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Evaluation of the number of people affected by post COVID-19 condition in Switzerland in 2023

Final report

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Summary

Since the early stages of the pandemic, it has been clear that the health consequences of SARS-CoV-2 infection are not restricted to the acute phase of coronavirus disease 2019 (COVID-19). Patients have reported symptoms lasting for months after infection. These symptoms have been called collectively with terms such as "long COVID" and "post COVID condition". According to the World Health Organization (WHO) definition released in 2021, post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually three months from the onset of COVID-19 with symptoms that last for at least two months and cannot be explained by an alternative diagnosis.

The estimation of the true burden of post COVID-19 condition in the population is challenging for various reasons, including the use of different definitions, the broad range of symptoms affecting multiple systems of the body, and the uncertainty about the history of past SARS-CoV-2 infections especially at present when testing is no longer frequent. To estimate the prevalence and burden of post COVID-19 condition in Switzerland, the Federal Office of Public Health (FOPH) mandated our group to perform an analysis combining literature searchers with mathematical modelling. We used a previously developed mathematical model of SARS-CoV-2 transmission and COVID-19 disease progression and complemented it with a module estimating the incidence and prevalence of post COVID-19 condition. The condition was divided into three main symptom groups: fatigue, neuropsychiatric disorders, and cardiopulmonary disorders. The transmission model was calibrated against the number of hospitalizations due to acute COVID-19. Estimates from the literature were used to parameterize the post COVID-19 module. We modelled a range of scenarios to reflect the uncertainty around the model inputs.

Because of the scarce availability and heterogeneity in evidence and definitions, providing a precise estimate of the true burden of post COVID-19 is unfeasible. Our results are based on a mechanistic representation of the SARS-CoV-2 transmission, a calculation of the expected cases that lead to different long-term symptoms based on the literature, and a comparison of the findings with estimates from other settings. The results are influenced by a large number of contributing factors, and consequently we ran multiple scenarios with different parameter values to gain a plausible range of the values instead of attempting to give a precise estimate. Estimates from the literature have suggested that about 2% to 4% of the overall population are affected by post COVID-19 condition, and that symptoms can persist for months or years. Our mechanistic modelling of the epidemic provided results that are in line with the literature findings, suggesting a prevalence of at least 2%, likely higher. Due to the high uncertainty associated with the available data, up to 10-fold differences in the results were observed. The relatively coherent findings between the existing literature and our modelling exercise provide helpful insights about the magnitude of the burden, but further evidence will be needed to confirm the validity of these findings.

1. Introduction

1.1 Post COVID-19 condition: background and definition

The first cases of Coronavirus disease 2019 (COVID-19) were observed in December 2019, and after only three months the situation had rapidly escalated into a global pandemic. In Switzerland, the first confirmed cases of infection with SARS-CoV-2, the pathogen causing COVID-19 disease, were reported on 25th February 2020. In mid-March 2020, a series of unprecedented restrictions on public life, including the closure of schools and non-essential shops and venues as well as strict restrictions on public gathering, were imposed by the Federal Council. For the subsequent two years, at least some level of mitigation measures were in place constantly, and to date COVID-19 has been estimated to have caused at least 14,000 deaths in Switzerland.[1]

In the early stages of the epidemic, the literature tended to distinguish between the (relatively rare) severe courses of COVID-19 versus the more common, mild or even asymptomatic course of SARS-CoV-2 infection. It however became apparent that some patients with mild symptoms during the acute infection reported complications weeks after the onset of infection, questioning the claim that for most people SARS-CoV-2 would be a harmless, self-limiting disease. The term “long COVID” was first time used in May 2020 on a Twitter message by a physician reflecting her personal experience.[2] The term came rapidly into broad use also among national and international health authorities. Nevertheless, in the early epidemic, because of the lack of long-term data and the multitude of symptoms and manifestations, the term remained mainly colloquial, describing the presence of long-term symptoms without any strict definition.

In October 2021, the World Health Organization (WHO) released a formal definition of *post COVID-19 condition* as “a condition that occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis.”[3] Alternative definitions also exist, suggested both by national or international health authorities and individual research groups. For example, the US Centers for Disease Control and Prevention (CDC) and the National Institute for Health and Care Excellence (NICE) define long COVID as symptoms that may occur already 4 weeks after acute COVID-19.[4,5] In this report, we will consistently use the term *post COVID-19 condition* and the WHO definition, although because of the various terms and definitions used in the literature the estimates adapted to parameterize our model may not always exactly match this definition.

Most existing definitions of post COVID-19 condition do not specify the types of syndromes or symptoms, meaning that the condition can in principle manifest with any type of symptoms, as long as the likely cause is in the past acute COVID-19 disease or SARS-CoV-2 infection. This brings additional challenges to the monitoring, management, and treatment of the condition. The definition is based on the pathogen, but only a fraction of the SARS-CoV-2 infections have been confirmed during the acute infection, so for most cases the diagnosis must be done by exclusion, i.e. excluding other possible causes of the symptoms. The commonly mentioned symptoms range from fatigue and depression to pain and cardiovascular manifestations, which are common sequelae of a number of diseases and conditions. In August 2023, the university hospitals of Bern and Geneva released recommendations for the treatment of post COVID-19 condition, which are based on nine common symptoms.[6] However, there exists so far no treatment for the condition itself.

Because of the challenges in the diagnosis of post COVID-19 condition, it is also very challenging to obtain reliable data on the incidence and prevalence, and the true burden of the condition is thus subject to high uncertainty. To estimate the prevalence and associated health burden of post COVID-19 condition in Switzerland, the Federal Office of Public Health (FOPH) commissioned us to perform this analysis that attempts to provide these estimates using mathematical modelling combined with literature data. The present final report will give a broad overview to this attempt, covering the starting position, the literature searches performed, the quantitative tools developed, an estimation of the disease burden, and an interpretation of the findings.

1.2 Specific objectives

This project has the following aims and objectives:

1) To rigorously evaluate the existing evidence on the frequency of post COVID-19 condition in the Swiss context
2) To estimate the prevalence and incidence of post COVID-19 condition in Switzerland in year 2023 among children and adolescents, adults, and elderly people

2. Initial situation and approaches to estimating the burden of post COVID-19 condition

The estimation of the true burden of post COVID-19 condition is challenging. Although the condition has now an officially recognized definition from WHO,[3] the concept is still very broad, and both the pathogen and manifestation are influenced by a number of complicating factors. First, the underlying pathogen – SARS-CoV-2 – has been circulating extensively in the population, and after the acute pandemic phase the infections are no longer well documented. Although the definition of post COVID-19 condition does not formally require the confirmation of a previous SARs-CoV-2 infection, the fact that the testing strategy and protective behaviour have changed has made it even more challenging to associate the long-term symptoms with the infection, especially if the course of the disease in the acute stage was mild. The definition of post COVID-19 condition includes also a heterogeneous spectrum of symptoms of various disease systems. Many of the symptoms like fatigue are also very common for other conditions.

The ideal method for data collection of investigating the prevalence of a disease would be to conduct a large-scale representative survey in the general population. In the case of post COVID-19, a cross-sectional survey would not be sufficient since it would be extremely difficult to identify whether any possible symptoms are consequences of COVID-19 or something else. A cross-sectional survey also cannot provide insights about the trends, for example whether the prevalence is decreasing or increasing, or how it is expected to continue. A prospective cohort study with regular follow up including SARS-CoV-2 tests and questionnaires about various symptoms would thus be necessary. Such a study would require massive resources and a long follow-up duration, meaning that it is not often feasible in practice. Although some cohort studies have also been conducted in Switzerland, their approach and coverage are not comprehensive enough to allow extrapolation to the entire population.[7,8] It is therefore justified to use model-based calculation methods together with available primary evidence to indirectly estimate the burden in Switzerland.

Mathematical modelling offers an efficient way to explore the epidemic indicators of communicable diseases when data sources are scarce and heterogeneous. Models can integrate background information, assumptions and parameters from various sources, and make projections that reflect the most likely status of the situation, including an estimation of the uncertainty around the findings. The uncertainty however increases with complexity, and model complexity in turn depends on the availability of the information (**Figure 1**). Should we have a reliable estimation of the underlying SARS-CoV-2 epidemic with regular and complete data, a mechanistic transmission model is not necessary and the post COVID-19 prevalence can be calculated directly using the past infections and research findings about the probability. If the data on infections is incomplete but the transmission process is expected to be fairly simple (e.g. stable contact patterns, limited reinfection probability, no or few vaccinations), a mechanistic model for the transmission dynamics is necessary but can be expected to be fairly robust since the number of free parameters is limited. However, in the case of COVID-19 in the post-pandemic era, none of these conditions is true. Therefore, modelling the underlying transmission is necessary but comes with large uncertainty.

Based on the above considerations, we acknowledge the fact that providing a precise estimate, even with uncertainty bounds, is not feasible. We will nevertheless aim to conduct a comprehensive evaluation of the situation using a range of assumptions, make plausibility checks where possible, and use this information to provide an estimate of the expected magnitude of the true burden in year 2023. The project was performed in three steps. First, we conducted a literature review to enhance the knowledge about post COVID-19 condition and identify adequate sources for quantitative estimates (Section **3.** Literature review). Partly in parallel, we developed a mathematical modelling tool by expanding an existing model (Section **4.** Mathematical model: methodology, structure and parameterization). Finally, the model was parameterized and ran to provide the desired estimates (Section **4.3.2** Results).

3. Literature review

3.1 Overview of the literature search aim and methods

The purposes of the literature review were to 1) gain thorough understanding of post COVID-19 condition including the definition, main manifestations, course, and determinants; and 2) to find quantitative values to parameterize the model. We started the review of the evidence by familiarizing ourselves with the post COVID-19 condition by reading the latest literature review commissioned by the FOPH[9] and identifying the main sources of data as well as research gaps and uncertainties that remain in this emerging field of research. The initial overview provoked a further study and reconciliation of contemporary data from the recent findings and publications. However, it is worth noting that we did not follow a systematic search strategy: we aimed to identify studies with large sample sizes, clear definitions, and that were completed recently in Switzerland or similar settings, but did not attempt to systematically synthesize all available evidence.

3.2 Key findings of the literature search

3.2.1 Definition of post COVID-19 condition

The WHO defines post COVID-19 condition as “occurring in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis.[3] **In this project, we decided to use the simplified dichotomization between “acute COVID-19” and “post COVID-19 condition”.** The former means the period following the infection immediately, which may either lead to recovery (often within a few days) or be prolonged through severe symptoms or hospitalization up to 3 months. By the latter, we cover (i) the time from 3 months since infection among patients who did not recover by then, or (ii) patients with new symptoms or conditions with onset after recovery since the time of their appearance (within 3 months of infection).

3.2.2 Symptoms and their categorization

Post COVID-19 condition manifests through a broad range of symptoms. Common symptoms in adults according to the WHO clinical case definition include, amongst others, fatigue, shortness of breath, and cognitive dysfunction.[3] In children, fatigue, altered smell/anosmia and anxiety are frequent.[10]

The Global Burden of Disease (GBD) study considered three syndromes: ongoing respiratory problems; cognitive problems; and persistent fatigue with bodily pain or mood swings.[11] Other studies and reviews have also identified typical symptom clusters. In a study of nearly 10,000 Americans, who had undergone either a confirmed or suspected COVID-19, researchers identified 12 symptoms that most set apart those with and without long COVID: post-exertional malaise, fatigue, brain fog, dizziness, gastrointestinal symptoms, heart palpitations, issues with sexual desire or capacity, loss of smell or taste, thirst, chronic cough, chest pain, and abnormal movements.[12] A review by Nalbandian *et al* classified the symptoms according to the organ systems into pulmonary, hematologic, cardiovascular, neuropsychiatric, renal, endocrine, gastrointestinal/hepatobiliary and dermatologic, as well as multisystem inflammatory syndrome in children (MIS-C).[13]

The recently released treatment guidance from Switzerland also mentioned nine different typical syndromes that are partly aligned with those proposed by Nalbandian *et al*: fatigue and post-exertional malaise; cognitive disorders; headaches; sleep disorders; psychiatric disorders; pain and paresthesia; dizziness; tinnitus; loss of taste or smell; dyspnea; cough and loss or change in voice; dermatological disorders; visual disorders; gastrointestinal disorders; and fever.[6]

These classifications are not mutually exclusive and may overlap in some cases. **We decided to adapt the categorization into the three groups of fatigue/malaise, neuropsychiatric symptoms, and cardiopulmonary symptoms.** This categorization reflects the most common types of symptoms while keeping the number of categories sufficiently simple. This is also in line, although not strictly corresponding, to the categorization used by the GBD study.[11]

3.2.3 Risk of post COVID-19 condition

The risk of post COVID-19 condition is not well established, as the definitions, methods and populations to measure it differ greatly between studies and estimations. In the population-based cohort studies available so far, the proportion of SARS-CoV-2 infected individuals with post COVID-19 defining symptoms has been estimated between 6% and 17%.[11,14,15]

A study of over 273,000 COVID-19 survivors by Taquet *et al* found that 57.0% had one or more long-COVID feature recorded during the whole 6-month period (i.e., including the acute phase), and 36.6% between 3 and 6 months.[16] The study provided also estimates on specific symptoms (breathing difficulties/breathlessness, fatigue/malaise, chest/throat pain, headache, abdominal symptoms, myalgia, other pain, cognitive symptoms, and anxiety/depression).

In a more recent study, the Long COVID Global Burden of Disease (GBD) Report found that out of 1.2 million individuals who showed symptoms of SARS-CoV-2 infection across 22 countries, 6.2% experienced persistent symptoms three months after the acute infection.[11] In Europe, a study published in December 2022 reported that more than 17 million people across the WHO European Region may have experienced Long COVID during the first two years of the pandemic (2020/21), based on surveys and modelling.[17]

The few existing population-based studies include an analysis from the United Kingdom by Bosworth and colleagues. In contrast to most other studies that were based on patients previously tested and confirmed for having COVID-19, Bosworth *et al* used population-based sample regularly for SARS-

CoV-2 infection including a regular long-term follow-up, which made it possible to assess the situation in a representative sample of all previously infected individuals regardless of the severity and testing policy.[18] The risks of Long COVID (self-reported, between 12 and 20 weeks) were 4.0% among adults and 1.6% among children aged <16 weeks.

Estimates of the risk of post COVID-19 condition are also available from Switzerland. A study based on the Zürich SARS-CoV-2 cohort recruited participants through the mandatory notifications.[7] Slightly more than half (55.3%) of the participants reported returning to the normal health status within one month of the infection, and 27.1% of the participants had not recovered within 3 months, corresponding with the WHO definition of post COVID-19 condition. At 6 months, 22.9% were still affected by symptoms, while in the measurements at 12, 18 and 24 months, the proportion fluctuated around 18% without a clear decreasing trend. For children, Dumont *et al* from the SEROCoV-KIDS study estimated an adjusted prevalence difference of post COVID-19 symptoms of 4.1% among children and adolescents; adolescents aged >12 years were clearly more affected than younger children.[8**Error! Reference source not found.**]

We selected the studies by Taquet *et al* [16] and Bosworth *et al* [18] as the main sources of the model: the estimates from the former study were used for adult patients who experienced a severe course of acute COVID-19, and the estimates from the latter for adults and children with mild to moderate course. There were multiple reasons for this choice. Both studies had large sample sizes (>100,000 individuals), the data were collected systematically and with clear inclusion criteria. The rationale for using two sources was that in studies that recruited participants retrospectively (such as Taquet *et al*) the participants have had a reason to get tested for COVID-19, indicating the likelihood of having symptoms; a population-based study (like Bosworth *et al*) in turn covers representatively those who do not necessarily have any clear symptoms during the acute phase. To estimate the influence of this choice, we also used alternative sources from Switzerland: Ballouz *et al* for adults with severe acute COVID-19,[7] and Dumont *et al* for adults and children with mild to moderate acute COVID-19 (assuming that the results from adolescents are generalizable for adults).[8] **The findings of Ballouz *et al* were used also in all analyses to determine the long-term course of post COVID-19 condition, i.e. the proportion of individuals who are expected not to recover within about half a year.[7]** The main (conservative) assumption was that the proportion of long-term patients was calculated assuming that all participants would have some form of post COVID-19 condition. In the alternative, we used the results directly, i.e. assuming that only those who reported symptoms for a duration of more than 3 months would be considered as having post COVID-19 condition.

4. Mathematical model: methodology, structure and parameterization

4.1 Overview

We developed a flexible mathematical model that is based on a previously published model of SARS-CoV-2 transmission and acute COVID-19 disease. To reliably estimate the incidence of post COVID-19 condition, the model needs to be able to robustly project the underlying SARS-CoV-2 transmission dynamics, even though the evaluation of the acute COVID-19 epidemic is not within the scope of this project. The full model consists therefore of an underlying SARS-CoV-2 transmission model as well as an appended post COVID-19 module that constantly interacts with the transmission model. Both modules are presented in the next two sections.

4.2 Transmission model

The structure of the transmission model is presented in **Figure 2**. The parameters for disease progression were mostly adapted from a similar model developed for Île-de-France, and revised later through calibration of the model.[19,20,21] We used hospitalizations as the main indicator in calibration since they are generally the most reliable data source, independent of the testing strategy and behavioural trends. Contact rates were adjusted by time-dependent coefficients reflecting the non-pharmaceutical interventions in place. Whereas the model was relatively easy to calibrate until the emergence of the omicron variant in late 2021, from 2022 onwards a straightforward approach using the same parameter values would have led to a severe overestimation of the observed hospitalizations. We therefore calibrated the model three times with different approaches. The rationale for multiple parameterizations is that with the increasing complexity, there is no longer a single unique solution that would provide the best fit. In general, the hospitalization curve is influenced by two factors: the incidence (which in turn depends on the contact patterns and infectiousness); and the severity. High incidence with low severity can produce similar outputs as low incidence with high severity; therefore, we tried three alternative parameterizations with different values for these two measures. In the **first alternative**, we allowed a modest continuous decrease in severity since mid-2022 together with the assumption that the overall contact rates became permanently slightly lower compared to pre-2020 values. The rationales behind these assumptions are that 1) when reinfections become more common, the symptoms will become also less severe; and 2) during the pandemic, people may have adopted protective behaviours that they will continue to apply even when the situation has returned to normal. In the **second scenario**, we assumed that the proportion of severe cases decreased more rapidly and, correspondingly, the contacts returned to almost normal level in early 2022. **Third,** we explored a **scenario** where the contacts stayed permanently on a very low level but there was no further decrease in the proportion of severe cases after mid-2022. The scenarios were selected to represent a plausible range of assumptions: the first one being the "point estimate", and the second and third representing the maximum and minimum plausible burden, respectively. We also conducted two alternative analyses for the main scenario about the impact of vaccines. In one sensitivity analysis, the share of moderate symptoms among the vaccinated was decreased and paucisymptomatic conditions correspondingly increased; and in the other analysis, we assumed that vaccinated individuals could also have severe symptoms, but with 50% lower rate than the non-vaccinated. We will present the results essentially as mean over all scenarios with the extremes.

A full description of the transmission model including the full parameterization and calibration results is shown in the **Appendix.**

4.3 Post COVID-19 module

4.3.1 Structure and parameterisation

The transmission model was complemented with a separate post COVID-19 module which consists of a script that interacts with the main model (**Figure 3**). The module tracks the number of post COVID-19 cases, stratified according to the main categories of symptoms. According to the findings of the literature review, we considered the following symptom categories:

- Fatigue and post-exertional malaise (PEM)
- Neuropsychiatric symptoms
- Cardiopulmonary symptoms

This categorization coincides at least partially both with the commonly proposed classification in the literature as well as the categories explicitly mentioned in the new Swiss treatment guidance.[6] The conditions were not stratified further according to severity or specific symptoms, i.e. the model provides only the projections of these three symptom clusters.

We split each compartment temporally into two parts: one representing the first months of post COVID-19 condition (initial phase), and the second one the long-term persistent condition. All patients progress from the first compartment by a rate corresponding to a mean duration of 6 months, based on the finding that the proportion of symptomatic individuals clearly decreases 6 months after infection.[7] The model tracks every day the number of new post COVID-19 cases based on the SARS-CoV-2 infection status in the transmission model, as well as the progression of the existing cases, including the development of new systems, progression from the initial phase to the long-term condition, and recovery.

For each parameter, we included in addition to the best estimate two alternative values, corresponding to the plausible range that may lead either to an optimistic or pessimistic projection, respectively (**Table 1**). The best estimates were based on the study of Taquet *et al* for adults and seniors who experienced severe acute symptoms, and on Bosworth *et al* for everyone with up to moderate course of acute infection, as described in Section **3.** Literature review above. The proportion of patients continuing to the long-term post COVID-19 phase was based on the conservative assumption that the denominator in the study by Ballouz *et al* represents all patients with at least some level of post COVID-19 symptoms.[7] This means in turn that 22% of post COVID-19 patients were assumed to stay in the long-term phase. The recovery rate from the long-term post COVID-19 stage was based on the finding of Ballouz *et al* that the proportion of patients with symptoms decreased from 22% to 17% between months 6 and 24.

The values corresponding to an optimistic scenario were also taken from the same studies, with some exceptions: we used the lower limits of the confidence intervals instead of best estimates; 15% probability of long-term post COVID-19; and twice as high probability to recover from long-term post COVID-19 than according to the best estimates. In the pessimistic scenario, rates for children and adults with up to moderate COVID-19 were taken from the SEROCoV-KIDS study, assuming that the rate among adults would be the same as among adolescents aged 12-17;[8] risk of long-term post COVID-19 was increased to 26%, recovery from long-term post COVID-19 set to zero, and for the risk among severe cases the upper limits of confidence intervals were used instead of point estimates. The three scenarios were combined with the different parameterizations of the transmission model. We present, in addition to the scenario based on best estimates, the full range (scenarios leading to lowest and highest cumulative cases of post COVID-19 overall for each age group).

Because of the model's assumptions, we assumed that all children would have no more than moderate symptoms, thus avoiding the need to consider children who had severe progression. Although the model does not explicitly follow individuals, we estimated the proportion of severe cases among all SARS-CoV-2 infections from the internal situation of the model 90 days earlier. The results are presented as cumulative new cases over two time periods (1st May – 31st July 2023; 1st October – 31st December 2023) and as prevalent cases at two time points (31st July and 31st December 2023).

4.3.2 Results

The underlying SARS-CoV-2 transmission dynamics fitted the observed hospitalizations well at the beginning of the pandemic, however since the end of 2021 until the end of observation period there was more substantial fluctuation. In the early waves, the number of projected daily infections grew to the magnitude of 50,000, which is clearly higher than the documented cases (especially during the first wave) although not implausible, taken the challenges in testing. During the subsequent waves until early 2022, the projected infections were about 2 to 3 times higher than confirmed cases, which should be plausible, taken that the testing was intensive but still not with 100% coverage. The main question relates to the situation thereafter. The model projected still several waves with peaks in the magnitude of 100,000 daily infections, whereas the reported cases were considerably lower (up to 8000/day in July 2022, and 5000/day in October 2022. In the end of 2023, the epidemic curves projected by the model had already become flatter, but still between 1000 and 30,000 daily infections were projected, depending on the scenario.

During the time period 1st May – 31st July 2023, the model in the main analysis projected 4000 (range: 1200-22,600) incident cases of post COVID-19 condition among children, 64,600 (12,900-190,800) among adults and 22,700 (5500-64,800) among seniors (**Figure 4**). This corresponds to about 30,000 new Post COVID-19 cases every month. Over time, the incidence of post COVID-19 condition followed approximately the trends of the acute SARS-CoV-2 infections, as can be expected. During the second observation period, the numbers were lower, resulting in altogether 68,200 new post COVID-19 cases, i.e. about 23,000 per month.

The number of prevalent post COVID-19 conditions increased over time. By the end of 2021, the projected number of individuals affected by post COVID-19 condition was 127,600 (61,000-308,000) while the steepest increase followed only in the year 2022 (**Figure 5**). The growth slowed down in early 2023, and apart from the upper limit scenario, the total number turned to (slow) decrease during the year. This demonstrates that the level of post COVID-19 burden is largely driven by the COVID-19 waves that happened during 2022, after the emergence of Omicron. On 31 July 2023, the model (main analysis) projected 338,700 (87,000-1,071,200) individuals – 16,300 (5500-96,100) children, 242,800 (59,200-742,000) adults, and 79,600 (22,200-233,000) seniors – to be affected by post COVID-19 condition (**Table 2**, **Figure 5Figure 6**). This corresponds to model predictions ranging from 2% to 12% of the Swiss population for the different selected scenarios. About 40% (27%-58%) of the individuals were in the long-term phase, i.e. suffering already more than 6 months from the condition (**Figure 6**). In the end of 2023, the total number of people with post COVID-19 condition had decreased slightly to 329,900 in the main scenario, but the overall range was broader (65,800-1,139,200).

5. Discussion

Our mathematical modelling analysis projects that at least 2% of the Swiss population – about half a million people according to the scenario we assumed to be most likely – were suffering from post COVID-19 condition in 2023. However, those results come with high uncertainty and require further investigation and validation. The common symptoms can be categorized into fatigue, neuropsychiatric disorders and cardiopulmonary disorders, of which neuropsychiatric were the most common. Modelling suggests that the number of prevalent post COVID-19 cases is slowly decreasing. The majority of the patients are expected to clear the condition within 6 months, and the incident cases are decreasing according to the model projections. However, about one fifth of all post COVID-19 cases are expected to persist on a longer term, and the burden of prevalent post COVID-19 conditions is expected to decrease over time only slowly.

The results come with broad uncertainty, which is due to the uncertainties at different steps of the evaluation procedure. The post COVID-19 cases are derived from the underlying SARS-CoV-2 infections, which are subject to many assumptions with questionable plausibility. Most scenarios projected waves with peaks of 50,000 to 100,000 daily infections during the year 2022, while the observed data showed a clearly decreasing trend. Primarily the findings should be interpreted as a rough estimate of the magnitude: it is estimated that between 100,000 and 1,000,000 people living in Switzerland are affected by at least some level of long-term consequences related to post COVID-19 condition. Although this is a very broad range with a 10-fold difference between the lower and upper bounds, the model suggests that even with optimistic assumptions post COVID-19 is affecting a substantial part of the population. The results also demonstrate that three main symptom categories are roughly equally present; and while for some individuals the symptoms may recover spontaneously, for about half of the affected people post COVID-19 could be a chronic long-term condition.

According to the model projections, about half of the people affected by post COVID-19 condition have suffered already over half a year of the symptoms. According to Ballouz *et al*, the proportion of COVID-19 patients who suffer from post COVID-19 condition will no longer significantly decrease after 6 months from acute infection, so it can be expected that these individuals will not recover soon.

This report shows the first results based on a mathematical model that includes a mechanistic representation of the underlying transmission dynamics of the SARS-CoV-2 virus, the progression of acute COVID-19, and the development and progression of post COVID-19 condition. The model fits relatively well to the indicators from the available data,[1] and the main findings were also in line with the literature estimates related to the prevalence of post COVID-19 condition.[11,17,22] Nevertheless, there are several limitations both in the model structure and the data and parameterization that need to be taken into account. While the model was able to fit the beginning of the pandemic well, in the later stages the level of complexity increased which also causes uncertainty in the dynamics of the model. For reproducing a sufficiently good fit, we could no longer rely only on explicitly defined interventions, but had to adjust the contact rates manually as well as make assumptions that are plausible but at least to some extent unverifiable, such as that the risk of severe acute COVID-19 has decreased over time. In addition, the risk of developing post COVID-19 itself may be associated with the variant and/or immunity, which was not taken into account by the model. Despite the main aim of the project being to estimate the burden and risk of post COVID-19 rather than modelling the transmission, the transmission dynamics strongly influence the risk of developing long-term symptoms. According to the model's projections, there is significant transmission of the virus going on in the population. Whereas the high test positivity rate and wastewater findings demonstrate that indeed SARS-CoV-2 continues to circulate in the population, the magnitude of the incidence is difficult to verify in practice.

We are not aware of other comprehensive mathematical modelling studies have attempted to estimate the burden of post COVID-19 condition accounting for the underlying transmission dynamics. Nevertheless, some estimates for the burden using other methods are available. A survey from France has estimated that about 4% of the population were affected by post COVID-19 condition in March-April 2022.[22] In Europe, about 17 million individuals were estimated to have post COVID-19 in the first two years of the pandemic, corresponding to about 2% of the total population.[17] These estimates are in line with our findings.

The parameterization of the post COVID-19 module was done rather conservatively. We assumed that those who had severe acute COVID-19 would be at highest risk of post COVID-19. The rationale for this assumption were the findings from individuals with mild symptoms that were clearly lower than those suggested by other studies. Hospitalization during acute COVID-19 was also found to be associated with an increased risk of post COVID-19 condition which supports this assumption.[7]

Both at the beginning of the pandemic, as well as recently after the intensive monitoring and control measures were lifted, it is however mostly those who develop severe or at least clear symptoms who will get tested and confirmed, therefore causing uncertainty on the estimates of those with mild or no symptoms.

The five alternative parameterisations produced a broad range of results, which is understandable due to the high uncertainty around the key parameters of the model. The differences however reflect not only the uncertainty of the input parameters, but also that of the definition. Taquet *et al* estimated that about 30% of the individuals with acute COVID-19 will have at least some long-term symptoms.[16] The study had clear criteria for the symptoms and also disaggregated the results according to the most common syndromes, and thanks to the large sample size these can be expected to reflect the situation in the population well. However, combining this with the estimates of Ballouz *et al* on the patients with long-term (>6 months) symptoms may underestimate the true burden.[7] However, we wanted to be careful with the assumptions: following the estimates of Ballouz *et al* directly would mean that even the majority of those fulfilling the definition of a post COVID-19 case would continue to suffer from the condition for at least two years. Moreover, the symptoms of the majority of patients with long-term post COVID-19 condition were mild.

In conclusion, we developed a novel approach to provide projections on the burden of post COVID-19 condition in Switzerland, based on dynamic modelling of the underlying epidemic and literature estimates on the risk of post COVID-19. However, the complexity of modelling the transmission dynamics, particularly in the later stages of the epidemic with new variants and changing immunity status, mean that this approach cannot provide a clear and precise estimate about the current burden of post COVID-19 condition in Switzerland. Our findings were nevertheless on a similar level as the few existing literature estimates from other settings, which supports the conclusion that a small but nevertheless notable proportion of the Swiss population is affected by post COVID-19 condition.

Tables

Table 1. Parameters of the post COVID-19 condition module. *The daily risks are applied to the number of people without post COVID-19 condition (from the transmission model) or to those who already have at least one post COVID-19 syndrome (internally from the post COVID-19 module).*

	Without post COVID-19			With other syndrome
	Children	Adults and seniors		
	Mild/ asympt.	Mild/ asympt.	Severe	
Best estimates				
Daily risk of developing fatigue syndrome	0.000017	0.000068	0.000672	0.002383
Daily risk of developing neuropsychiatric syndrome	0.000055	0.000220	0.002315	0.013467
Daily risk of developing cardiopulmonary syndrome	0.000040	0.000159	0.001629	0.002486
Mean duration of primary post COVID-19 condition	180 days	180 days	180 days	-
Probability of long-term post COVID-19 condition	0.22	0.22	0.22	-
Exit rate from long-term post COVID-19 condition	0.000525	0.000525	0.000525	-
Optimistic values				
Daily risk of developing fatigue syndrome	0.000010	0.000041	0.000650	0.002383
Daily risk of developing neuropsychiatric syndrome	0.000033	0.000132	0.001832	0.013467
Daily risk of developing cardiopulmonary syndrome	0.000024	0.000095	0.000894	0.002486
Mean duration of primary post COVID-19 condition	180 days	180 days	180 days	-
Probability of long-term post COVID-19 condition	0.15	0.15	0.15	-
Exit rate from long-term post COVID-19 condition	0.001107	0.001107	0.001107	-
Pessimistic values				
Daily risk of developing fatigue syndrome	0.000070	0.000142	0.000694	0.002383
Daily risk of developing neuropsychiatric syndrome	0.000226	0.000462	0.002460	0.013467
Daily risk of developing cardiopulmonary syndrome	0.000163	0.000333	0.001682	0.002486
Mean duration of primary post COVID-19 condition	180 days	180 days	180 days	-
Probability of long-term post COVID-19 condition	0.26	0.26	0.26	-
Exit rate from long-term post COVID-19 condition	0	0	0	-

Table 2. Projected number of children, adults and seniors affected by post COVID-19 condition in Switzerland on 31st July and 31st December 2023. *The range presents the minimum and maximum values over all combinations of parameterizations.*

	31st July 2023	**31st December 2023**
Children aged 0-17 years	16,268 (5,513-96,113)	15,425 (4,088-99,882)
Adults aged 18-64 years	242,818 (59,198-742,052)	236,087 (44,656-787,692)
Seniors aged ≥65 years	79,620 (22,258-233,026)	78,391 (17,020-251,453)
Total	**338,724 (86,969-1,071,191)**	**329,903 (65,764-1,139,027)**

Figures

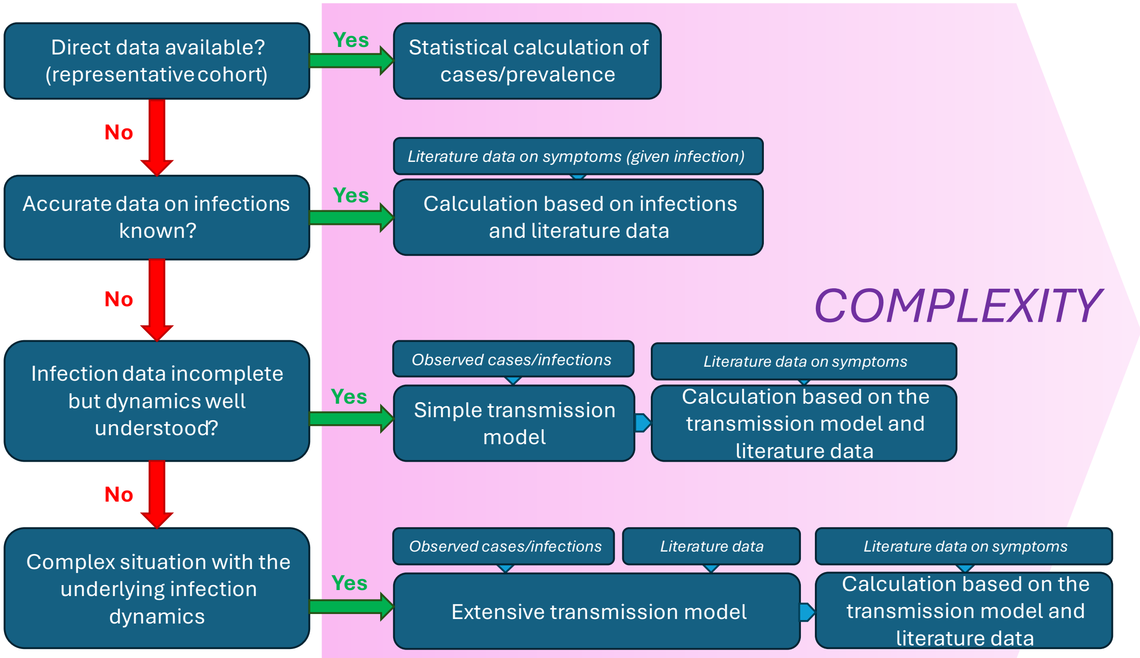

Figure 1. Illustration of different options to estimate the burden of chronic conditions resulting from communicable diseases. *For the case of post COVID-19 condition at present, the last and most complex option is the closest to the real situation.*

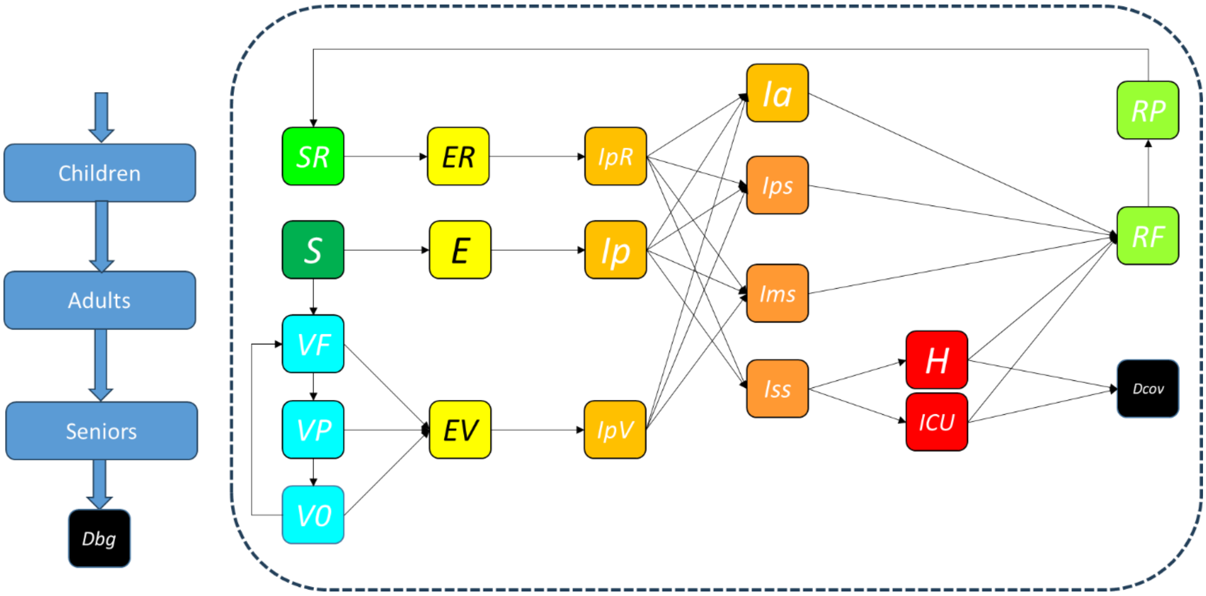

Figure 2. Schematic representation of the transmission model. *The population is divided into children (0-17 years), adults (18-64 years) and seniors (≥65 years); each age group is further split into compartments that account for the infection status, immunity and symptoms of acute COVID-19. A description of each compartment is given in the* ***Appendix.***

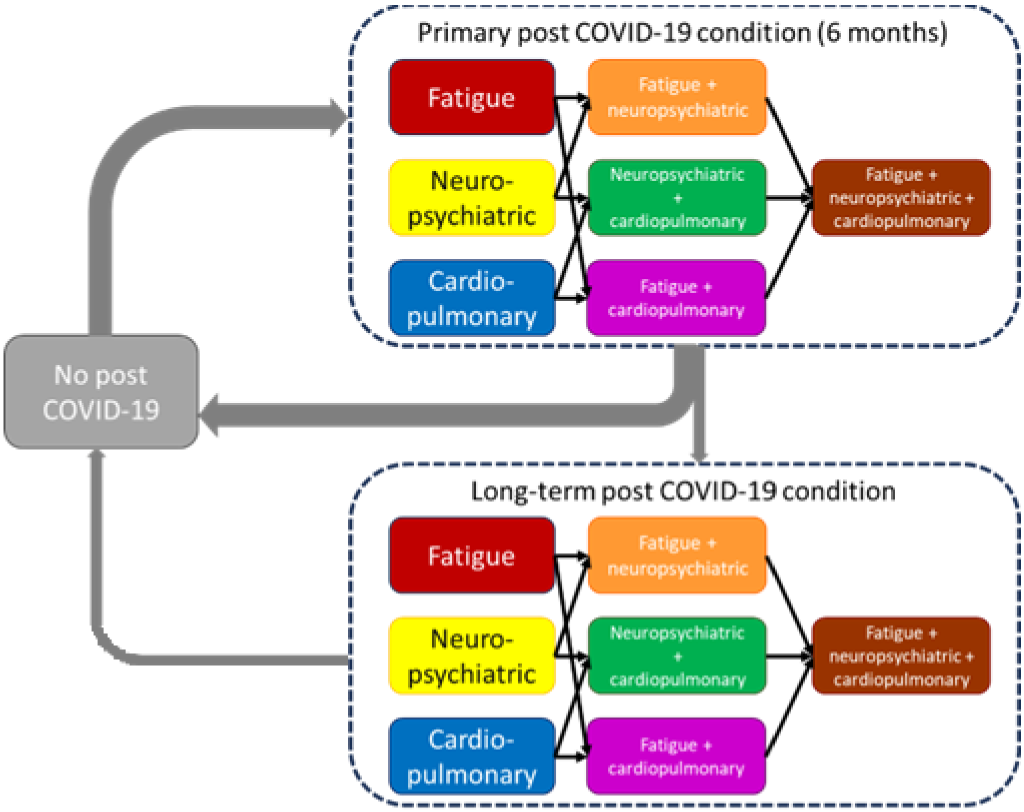

Figure 3. Schematic representation of the post COVID-19 module of the mathematical model.

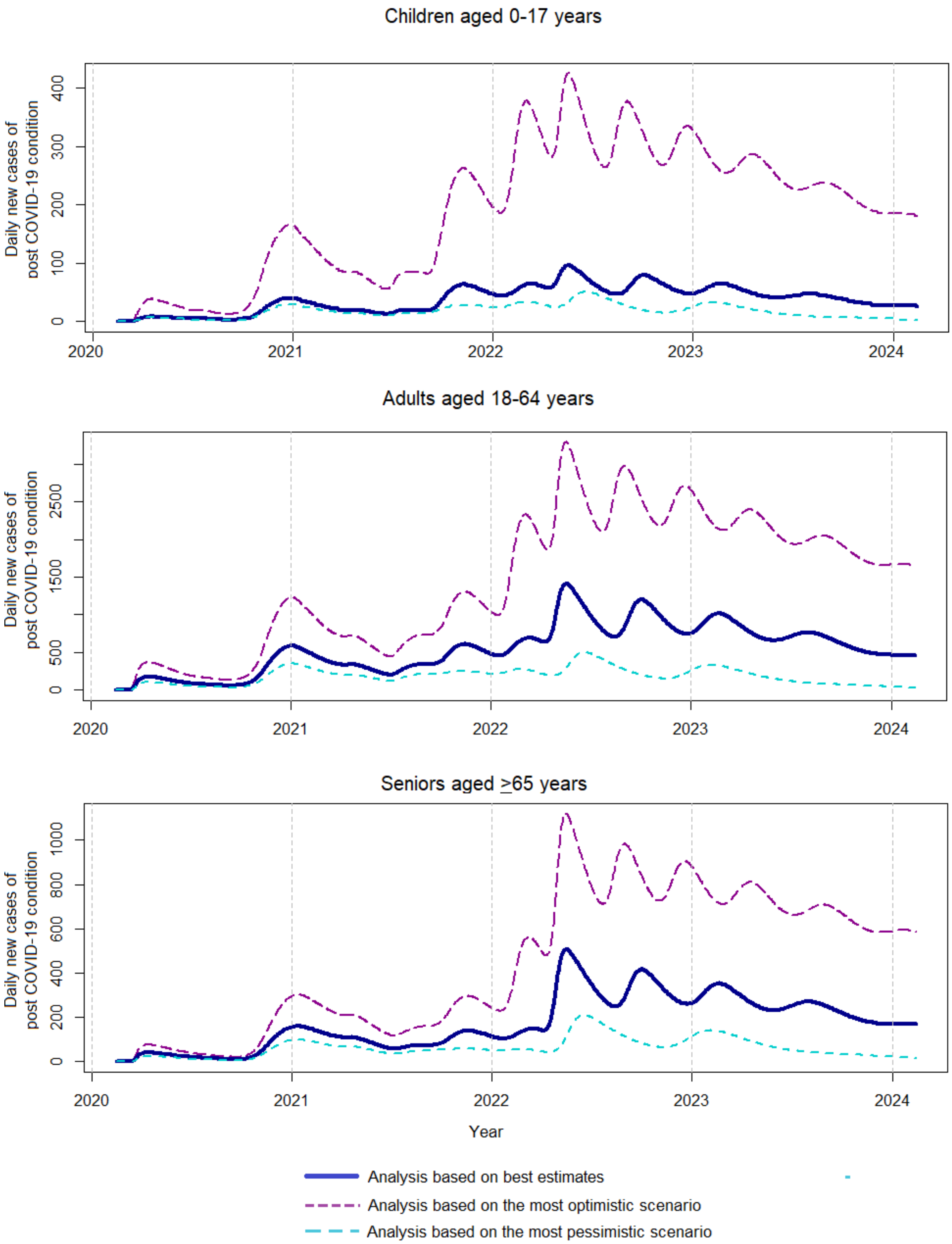

Figure 4. Incidence of post COVID-19 condition in Switzerland among children (top panel, 0-17 years), adults (middle panel, 18-64 years) and seniors (≥65 years). *The graph presents all new cases of post COVID-19 condition regardless of the primary syndrome.*

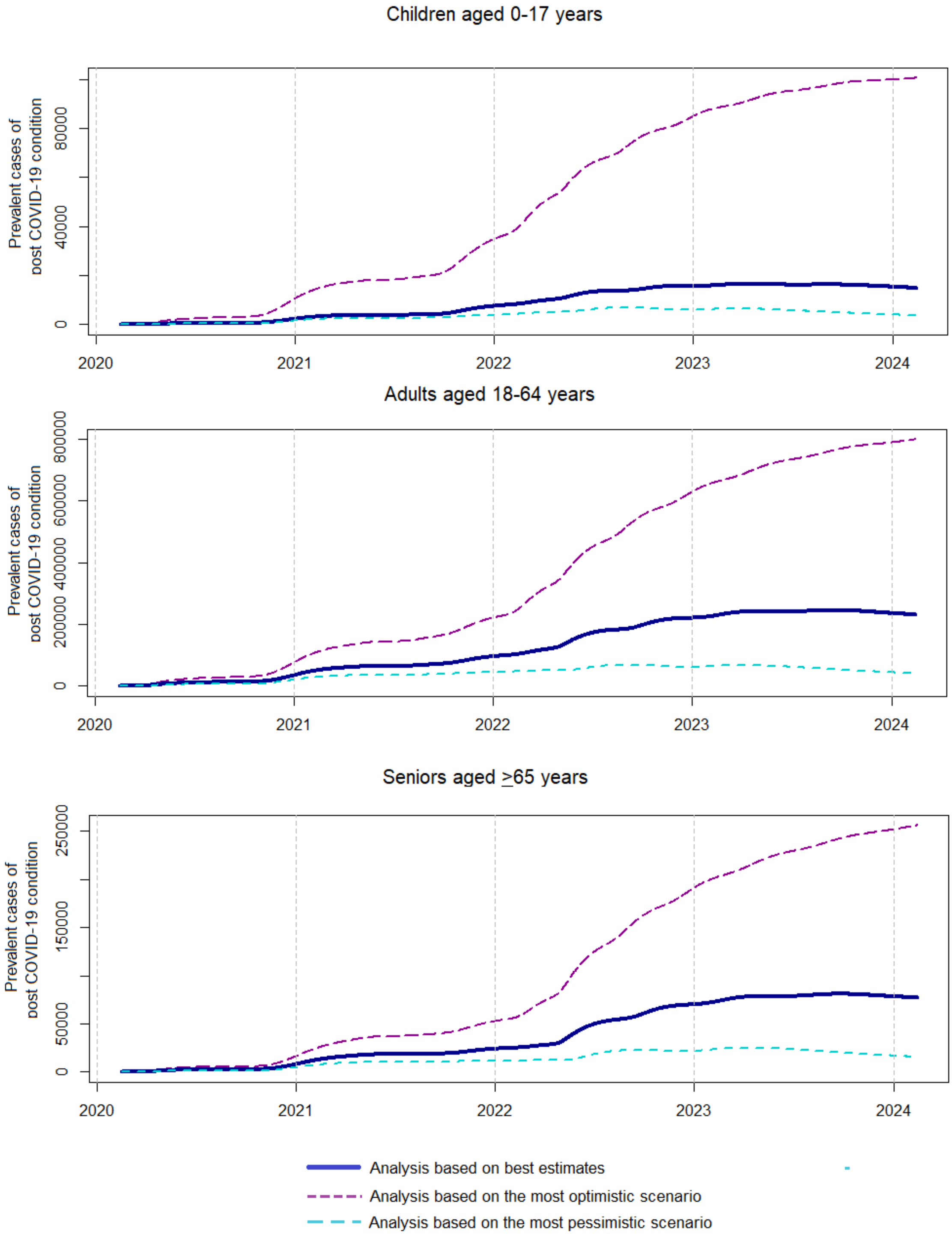

Figure 5. Prevalence of post COVID-19 condition in Switzerland among children (top panel, 0-17 years), adults (middle panel, 18-64 years) and seniors (≥65 years). *The graph presents all prevalent cases of post COVID-19 condition regardless of the primary syndrome.*

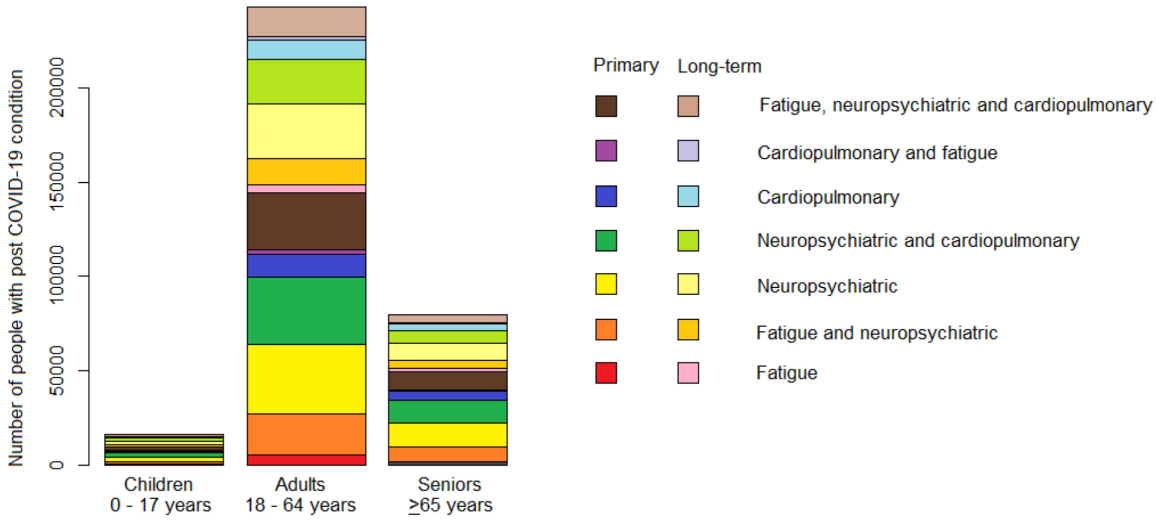

Figure 6. Projected number of people with post COVID-19 condition on 31st July 2023. *The results are stratified by age group, presence of different syndromes, and stage. Primary stage refers to the approximately 6 months after which recovery is possible; long-term stage to the time beyond 6 months without recovery possibility.*

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Appendix

Description of the SARS-CoV-2 transmission model

Structure and parameterization

The transmission model is built on an existing model published earlier, based on an extended SEIRS (susceptible-exposed-infectious-recovered-susceptible) structure.[19] A full description including the model code of the original version can be found on the GitHub repository.[20] The population is divided into three age groups: children (0 to 17 years), adults (18 to 64 years) and seniors (65 years and above). Each age class is further divided into the following compartments depending on the SARS-CoV-2/COVID-19 status: susceptible with no previous infection; susceptible after being infected at least once; exposed (infected but not yet infectious); pre-symptomatic (infectious, symptoms); four parallel compartments for different levels of symptoms (asymptomatic; paucisymptomatic; with moderate symptoms; with severe symptoms); two compartments for those hospitalized (depending on whether they were admitted to ICU at some stage of the hospitalization or not); recovered with full protection; recovered with partial protection; vaccinated with maximum protection; vaccinated with partial protection; vaccinated with minimal protection; and died. The exposed and presymptomatic stages are further divided according to whether the persons were previously infected or vaccinated to determine the further progression. After being infected, the individuals flow through the different compartments until the symptomatic/asymptomatic stage and then recover, with the exception of those who develop severe symptoms who will be hospitalized and may die instead of recover. The structure of the transmission model is illustrated in **Figure 2** of the main document, with details of the compartments presented in **Appendix Table A1**.

The parameters for the original (simpler) version were adapted from a similar model developed for Île-de-France, and revised later through calibration of the model.[21] The contact rates between different age groups were estimated from the POLYMOD study.[23] We used an average of rates from other Western European countries from which primary data were available. The contact rates were adjusted by time-dependent coefficients reflecting the non-pharmaceutical interventions in place. The contact rate reductions were made following the actual policies and restrictions, but also adjusted in calibration if necessary. The main indicator used in the calibration was the number of daily hospitalizations which is much stabler than the daily confirmed cases that depend strongly on the testing practices.

Different variants were not explicitly included in the model, but we instead allowed some parameters to change during the times that the Alpha, Delta and Omicron variants took over. The assumption was that the new variants were always at least as infectious as the previous ones, i.e. the basic infectiousness parameter was allowed to increase. The proportions of severe symptoms and the mortality rates varied also by variant, assuming that the proportion of severe cases was higher with alpha and delta than with the wild type/early variants, but lower with omicron. In addition, because of the compartmental structure, the model is able to take into account the effect of previous infections only in a limited way.

Calibration

Whereas the model was relatively easy to calibrate until the emergence of the omicron variant in late 2021 using the parameters from the original model[19] based on a priori knowledge with some fine adjustments of individual parameters, from 2022 onwards a straightforward approach using the same parameter values would have led to a severe overestimation of the observed hospitalizations. We therefore calibrated the model three times with different approaches. In the main analysis, we aimed to have the best possible fit to the hospitalizations by allowing a modest continuous decrease in the severity since mid-2022 together with the assumption that the overall contact rates became permanently slightly lower compared to pre-2020 values. The rationales behind these assumptions are that 1) when reinfections become more common, the symptoms will become also less severe; and 2) during the pandemic, people may have adopted protective behaviours that they will continue to apply even when the situation has returned to normal. Essentially, only these two parameters (proportion of severe cases requiring hospitalization; and the overall contact rate) can sufficiently influence the number of hospitalizations. In addition to the main scenario where we assumed that both factors played a role, we ran two alternative scenarios: one where the proportion of severe cases was assumed to decrease more rapidly and correspondingly the contacts returned to almost normal level in early 2022; and one where the contacts stayed permanently on a very low level but there was no further decrease in the proportion of severe cases after mid-2022.

Some other parameters, such as the vaccine efficacy or assumptions about the duration of natural immunity will also have an impact on the development of the epidemic. However, increasing the duration of full protection by the vaccine or after infection (now assumed at 3 and 2 months, respectively, during the omicron dominated period), would be against the present knowledge. Nevertheless, we also conducted made two alternative assumptions about the impact of vaccines. In one of these scenarios, the share of moderate symptoms among the vaccinated was decreased and paucisymptomatic conditions correspondingly increased; and in the other scenario, we assumed that vaccinated individuals could also have severe symptoms, but with 50% lower rate than the non-vaccinated.

The full list of parameters is given in **Appendix Table A2**. The general infectiousness parameter, probability of severe symptoms (and hospitalization), and COVID-19 related mortality were assumed to evolve over time because of differences in the dominant virus variant and overall level of immunity in the population. The contact rates between the different age groups including the restrictions over time are shown in **Appendix Table A3** and **Appendix Figure A1**. **Appendix Table A4** presents the vaccination and booster rates over time. The rates were aligned with the changes in eligibility and adjusted by calibrating the numbers of vaccinated individuals with the data provided by the FOPH.[1]

The outputs of the transmission model are presented as the results of the main analysis together with the minimum and maximum values gained through the different combinations of parameterization and vaccine efficacy assumptions. The calibration of new hospitalizations is shown in **Appendix Figure A2.** According to the model projection, substantial SARS-CoV-2 transmission has continued in the population also in 2023 (**Appendix Figure A3**). The infections tend to come in waves which are 3 to 4 months apart. Obviously, these numbers can be questioned since the number of confirmed cases has remained on a low level since the measures were lifted. Nevertheless, the constantly high positivity rates of the tests indicate a high number of undocumented infections. The peaks in test positivity rates in March and August 2023, as well as the relatively high wastewater concentration in April 2023, also show that despite the relatively stable situation on the observation level, the epidemic continues to evolve in the background.[1]

The modelling further predicts that at present, almost the entire population of Switzerland has undergone at least one SARS-CoV-2 infection. At present, 25-35% of adults and seniors have also been infected recently (within the past 4 months). Only in children a non-negligible number of completely naïve individuals was projected – essentially this includes the newborns. Children were also the only age group where we assumed vaccinations to continue, due to children reaching the age of eligibility: it can be expected to be rare that individuals who previously refused vaccination would choose to get vaccinated now.

Appendix Tables and Figures

Appendix Table A1. Full list of compartments in the SARS-CoV-2 transmission model. *Each compartment is further split by age into children (0-17 years), adults (18-64 years) and seniors (≥65 years). The symbol represents the name in the model code (* is either C for children, A for adults, or S for seniors). The flows between the compartments are shown in* ***Figure 2*** *of the main document.*

Name	Symbol	Explanation
Susceptible – naïve	S*	Currently uninfected; never infected with, nor vaccinated against, SARS-CoV-2
Susceptible – recovered	SR*	Currently uninfected; previously infected with SARS-CoV-2 at least once; no immunity
Vaccinated – full protection	VF*	Currently uninfected; never infected with SARS-CoV-2; vaccinated with maximum protection (recent vaccination or booster)
Vaccinated – partial protection	VP*	Currently uninfected; never infected with SARS-CoV-2; vaccinated with partial protection
Vaccinated – no protection	V0*	Currently uninfected; never infected with SARS-CoV-2; vaccinated but no more protection
Exposed – naïve	E*	Infected but not yet infectious; never infected with, nor vaccinated against, SARS-CoV-2
Exposed – vaccinated	EV*	Infected but not yet infectious; never infected with SARS-CoV-2 but vaccinated
Exposed – reinfection	ER*	Infected but not yet infectious; previously infected with SARS-CoV-2 at least once
Prodomic - naïve	Ip*	Infectious but not yet symptomatic; never infected with, nor vaccinated against, SARS-CoV-2
Prodomic – vaccinated	IpV*	Infectious but not yet symptomatic; never infected with SARS-CoV-2 but vaccinated
Prodomic - reinfection	IpR*	Infectious but not yet symptomatic; previously infected with SARS-CoV-2 at least once
Asymptomatic infection	Ia*	Infectious and (permanently) asymptomatic
Paucisymptomatic infection	Ips*	Infectious, only
Symptomatic mild infection	Ims*	Infectious, mild symptoms
Symptomatic severe infection	Iss*	Infectious, severe symptoms requiring hospitalization
Hospitalized without ICU	H*	Hospitalized, without need of intensive care
Hospitalized needing ICU	ICU*	Hospitalized, requires intensive care at least at some stage
Recovered, full protection	RF*	Recovered, full immunity because of recent infection
Recovered, partial protection	RP*	Recovered, partial immunity
Dead – for COVID-19	Dcov*	Died for COVID-19 related mortality (after severe symptoms)
Dead – for other reasons	Dbg*	Died because of natural or other reasons (age-dependent)

Appendix Table A2. Full list of parameters (excluding contact rates, non-pharmaceutical interventions and vaccination) in the transmission model.

Parameter	Value	Minimum	Maximum	Source
Time period				
Starting date	15 Feb 2020	15 Feb 2020	15 Feb 2020	[19]
End date of simulation	14 Feb 2024	14 Feb 2024	14 Feb 2024	Choice
Infection process				
Relative infectiousness of prodomic, asymptomatic and paucisymptomatic patients compared to symptomatic	0.510	0.510	0.510	[21]
Infectiousness parameter until 31 Dec 2020*	0.680	0.680	0.680	Calibration
Infectiousness parameter from 20 Jul 2021* until 7 Dec 2021	1.360	1.360	1.360	Calibration
Infectiousness parameter from 6 Jan 2022**	1.600	1.600	1.600	Calibration
Progression of the infection				
Incubation time before 29 Aug 2021*	1.5 days	1.5 days	1.5 days	[19]
Incubation time from 28 Sep 2021*	0.75 days	0.75 days	0.75 days	Assumption
Duration of prodomic phase before Omicron phase*	3.7 days	3.7 days	3.7 days	[21]
Duration of prodomic phase during Omicron phase*	1.85 days	1.85 days	1.85 days	Assumption
Probability to have any symptoms	0.500	0.500	0.500	[19,21]
Probability for symptomatic children to have mild symptoms	0	0	0	[2121]
Probability for unvaccinated*** symptomatic adults to have mild symptoms	0.700	0.700	0.700	[2121]
Probability for unvaccinated*** symptomatic seniors to have mild symptoms	0.775	0.775	0.775	[19], calibration
Probability for vaccinated* symptomatic adults to have mild symptoms**	0.723	**0.362**	0.723	Calibration
Probability for vaccinated* symptomatic seniors to have mild symptoms**	0.912	**0.456**	0.912	Calibration
Probability for unvaccinated*** symptomatic adults to have severe symptoms until 31 Dec 2020*	0.005	0.005	0.005	[19], calibration
Probability for unvaccinated*** symptomatic adults to have severe symptoms from 17 Mar 2021* until 29 Aug 2021*	0.011	0.011	0.011	Calibration
Probability for unvaccinated*** symptomatic adults to have severe symptoms on 28 Sep 2021*	0.004	0.004	0.004	Calibration
Probability for unvaccinated*** symptomatic adults to have severe symptoms from 25 Jul 2022*, **	0.003, 3% daily decrease	0.003, **20% daily decrease**	0.003 **(constant)**	Calibration
Probability for unvaccinated*** symptomatic seniors to have severe symptoms until 29 Aug 2021*	0.053	0.053	0.053	Calibration
Probability for unvaccinated*** symptomatic seniors to have severe symptoms from 28 Sep 2021* until 25 Jul 2022*	0.017	0.017	0.017	Calibration

Probability for unvaccinated*** symptomatic seniors to have severe symptoms from 25 Jul 2022**	0.017, 0.5% daily decrease	0.017, **5% daily decrease**	0.017 **(constant)**	Calibration
Probability for vaccinated* symptomatic adults to have severe symptoms**	0	0	**0.002 to 0.006**	Assumption
Probability for vaccinated* symptomatic seniors to have severe symptoms**	0	0	**0.009 to 0.027**	Assumption
Probability of hospitalization if severe symptoms	1	1	1	[21]
Probability of needing ICU if hospitalized: adults	0.25	0.25	0.25	[19]
Probability of needing ICU if hospitalized: seniors	0.20	0.20	0.20	[21]
Duration of symptomatic phase unless hospitalized	2.3 days	2.3 days	2.3 days	[21]
Duration of hospitalization phase: adults not needing ICU	27 days	27 days	27 days	[19]
Duration of hospitalization phase: seniors not needing ICU	38 days	38 days	38 days	[19]
Duration of hospitalization phase: adults needing ICU	71 days	71 days	71 days	[19]
Duration of hospitalization phase: seniors needing ICU	71 days	71 days	71 days	[19]
Probability of COVID-19 related death for hospitalized adults until 13 Aug 2020*	0.005	0.005	0.005	[19], calibration
Probability of COVID-19 related death for hospitalized adults from 3 Jan 2021*	0.002	0.002	0.002	Calibration
Probability of COVID-19 related death for hospitalized seniors until 13 Aug 2020*	0.141	0.141	0.141	[19], calibration
Probability of COVID-19 related death for hospitalized seniors from 3 Jan 2021* until 29 Aug 2021*	0.014	0.014	0.014	Calibration
Probability of COVID-19 related death for hospitalized seniors from 28 Sep 2021*	0.004	0.004	0.004	Calibration
Immunity due to natural infection and vaccination				
Duration of full protection after recovered infection	60 days	60 days	60 days	Assumption
Duration of partial protection**** after recovered infection	60 days	60 days	60 days	Assumption
Duration of maximal vaccine efficacy	90 days	90 days	90 days	Assumption
Duration of partial vaccine efficacy	90 days	90 days	90 days	Assumption
Duration of minimal vaccine efficacy	90 days	90 days	90 days	Assumption
Reduction in susceptibility if vaccinated (maximal efficacy)	0.910	0.910	0.910	Calibration
Reduction in susceptibility if vaccinated (partial efficacy)	0.500	0.500	0.500	Calibration
Reduction in susceptibility if vaccinated (minimal efficacy)	0	0	0	Assumption
Demographic parameters				
Daily number of births	233	233	233	[24]
Background mortality rate after age 65 years	0.00015/day	0.00015/day	0.00015/day	[24]

**During the time between dates when no value is given, the value increased or decreased linearly*

***The value was assumed to decrease gradually over time from the given date*

****Vaccinated = anyone with at least minimal protection left*

Appendix Table A3. Contact rates between the different age groups. *Panel A shows the relative baseline contact rates as they were prior to the pandemic, and panel B the different nonpharmaceutical interventions that we considered with their definitions in terms of contact reduction. The time of application for each non-pharmaceutical intervention is shown in* ***Appendix Figure A1.***

A – Baseline (pre-pandemic) relative contact rates

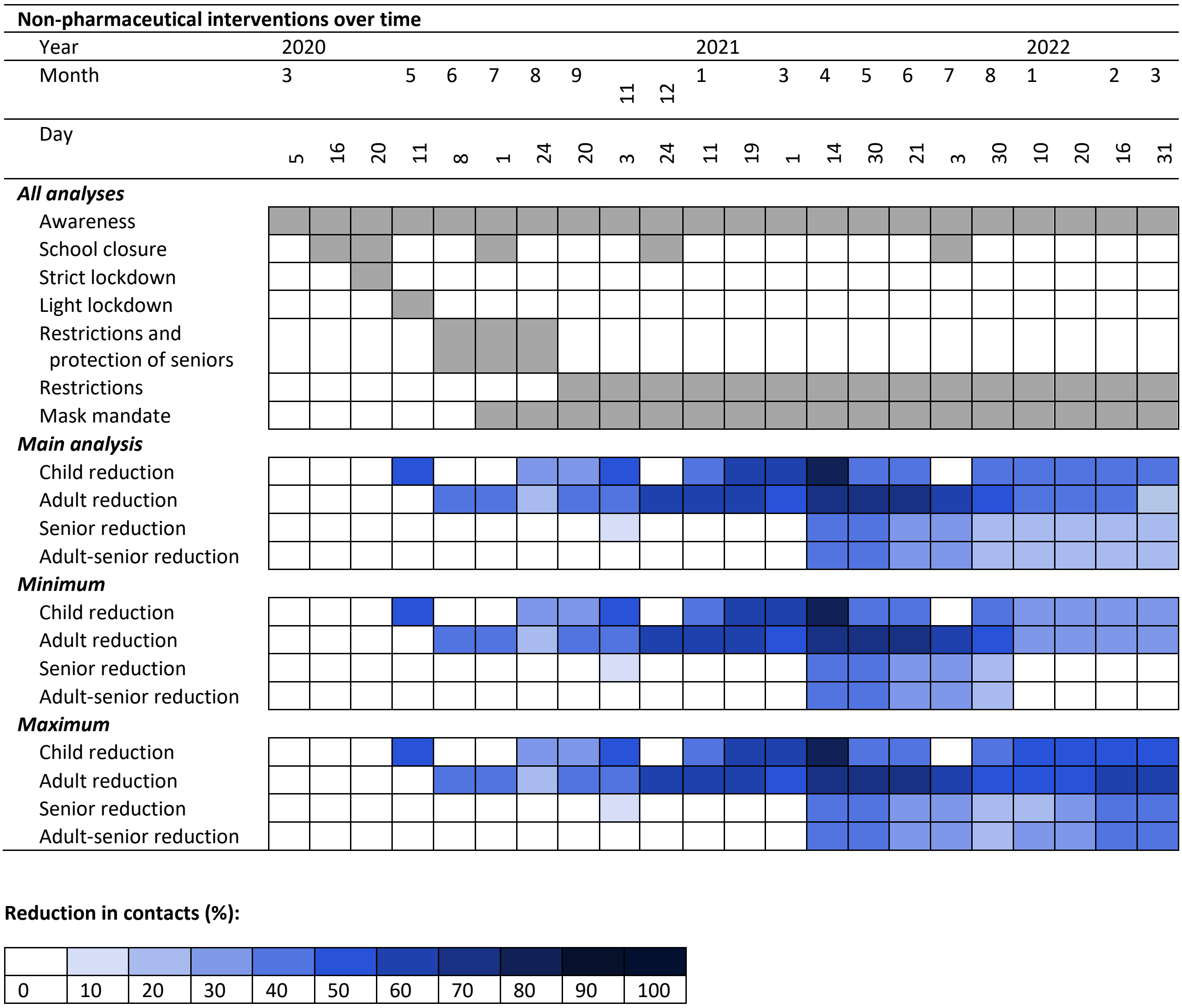
	Children (0-17y)	Adults (18-64y)	Seniors (≥65y)
Children (0 – 17 years)	1.20	0.35	0.14
Adults (18 – 64 years)	0.35	1.00	0.40
Seniors (≥65 years)	0.14	0.40	1.00

B – Definitions of non-pharmaceutical interventions

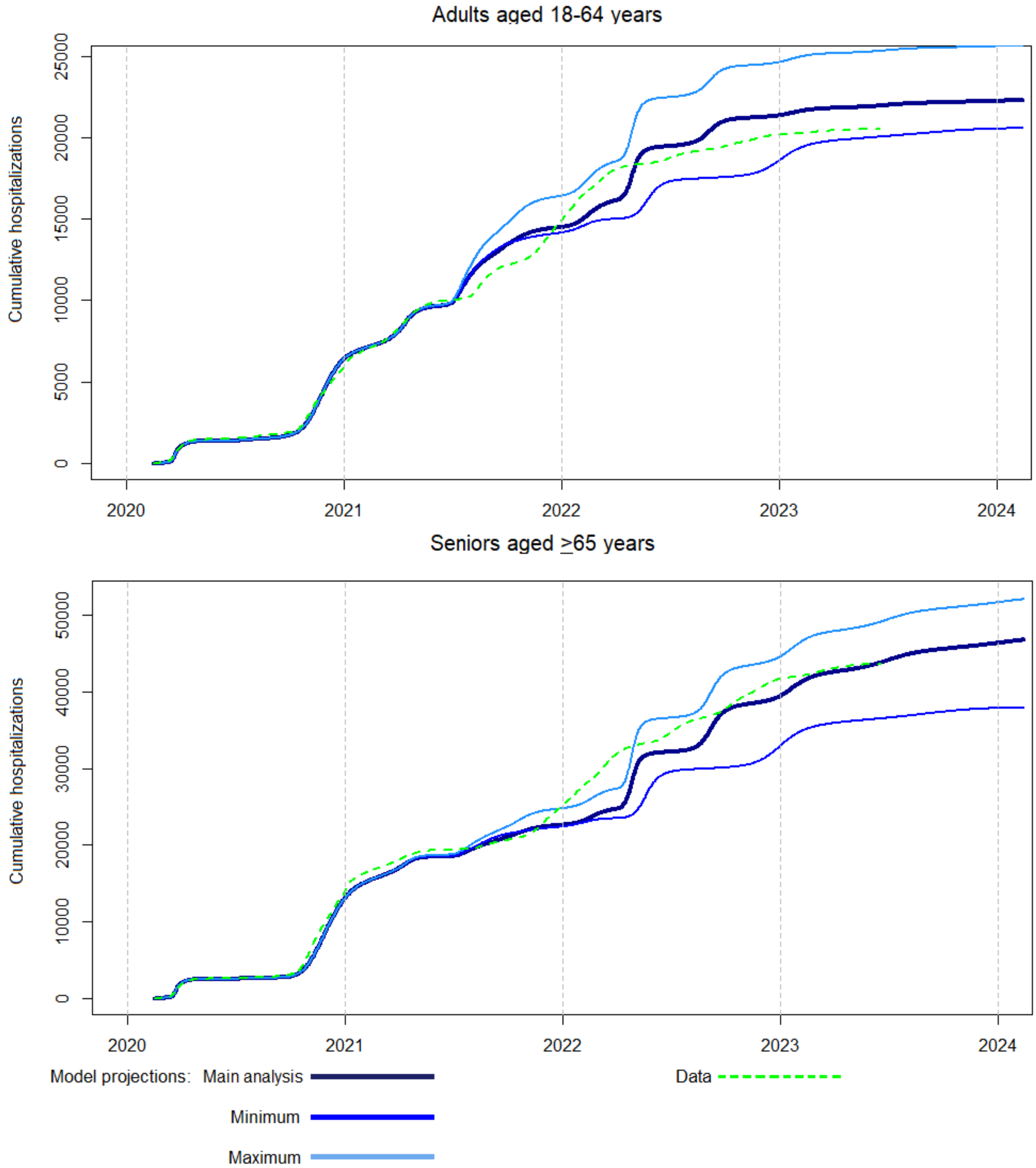
Intervention	***Interpretation***
Awareness	22% reduction in contacts involving seniors; 9% reduction in other contacts
School closure	95% reduction in contacts between children
Strict lockdown	90% reduction in contacts among adults and seniors; 44% reduction in contacts among children and between children and adults; 56% reduction in contacts between children and seniors
Light lockdown	As strict lockdown but contacts between adults restricted only by 85%
Restrictions and protection of seniors	78% restriction in contacts involving seniors, 22% restriction in other contacts
Restrictions	50% restriction in contacts between seniors, 40% restriction between seniors and adults, 28% between seniors and children, and 22% in other contacts
Mask mandate	5% restriction in contacts between children, 10% between children and adults/seniors, and 20% in other contacts
Child reduction	Reduction in contacts involving children at a given parameter
Adult reduction	Reduction in contacts involving children at a given parameter
Senior reduction	Reduction in contacts involving children at a given parameter
Adult-senior reduction	Reduction in contacts between adults and seniors at a given parameter

Appendix Table A4. Daily rates of vaccinations and boosters among children (C, 0-17 years), adults (A, 18-64 years) and seniors (S, >65 years). *Complete vaccination refers to receiving the second dose.*

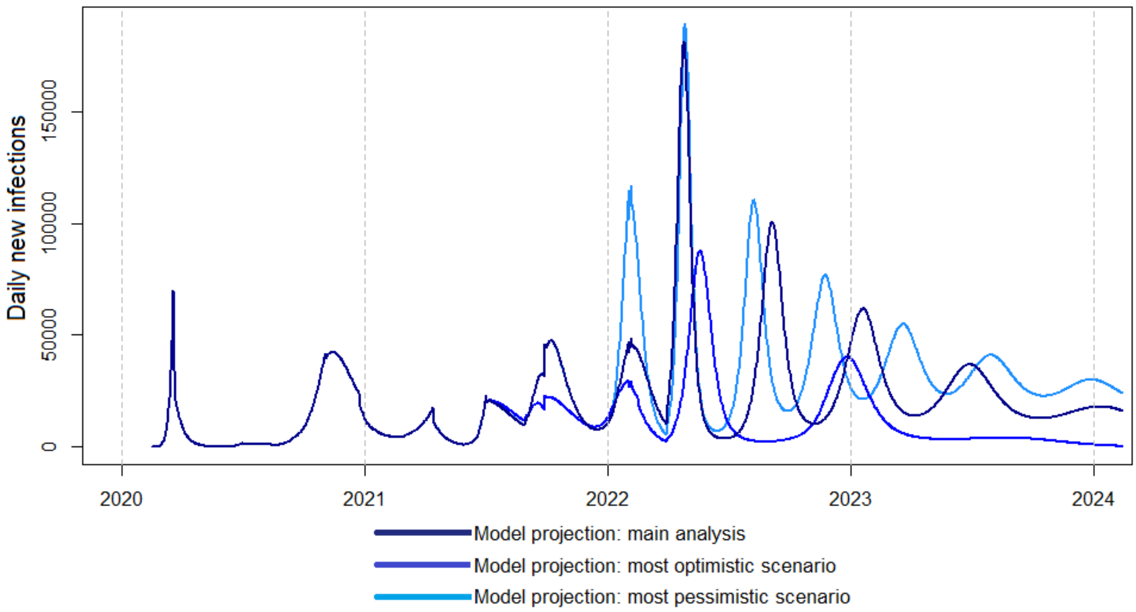
Start date	End date	Complete vaccinations			Boosters		
		C	A	S	C	A	S
15 Feb 2020	31 Dec 2020	0	0	0	0	0	0
1 Jan 2021	28 Feb 2021	0	0	0.0002	0	0	0
1 Mar 2021	14 Apr 2021	0	0.0010	0.0073	0	0	0
15 Apr 2021	31 May 2021	0.0001	0.0022	0.0198	0	0	0
1 Jun 2021	31 Aug 2021	0.0010	0.0088	0.0055	0	0	0
1 Sep 2021	16 Nov 2021	0.0033	0.0079	0.0026	0	0	0
17 Nov 2021	30 Jan 2022	0.0017	0.0026	0.0007	0.0063	0.840	0.250
31 Jan 2022	30 Mar 2022	0.0046	0	0	0.0900	0.800	0.250
31 Mar 2022	30 May 2022	0.0005	0	0	0.2500	0.800	0.250
31 May 2022	14 Feb 2024	0.0005	0	0	0	0	0.001



Appendix Figure A1. Application of different mitigation measures over time. *The reduction of contacts for each specific intervention in the top panel is presented in Appendix Table A3. The generic contact reductions in the lower panels refer to the relative reduction in contacts among children, adults and seniors, as well as between adults and seniors, as percentages.*



Appendix Figure A2. Cumulative number of hospitalizations due to acute COVID-19 in Switzerland. *The top panel shows the hospitalizations in adults aged 18-64 years and the bottom panel in children (≥65 years). The solid blue lines show the model projections in the three different analyses and the green dashed line the data provided by the FOPH.*



Appendix Figure A3. Daily new SARS-CoV-2 infections in Switzerland according to the model projections. *The results include the main analysis (dark blue) and the scenarios with assumptions resulting in the minimum (blue) and maximum (light blue) numbers of cases.*