, ML.**, Hodcroft, EB., Riou, J., Neher, RA., Hens, N., Althaus, CL., (2022). Impact of cross-border-associated cases on the SARS-CoV-2 epidemic in Switzerland during summer 2020 and 2021. *Epidemics*.
- Zürcher, K., Dupont, C., Weber, P., Grunt S., Wilhelm, I., Eigenmann, DE., **Reichmuth, ML.**, Fenner, L. (2022). Use and caregiver-reported efficacy of medical cannabis in children and adolescents in Switzerland. *European Journal of Pediatrics*.
- Hauser, A., Goldstein, F, **Reichmuth, ML.**, Kouyos, RD., Wandeler, G., Egger, M., Riou, J. (2022). Acquired HIV drug resistance mutations on first-line antiretroviral therapy in Southern Africa: Systematic review and Bayesian evidence synthesis. *Journal of Clinical Epidemiology*.
- Althaus, CL., Baggio, S., **Reichmuth, ML.**, Hodcroft, E. B., Riou, J., Neher, RA, . . . Eckerle, I. (2021). A tale of two variants: Spread of SARS-CoV-2 variants Alpha in Geneva, Switzerland, and Beta in South Africa. *medrxiv*.
- Hodcroft, EB, Zuber, M., Nadeau, S., Vaughan, TG, Crawford, KHD., Althaus, CL., **Reichmuth, ML.**, . . . Neher, RA (2021). Spread of a SARS-CoV-2 variant through Europe in the summer of 2020. *Nature*.
- **Reichmuth, ML.**, Zürcher, K., Ballif, M., Loiseau, C., Borrell, S., Reinhard, M., . . . Egger, M. (2021). Mortality from drug-resistant tuberculosis in high-burden countries comparing routine drug susceptibility testing with whole-genome sequencing: A multicentre cohort study. *The Lancet Microbe*.
- **Reichmuth, ML.**, Chaudron, S., Bachmann, N., Nguyen, H., Böni, J., Metzner, K., . . . the Swiss HIV Cohort Study. (2020). Using longitudinally sampled viral nucleotide sequences to characterize the drivers of HIV-1 transmission. *HIV Medicine*.
- **Reichmuth, ML.**, Hömke, R., Zürcher, K., Sander, P., Avihingsanon, A., Collantes, J., . . . Keller, P. M. (2020). Natural polymorphisms in Mycobacterium tuberculosis conferring resistance to delamanid in drug-naive patients. *Antimicrobial Agents and Chemotherapy*.

Declaration of Originality

Last name, first name: Reichmuth, Martina

Matriculation number: XX-XXX-XXX

I hereby declare that this thesis represents my original work and that I have used no other sources except as noted by citations.
All data, tables, figures and text citations which have been reproduced from any other source, including the internet, have been explicitly acknowledged as such.
I am aware that in case of non-compliance, the Senate is entitled to withdraw the doctorate degree awarded to me on the basis of the present thesis, in accordance with the "Statut der Universität Bern (Universitätsstatut; UniSt)", Art. 69, of 7 June 2011.

Bern, February 24, 2024

Martina Reichmuth