Assessing real-world vaccine effectiveness against severe forms of SARS-CoV-2 infection: an observational study from routine surveillance data in Switzerland

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Summary

BACKGROUND: In Switzerland, SARS-CoV-2 vaccination campaigns started in early 2021. Vaccine coverage reached 65% of the population in December 2021, mostly with mRNA vaccines from Moderna and Pfizer-BioNtech. Simultaneously, the proportion of vaccinated among COVID-19-related hospitalisations and deaths rose, creating some confusion in the general population. We aimed to assess vaccine effectiveness against severe forms of SARS-CoV-2 infection using routine surveillance data on the vaccination status of COVID-19-related hospitalisations and deaths, and data on vaccine coverage in Switzerland.

METHODS: We considered all routine surveillance data on COVID-19-related hospitalisations and deaths received at the Swiss Federal Office of Public Health from 1 July to 1 December 2021. We estimated the relative risk of COVID-19-related hospitalisation or death for not fully vaccinated compared with fully vaccinated individuals, adjusted for the dynamics of vaccine coverage over time, by age and location. We stratified the analysis by age group and by calendar month. We assessed variations in the relative risk of hospitalisation associated with the time since vaccination.

RESULTS: We included a total of 5948 COVID-19-related hospitalisations of which 1245 (21%) were fully vaccinated patients, and a total of 739 deaths of which 259 (35%) were fully vaccinated. We found that the relative risk of COVID-19 related hospitalisation was 12.5 (95% confidence interval [CI] 11.7–13.4) times higher for not fully vaccinated than for fully vaccinated individuals. This translates into a vaccine effectiveness against hospitalisation of 92.0% (95% CI 91.4–92.5%). Vaccine effectiveness against death was estimated to be 90.3% (95% CI 88.6–91.8%). Effectiveness appeared to be comparatively lower in age groups over 70 and during the months of October and November 2021. We also found evidence of a decrease in vaccine effectiveness against hospitalisation for individuals vaccinated for 25 weeks or more, but this decrease appeared only in age groups below 70.

CONCLUSIONS: The observed proportions of vaccinated among COVD-19-related hospitalisations and deaths in Switzerland were compatible with a high effectiveness of mRNA vaccines from Moderna and Pfizer-BioNtech against hospitalisation and death in all age groups. Effectiveness appears comparatively lower in older age groups, suggesting the importance of booster vaccinations. We found inconclusive evidence that vaccine effectiveness wanes over time. Repeated analyses will be able to better assess waning and the effect of boosters.

Introduction

The continuous assessment of vaccine efficacy and effectiveness against SARS-CoV-2 is critically important for informing national vaccination campaigns and the public health response against the COVID-19 pandemic. Randomised controlled trials are the gold standard to estimate vaccine efficacy against symptomatic infection, hospitalization and death. Several randomised controlled trials have reported high levels of efficacy for several SARS-CoV-2 vaccines [1, 2]. For technical and ethical reasons, such trials have limitations when it comes to estimating vaccine effectiveness in real world conditions and over longer periods of time [3, 4]. Even though not ideal in terms of potential bias, observational data can be used to estimate vaccine effectiveness. When rich longitudinal data are available (e.g. insurance data or cohort studies), it becomes possible to directly estimate and compare the risk of symptomatic infection, hospitalisation or death in vaccinated and non-vaccinated individuals (adjusting for key characteristics) [5, 6]. When the vaccination status of SARS-CoV-2-negative controls is collected, a test-negative design can be used [7, 8].

Routine surveillance data often do not include any follow-up or control group. In Switzerland, routine surveillance

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data on COVID-19 contains detailed information only on reported confirmed cases, hospitalisations and deaths. The proportion of vaccinated individuals in surveillance reports can, however, be misleading as it is highly dependent on vaccine coverage [9]. Vaccine coverage can be heterogeneous and can vary by time, location and other characteristics, first of all age. In Switzerland, SARS-CoV-2 vaccination campaigns started in early 2021, first focusing on vulnerable groups (aged above 65 with comorbid conditions), then being gradually extended to younger age groups. Until May 2021, vaccination with vaccines from Moderna and Pfizer-BioNtech was roughly equal, but from this point onward the Moderna vaccine was more commonly used. Vaccination with the Johnson-Johnson vaccine started only in October 2021.

In this study, we used a reformulation of the screening method [10, 11] to estimate vaccine effectiveness against severe forms of SARS-CoV-2 infection in real-world settings from routine surveillance data in Switzerland, accounting for the levels of vaccine coverage by week, age group and location. We also assessed the variation in vaccine effectiveness by age, vaccine type, calendar time and – importantly – by time since vaccination.

Methods

Setting and data

We considered all routine surveillance data on laboratory-confirmed COVID-19-related hospitalisations and deaths received at the Federal Office of Public Health (FOPH) until 1 December 2021. These data included vaccination status at the individual level, which comprised the type of vaccine, the number of doses and the existence of a previous positive test. Individuals were considered fully vaccinated if they received either two doses of the Moderna or Pfizer-BioNtech vaccines, one dose of the Johnson-Johnson vaccine, or one dose of the Moderna or Pfizer-BioNtech vaccines with a previous positive test. Individuals were considered partially vaccinated if they received just one dose of Moderna or Pfizer-BioNtech without a previous positive test. Individuals were considered not vaccinated if they reported having not received any dose.

We included only COVID-19-related hospitalisations and deaths from 1 July 2021. Indeed, the proportion of missing vaccination status among hospitalisations and deaths was high (30–60%) during the early months of 2021, but rapidly decreased to around 10–15% from the month of July 2021 onward (supplementary fig. S1 in the appendix).

We treated missing information on the vaccination status as follows. For the baseline analysis, we defined as not fully vaccinated individuals who reported being either non-vaccinated or partially vaccinated, and excluded individuals with missing vaccination status. This assumes that vaccination status is missing at random (non-fully vaccinated individuals are equally likely to have missing vaccination status as fully vaccinated individuals). We then conducted several sensitivity analyses. First, we imputed missing vaccination status based on age group, canton, week and vaccine coverage using multiple imputation with chained equations [12]. Second, we assumed that all individuals with missing vaccination status were not fully vaccinated ("Best case scenario"). Third, we assumed that all

individuals with missing vaccination status and all partially vaccinated were fully vaccinated ("Worst case scenario").

Vaccine coverage data were obtained at the FOPH from the Vaccine Monitoring Data Lake database, which records every vaccination event. We considered individuals as fully vaccinated using the same criteria as for COVID-19-related hospitalisations and deaths. We aggregated this data by week, canton and age group.

Statistical model

We use a statistical model to assess the relative risk (RR) of hospitalisation among non-fully vaccinated individuals compared with fully vaccinated. The intuition is that, if vaccine had no influence on the risk of hospitalisation, the proportion of vaccinated among hospitalised people would be the same as the proportion of vaccinated in the population. The more vaccination reduces the risk of hospitalisation, the lower the proportion of vaccinated among hospitalised people will be.

More specifically, we defined the RR of hospitalization among non-fully vaccinated individuals (V_N) compared to fully vaccinated as:

$$RR = \frac{\Pr(H|V_N)}{\Pr(H|V)}$$

where Pr(H|V) refers to the probability of hospitalisation given non-fully vaccinated status and Pr(H|V) to the probability of hospitalisation given fully vaccinated status. This models allows us to estimate *RR* while accounting for the dynamics of vaccine coverage over time, by age group and by canton. The approach, which is detailed in the appendix, is equivalent to the screening method [10]. Briefly, we considered the expected probability that a hospitalised individual is vaccinated [(Pr(V|H)] given the vaccine coverage at the time of hospitalisation in the same age group and canton [Pr(V)], and given the value of RR from the following equation:

$$\Pr(V|H) = \frac{\Pr(V)}{\Pr(V) + RR(1 - \Pr(V))}$$

We estimated the RR by comparing the expected probability Pr(V|H) to the actual vaccination status of every individual using a Bernoulli likelihood within a maximum likelihood framework. The RR can also be expressed as a relative risk reduction (1 – 1/RR). This last quantity is closely related to vaccine effectiveness against hospitalisation if we assume that all the other factors influencing the risk of COVID-19 hospitalisation (e.g., behaviour or exposure) are independent of the vaccination status.

This model also applies to vaccine effectiveness against death, and can be extended to assess variations in vaccine effectiveness across different stratification groups. We considered stratification by age group and calendar month. We also extended the approach to a situation where we compared more than the initial two categories (fully vaccinated or not) using a generalisation of the equations above (appendix).

This allows assessment of variations in the RR associated with time since vaccination in three groups (vaccinated for up to 12 weeks, for 13 to 24 weeks, or for 25 weeks or more). We restricted this analysis to fully vaccinated individuals with non-missing time since vaccination, assuming that this variable is missing at random. We also stratified by age group and by vaccine type (restricted to Moderna or Pfizer-BioNtech).

We did this research using surveillance data collected by the Federal Office of Public Health according to the Swiss law on communicable diseases (EpG, SR 818.101). No ethics committee approval was required. The code is available at https://github.com/jriou/vaccine_effectiveness. More details and a simulation study validating the statistical approach are available in the appendix. As data contain sensitive information at the individual level, it is only available on motivated request to the Swiss Federal Office of Public Health.

Results

From 1 July to 1 December 2021 we included a total of 5948 hospitalisations and 739 deaths (table 1). Among all hospitalisations and deaths the proportion of fully vaccinated patients increased over time to around 40% (fig. 1A). During the same period, vaccine coverage in the population increased to 65.7%, with important differences across age groups (fig. 1B). There were also geographical differences in vaccine coverage and the type of vaccine used (fig. 1C), highlighting the importance of accounting for vaccine coverage by time, age group and location.

Of hospitalised individuals, 1245 (21%) were reported as being fully vaccinated (table 1). This number was 259 (35%) for deaths. Vaccination status was missing for 834 (14%) of hospitalisations and 98 (13%) of deaths. The age distribution of hospitalised patients was shifted towards older age groups with 1 1 (1) being and older.

This is even more pronounced for deceased patients, with 464 (63%) being 80 and older. Almost all individuals received the mRNA vaccines of Moderna or Pfizer-BioNtech. Among the fully vaccinated, 373 (30%) of hospitalisations and 133 (51%) of deaths had been vaccinated for 25 weeks or more. Information about time since vaccination was missing for 584 (47%) of hospitalisations and 83 (32%) of deaths.

Accounting for vaccine coverage by week, age group and canton, we found that the RR of hospitalisation without full vaccination compared with full vaccination was 12.5 (95% confidence interval [CI] 11.7–13.4) (fig. 2A, supplementary table S1). This corresponded to a relative risk reduction against hospitalisation (or vaccine effectiveness) of 92.0% (95% CI 91.4–92.5%). Results from sensitivity analyses with alternative handling of missing vaccination status ranged between RRs of 6.6 (95% CI 6.2–7.0) and 15.7 (95% CI 14.7–16.8). The RR of hospitalisation decreased in older age groups. We also found a decrease of the RR of hospitalisation over time, which also constitutes indirect evidence of waning. After stratifying by both age group and month, we found evidence for a decrease in RR in October and November 2021 in age groups 70–79 and 80+, but inconclusive evidence for other age groups (supplementary fig. S3).

The RR of death without full vaccination compared with full vaccination was 10.4 (95% CI 8.8–12.2) (fig. 2B, supplementary table S2), corresponding to a relative risk reduction against death of 90.3% (95% CI 88.6–91.8%). The RR of death decreased for older ages and over time, which again constitutes indirect evidence of waning. However, the small number of deaths leads to imprecise estimates with large confidence intervals.

To study direct evidence of waning, we restricted analyses only to fully vaccinated individuals with information about time since vaccination. Because of the large proportion of missing information on time since vaccination this analysis should be seen as exploratory.

Table 1:

Description of included COVID-19-related hospitalised and deceased persons from 1 July to 1 December 2021.

		Hospitalisations	Deaths
Total		5948 (100%)	739 (100%)
Vaccination status	Fully vaccinated	1245 (21%)	259 (35%)
	Partially vaccinated	69 (1%)	6 (1%)
	Not vaccinated	3800 (64%)	376 (51%)
	Missing	834 (14%)	98 (13%)
Age (years)	0–9	115 (2%)	0 (0%)
	10–19	57 (1%)	0 (0%)
	20–29	224 (4%)	1 (0%)
	30–39	516 (9%)	4 (1%)
	40–49	773 (13%)	8 (1%)
	50–59	1050 (18%)	44 (6%)
	60–69	999 (17%)	80 (11%)
	70–79	993 (17%)	138 (19%)
	80+	1221 (21%)	464 (63%)
Vaccine type (among fully vaccinated)	Moderna	310 (25%)	54 (21%)
	Pfizer-BioNtech	357 (29%)	120 (46%)
	Johnson-Johnson	14 (1%)	0 (0%)
	Missing	564 (45%)	85 (33%)
Weeks since vaccination (among fully vaccinated)	0–12 weeks	88 (7%)	17 (7%)
	13–24 weeks	200 (16%)	26 (10%)
	25+ weeks	373 (30%)	133 (51%)
	Missing	584 (47%)	83 (32%)

The outcome of interest is now the relative change in the RR of hospitalisation compared with the reference group of individuals vaccinat-ed for up to 12 weeks. Compared with the reference group, the RR of hospitalisation did not change when the time since vaccination was between 13 and 24 weeks, but increased by 1.5 (95% CI 1.1–2.1) when the time since vaccination was above 25 weeks (fig. 3A). With stratification by age group, this increase in the RR of hospitalisation 25 weeks after vaccination was significant only in the age groups 0–59 (4.0, 95% CI 2.0–7.8) and 60–69 (2.9, 95% CI 1.4–5.7), but not in age groups 70–79 (1.6, 95% CI 0.9–2.8) and 80+ (0.7, 95% CI 0.5–1.2; fig. 3B). With stratification by vaccine type, the increase in RR of hospitalisation appeared significant for both Moderna (1.8, 95% 1.1– .) and Pfi er Bio tech (. 1. – . fig.).

Discussion

Using surveillance data on COVID-19-related hospitalizations and deaths from Switzerland between 1 July 2021 to 1 December 2021 and accounting for the dynamics of vaccine coverage over time, by age and location, we estimated that non-fully vaccinated individuals have 12.5 times the risk of hospitalization and 10.4 times the risk of death compared with fully vaccinated individuals. This corresponds to a vaccine effectiveness of 92% against hospitalisation and 90.3% against death. This is in agreement with other studies about vaccine effectiveness of mRNA vaccines [13–16]. Note that delta was the dominant SARS-CoV-2 variant in Switzerland during this time period.

We also investigated the potential waning of vaccine effectiveness over time. We found evidence of a lower vaccine effectiveness in age groups above   which could be

Figure 1: (A) Proportion of hospitalised and deceased COVID-19 patients reported as fully vaccinated among all reported COVID-19-related hospitalisations and deaths. The dashed vertical line corresponds to the starting date of the analysis. (B) Evolution of SARS-CoV-2 vaccine coverage in the population by age group. (C) Cantonal differences regarding the overall SARS-CoV-2 vaccine coverage and the proportion of fully vaccinated individuals having received the Moderna vaccine in the population (as of one week before the end of the study period).
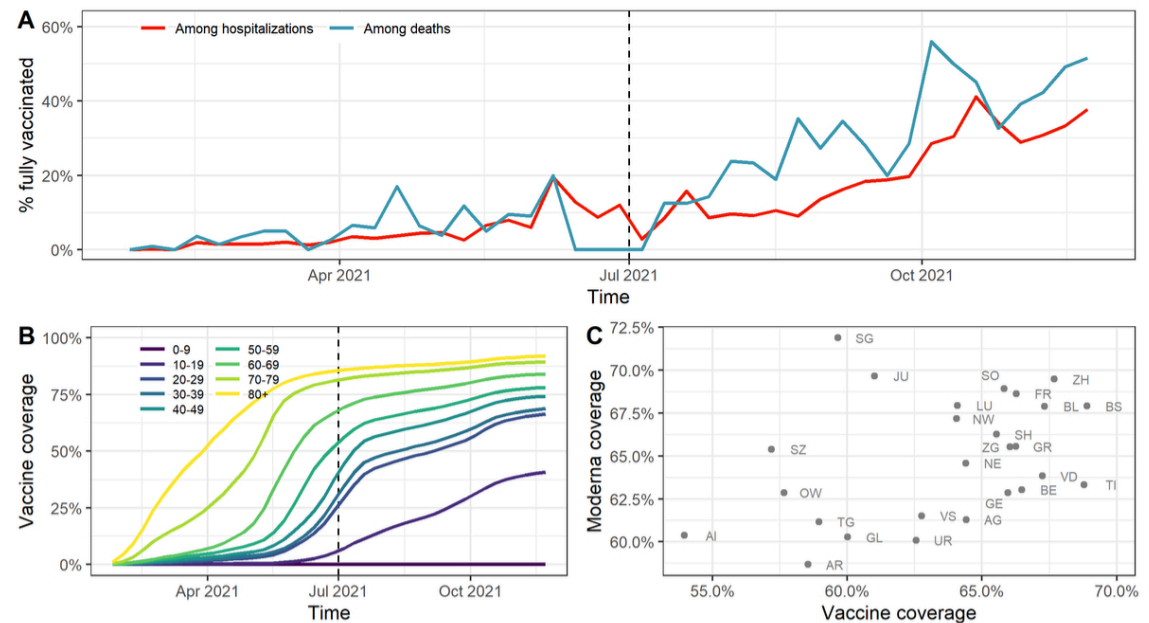

Figure 3: Change in the relative risk (RR9 of COVID-19-related hospitalisation depending on the time since vaccination in weeks (reference is 0–12 weeks), overall (panel A), by age group (panel B) and by vaccine type (panel C). Numbers correspond to group sizes (n), analysis for vaccine type (panel C) is based on fewer observations, as people with unknown vaccine type (n = 120, 19%) were excluded.
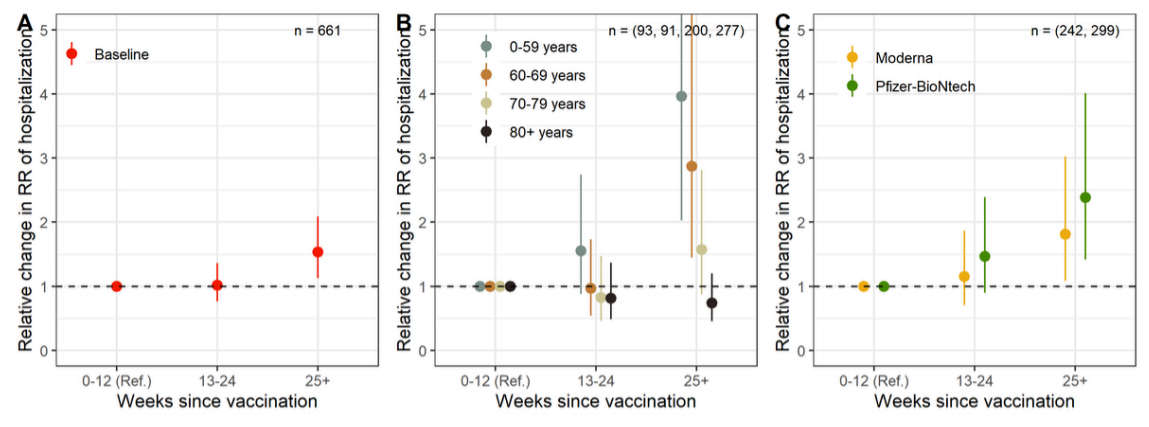
caused by a weaker immune response, but could also be interpreted as an indirect evidence of waning, as older age groups were vaccinated first. Similarly, we found a decrease in vaccine effectiveness in the months of October and November 2021, which also constitutes indirect evidence of waning. Directly investigating the variation in vaccine effectiveness by time since vaccination, we did not find evidence of a reduction of vaccine effectiveness in the group 13 to 24 weeks after vaccination compared to the reference group 0 to 12 weeks. In the group 25+ weeks after vaccination, vaccine effectiveness appeared to be moderately reduced (increase in the RR of hospitalisation by 1.5). To give a sense of the effect size, this value of 1.5 would correspond to a reduction of vaccine effectiveness from 92% to 88%.

On a closer look, this reduction of vaccine effectiveness in the group of people vaccinated for 25 weeks and more did not appear consistently across age groups. It was visible only in the age groups below 70, to a lesser extent in the age group 70 to 79, but not in the age group 80+. This pattern could reflect an actual faster waning of immunity in

younger individuals [17], although an opposite effect with a faster waning at older age ("immunosenescence") has also been described [18]. It could also have been due to a confounding effect, whereby individuals younger than 70 with comorbidities were more likely to have been vaccinated for a longer time (as they were prioritised in the early stages of the vaccination campaign) and were also more likely to be hospitalised upon infection with SARS-CoV-2. Confounding by occupation could also play a role, as for instance healthcare workers were both more likely to have received vaccination early and more likely to be exposed to SARS-CoV-2. In any case, this apparent decrease of vaccine effectiveness in age groups below 70 has to be seen in relation to a higher baseline vaccine effectiveness.

The reduction in vaccine effectiveness was apparent for both the Moderna and the Pfizer-BioNtech vaccines. We thus found some direct but inconclusive evidence of a moderate waning of mRNA vaccine effectiveness against hospitalisation after 25 weeks, which is in agreement with data from Israel [19], Qatar [20] and New York state [21]. However, our findings are in contrast with other studies that showed considerably faster waning among older individuals after more than 6 months [22]. Of note, the direct comparison of vaccine types suggested that Pfizer-BioNtech is associated with a slightly higher RR of hospitalisation than Moderna (relative change of 1.8, 95% CI 1.5–2.1; supplementary fig. S4), as was shown in previous studies [14].

This study has some strengths and limitations. There was a substantial proportion of hospitalisations and deaths with missing data on the vaccination status. We proposed several sensitivity analyses to circumvent this issue. Applicable without control group or long follow-up times, our approach used individual data and reverse conditionality to estimate the RR of hospitalisation or death for not fully vaccinated compared with fully vaccinated persons, taking into account the dynamics of vaccine coverage by age group and location. This quantity can be estimated using different types of stratification, and is closely related to vaccine effectiveness. Our approach relied on several assumptions. In order to interpret the RR in terms of vaccine effectiveness, we assumed that, within a population of the same age group, in the same location and during the same time frame, fully vaccinated and non-fully vaccinated individuals (1) are as likely to be exposed to the disease; (2) are as likely to be reported to surveillance authorities if they are hospitalised or deceased; and (3) are as likely to disclose their vaccination status if they are reported. Since our study looked at hospitalisations, we believe that assumptions (2) and (3) are likely to hold, but assumption (1) might be violated. If, for example, vaccinated individuals were feeling more protected owing to the vaccination, they might have been less careful and thus more exposed to the disease. This in turn would mean that the estimated RR in our study would lead to an underestimate of vaccine effectiveness. We grouped the small number of partially vaccinated individuals with the non-vaccinated, which may have led to a slight underestimation of vaccine effectiveness. However, due to the very small number of partially vaccinated (as people only remain in this state for a few weeks), the influence of partially vaccinated individuals on the overall results are likely to have been negligible. We

Figure 2: (A) Relative risk (RR) of COVID-19-related hospitalisation for individuals without full vaccination compared to individuals with full vaccination in the baseline analysis, in three sensitivity analyses, by age group, and by month. (B) Relative risk of death for individuals without full vaccination compared to individuals with full vaccination in the baseline analysis, in three sensitivity analyses, by age group, and by month. Numbers correspond to group sizes (n).
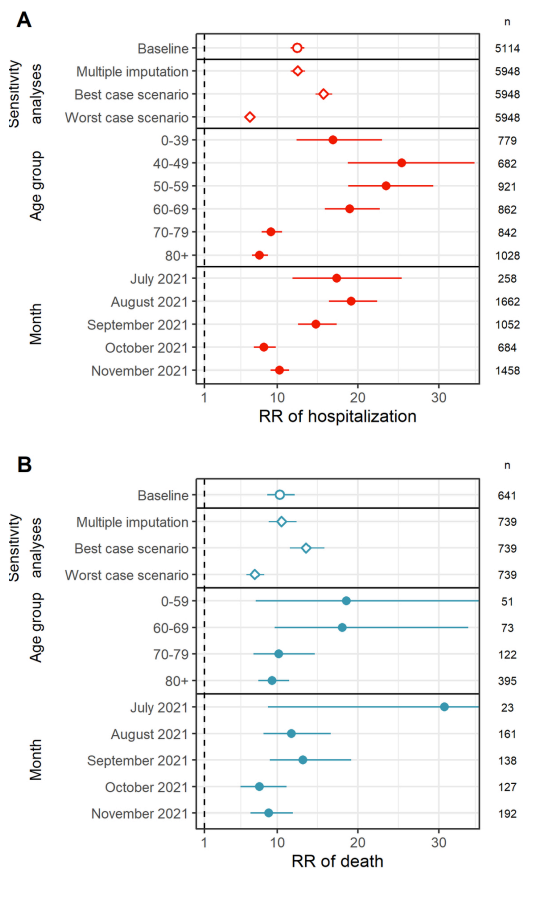
also ignored the healthy vaccinee effect, whereby newly vaccinated people are likely to be healthier than the general population, reducing the risk of severe outcomes upon infection. We did not account for other potential confounding factors associated with both vaccination and the risk of hospitalisation or death besides age, time and location. Next to comorbid conditions and occupation, potential confounding factors include socioeconomic status [23] and differential behaviour between vaccinated and non-vaccinated people. We also did not account for increasing levels of natural immunity among non-vaccinated people as time passes, which would lead to an underestimation of effectiveness of vaccines. Investigating this last point would require precise knowledge of the history of infection in hospitalised patients and in the general population.

Conclusions

We assessed real-world vaccine effectiveness against severe forms of SARS-CoV-2 infection from routine surveillance data in Switzerland, confirming the high effectiveness of mRNA vaccines from Moderna and Pfizer-BioNtech against hospitalisation and death in all age groups. Effectiveness appeared comparatively lower in age groups over 70, suggesting the importance of booster vaccinations. We found some evidence that the effectiveness is moderately waning over time. However, confounding by comorbid conditions and the increasing levels of natural immunity among non-vaccinated in time was not accounted for. Repeated analyses will be able to better assess waning and the effect of boosters. This approach could be implemented in most routine surveillance settings to monitor vaccine effectiveness in real time.

Potential competing interests
All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest was disclosed.

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Supplementary appendix to "Assessing real-world vaccine effectiveness from routine surveillance data in Switzerland, an observational study"

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1 Methods

1.1 Model structure

We use a model to estimate vaccine effectiveness against hospitalization or death from routine surveillance data, accounting for the varying dynamics of vaccination coverage by age and canton. We present the model using hospitalizations and vaccine effectiveness against hospitalization as an example, but the same applies to deaths.

Consider only all reported COVID-19 hospitalizations H, that can be either fully vaccinated (V) or not fully vaccinated $(\bar{V})$. We define the relative risk of hospitalization without full vaccination compared to with full vaccination

$$RR = \frac{\Pr(H|\bar{V})}{\Pr(H|V)}$$

where $\Pr(H|V)$ and $\Pr(H|\bar{V})$ refer to the probability of becoming hospitalized despite full vaccination or without full vaccination, respectively. The relative risk of hospitalization without full vaccination compared to with full vaccination translates into a relative risk reduction of hospitalization through:

$$RRR = 1 - \frac{1}{RR}$$

Now consider the observed proportion of fully vaccinated among hospitalizations, $\Pr(V|H)$. If the vaccine has no effect at all, that is if $RR = 1$, we expect it to be the same as the proportion of fully vaccinated in the general population at this time and place

$$\Pr(V|H) = \Pr(V).$$

If, however, the vaccine helps preventing hospitalizations, this equality will not hold. Bayes rule tells us that

$$\Pr(V|H) = \frac{\Pr(H|V)\Pr(V)}{\Pr(H)}.$$

We can apply the law of total probability to the denominator

$$\Pr(V|H) = \frac{\Pr(H|V)\Pr(V)}{\Pr(H|V)\Pr(V) + \Pr(H|\bar{V})\Pr(\bar{V})}$$

and then, using equation 1, replace $\Pr(H|\bar{V})$ by $RR \times \Pr(H|V)$

$$\Pr(V|H) = \frac{\Pr(H|V)\Pr(V)}{\Pr(H|V)\Pr(V) + RR \times \Pr(H|V)\Pr(\bar{V})}$$

and simplify to finally obtain

$$\Pr(V|H) = \frac{\Pr(V)}{\Pr(V) + RR(1 - \Pr(V))}.$$

We rely upon the assumption that the vaccination status was captured without bias among hospitalized.

1.2 Estimation

If we have data about the proportion of fully vaccinated in the population and about the proportion of fully vaccinated among hospitalized COVID-19 cases, then it becomes possible to estimate vaccine effectiveness against hospitalization.

For that we use a likelihood-based approach. Let y_i be the vaccination status of case i (1 is fully vaccinated, 0 is not fully vaccinated). We also need the information about the vaccine coverage corresponding to case i. at the time that case i was reported t_i. We know that in Switzerland, the vaccination campaigns were cantonal and prioritized vulnerable populations (that can be approximated by age). As a result, vaccination coverage progressed differently in different age groups, and progressed at different rates in different cantons.

Therefore we consider v_i, the vaccination coverage at time t_i in the population of the same canton and age group as case i. We can then write the following likelihood:

$$\Pr(y_i|RR) = \text{Bernoulli}(p_i)$$

where p_i is the expected probability that case i is fully vaccinated

$$p_i = \frac{v_i}{v_i + RR(1 - v_i)}.$$

We can then estimate $\widehat{RR}$ by optimizing

$$\mathcal{L}(y, RR) = \prod_i \text{Bernoulli}(p_i).$$

Note that RR is strictly positive. We consider $\widehat{RR}$ as an estimator of the relative risk of hospitalization without full vaccination compared to with full vaccination, adjusted for the dynamics of vaccine coverage by canton and age group.

1.3 Covariates

We may consider that vaccine effectiveness against vaccination can vary according to individual characteristics, unrelated to the dynamics of vaccine coverage. Following the principles of general linear models, we extend the model to allow for such variation and consider RR as a linear combination (on the log scale) of

$$RR = \exp(\alpha + X\beta)$$

where α is an intercept, β is a vector of coefficients and X is a matrix of covariates. The exponential function ensures that RR remains positive. With this formulation, we can study the variation of vaccine effectiveness by age group or time since vaccination. If there is only 1 covariate, this approach will lead to the same results as stratification by levels of the covariate.

1.4 Relative change in RR by vaccine type

The present model also applies to relative effectiveness between Moderna and Pfizer-BioNtech. In that case, the analysis is limited to fully vaccinated only, and the comparison is on the proportion of each type of vaccine among fully vaccinated hospitalizations. The equations above hold if we replace V and $\bar{V}$ (meaning fully vaccinated or not fully vaccinated) by V_M and V_P (meaning vaccinated with Moderna or vaccinated with Pfizer-BioNtech). In this situation of course, we only conclude on the relative effectiveness of one type of vaccine compared to another, without any consideration for the overall effectiveness that can be high for both.

1.5 Relative change in RR by time since vaccination

The previous approach can be extended to assess the change in the RR of hospitalization by time since vaccination. In that case, the analysis is limited to fully vaccinated only, and the comparison is on the proportion of hospitalized people that have been vaccinated for 0 to 12 weeks (V_1), for 13 to 24 weeks (V_2) or for 25 weeks or more (V_3). In this case we use three equations:

$$\Pr(V_1|H) = \frac{\Pr(V_1)}{\Pr(V_1) + \gamma_2 \Pr(V_2) + \gamma_3 \Pr(V_3)}$$

for the expected proportion of V_1,

$$\Pr(V_2|H) = \frac{\Pr(V_2)}{1/\gamma_2 \Pr(V_1) + \Pr(V_2) + \gamma_3/\gamma_2 \Pr(V_3)}$$

for the expected proportion of V_2, and

$$\Pr(V_3|H) = 1 - \Pr(V_1|H) - \Pr(V_2|H)$$

for the expected proportion of V_3. We can then estimate γ_2 and γ_3 by maximizing a categorical likelihood. The values of γ_2 and γ_3 can then be interpreted as the relative change in the RR of hospitalization for individuals of group V_2 and V_3, respectively, compared to the reference group V_1.

2 Additional results

2.1 Missing vaccination status

There was high missing of vaccination status early 2021, which gradually decreased down to around 10-15% in the last few months (Figure S1). This was due to the fact that the clinical notification form was adapted to collect information about vaccination status in early 2021, but this new version was not immediately adopted by all health professionals.
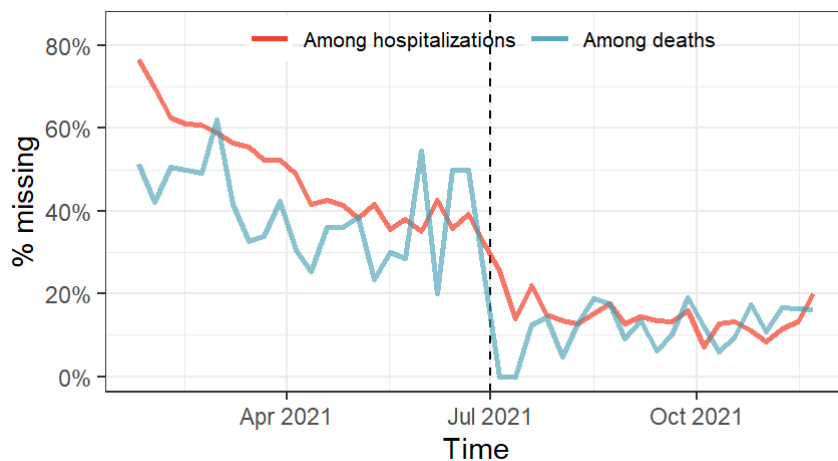

Figure S1. Proportion of hospitalizations and deaths with missing information about the vaccination status. The dashed vertical lien corresponds to the starting date of our analyses.

2.2 Vaccine types

Early vaccination campaigns in Switzerland used about equally Moderna or Pfizer-BioNtech, but Moderna was used more often from June 2021 onwards. Johnson-Johnson started being used in October 2021.
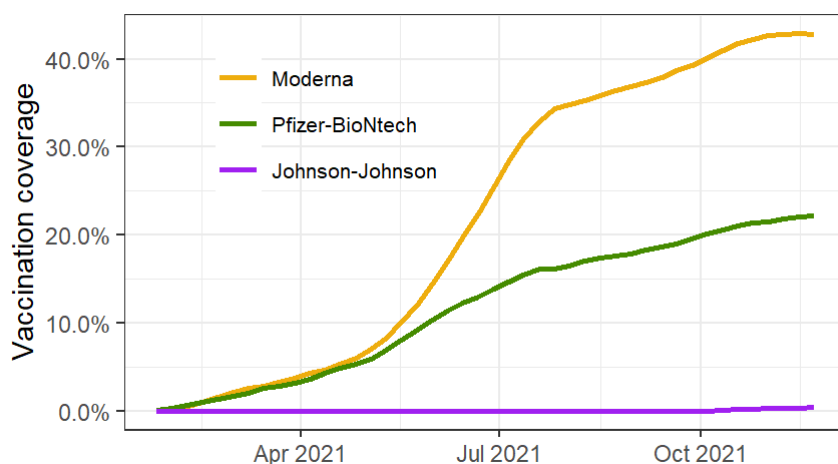

Figure S2. Vaccine coverage in Switzerland over time by type of vaccine (Moderna, Pfizer-BioNtech and Johnson-Johnson).

2.3 Vaccine effectiveness against hospitalization and death

These tables show the estimates of RR of hospitalization or death without full vaccination compared to full vaccination used to produce Figure 2 in the main article. We also show the corresponding values of the relative risk reduction against hospitalization or death ($1-1/RR$), that can be interpreted as estimates of vaccine effectiveness.

Table S1. Relative risk of hospitalization (and 95% confidence intervals) for non-fully vaccinated compared to fully vaccinated, with the corresponding estimations of vaccine effectiveness against hospitalization.

Stratification		Relative risk of hospitalization	Vaccine effectiveness against hospitalization
None	Baseline	12.5 (11.7-13.4)	92.0% (91.4-92.5%)
	Multiple imputation	12.6 (11.7-13.5)	92.1% (91.5-92.6%)
	Best case scenario	15.7 (14.7-16.8)	93.6% (93.2-94.1%)
	Worst case scenario	6.6 (6.2-7.0)	84.9% (84.0-85.7%)
Age group	0-39	16.9 (12.4-23.0)	94.1% (92.0-95.7%)
	40-49	25.4 (18.8-34.4)	96.1% (94.7-97.1%)
	50-59	23.5 (18.8-29.3)	95.7% (94.7-96.6%)
	60-69	19.0 (15.9-22.7)	94.7% (93.7-95.6%)
	70-79	9.3 (8.1-10.6)	89.2% (87.6-90.6%)
	80+	7.8 (6.9-8.9)	87.2% (85.5-88.7%)
Month	July 2021	17.4 (11.9-25.4)	94.2% (91.6-96.1%)
	August 2021	19.2 (16.4-22.4)	94.8% (93.9-95.5%)
	September 2021	14.8 (12.6-17.4)	93.2% (92.1-94.2%)
	October 2021	8.4 (7.1-9.8)	88.0% (85.9-89.8%)
	November 2021	10.3 (9.2-11.5)	90.3% (89.1-91.3%)

Table S2. Relative risk of death (and 95% confidence intervals) for non-fully vaccinated compared to fully vaccinated, with the corresponding estimations of vaccine effectiveness against death.

Stratification		Relative risk of death	Vaccine effectiveness against death
None	Baseline	10.4 (8.8-12.2)	90.3% (88.6-91.8%)
	Multiple imputation	10.8 (9.1-12.8)	90.7% (89.0-92.2%)
	Best case scenario	13.6 (11.6-15.9)	92.6% (91.4-93.7%)
	Worst case scenario	7.2 (6.2-8.4)	86.2% (83.9-88.1%)
Age group	0-59	18.5 (7.3-46.9)	94.6% (86.4-97.9%)

Stratification		Relative risk of death	Vaccine effectiveness against death
	60-69	18.1 (9.7-33.6)	94.5% (89.7-97.0%)
	70-79	10.2 (7.1-14.7)	90.2% (85.8-93.2%)
	80+	9.4 (7.7-11.5)	89.3% (86.9-91.3%)
Month	July 2021	30.7 (8.9-106.1)	96.7% (88.8-99.1%)
	August 2021	11.8 (8.3-16.6)	91.5% (88.0-94.0%)
	September 2021	13.2 (9.1-19.1)	92.4% (89.0-94.8%)
	October 2021	7.8 (5.5-11.2)	87.2% (81.7-91.1%)
	November 2021	8.9 (6.7-12.0)	88.8% (85.1-91.6%)

2.4 Relative risk of hospitalisation by month and age group

Figure 2 of the main paper, together with table S1, shows estimates of the RR of hospitalization without full vaccination compared to full vaccination stratified by age group or by month. We also considered stratifying by age group and by month, in order to assess whether the decrease of RR with calendar time is different depending on the age group. The decrease in October and November can be observed in age groups 70-79 and 80+. The low number of hospitalizations leads to high levels of uncertainty among younger age groups.
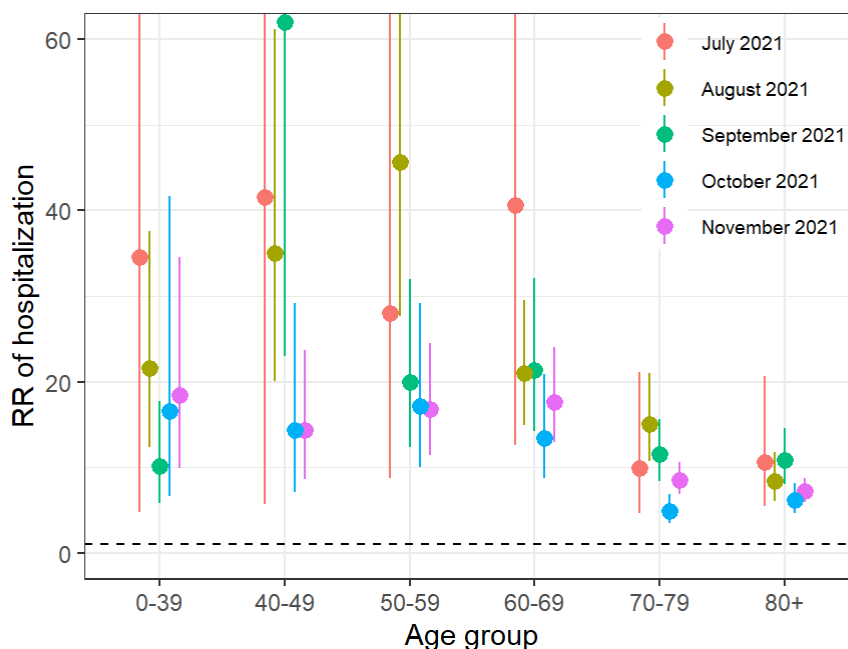

Figure S3. Relative risk of hospitalization for non-vaccinated individuals compared to vaccinated individuals stratified by age group and month.

2.5 Comparing vaccine types

Because the vaccine type was missing in a large proportion of fully vaccinated hospitalized cases (Table 1), we could not directly estimate the RR of hospitalization for non-fully vaccinated compared to fully vaccinated by vaccine type. However, restricting the analysis to fully vaccinated hospitalized cases with known vaccine type, we could assess the relative effectiveness between Moderna and Pfizer-BioNtech (see Methods section). This comes with the assumption that hospitalized cases are as likely to display which vaccine they received if they received Moderna or PfizerBioNtech. We did not consider Johnson-Johnson here give the low number of cases. We estimate that the RR of hospitalization for fully vaccinated with Pfizer-BioNtech compared to fully vaccinated with Moderna was 1.8 (95%CI: 1.5 to 2.1). We also consider a stratification by age or by month (Figure S4).
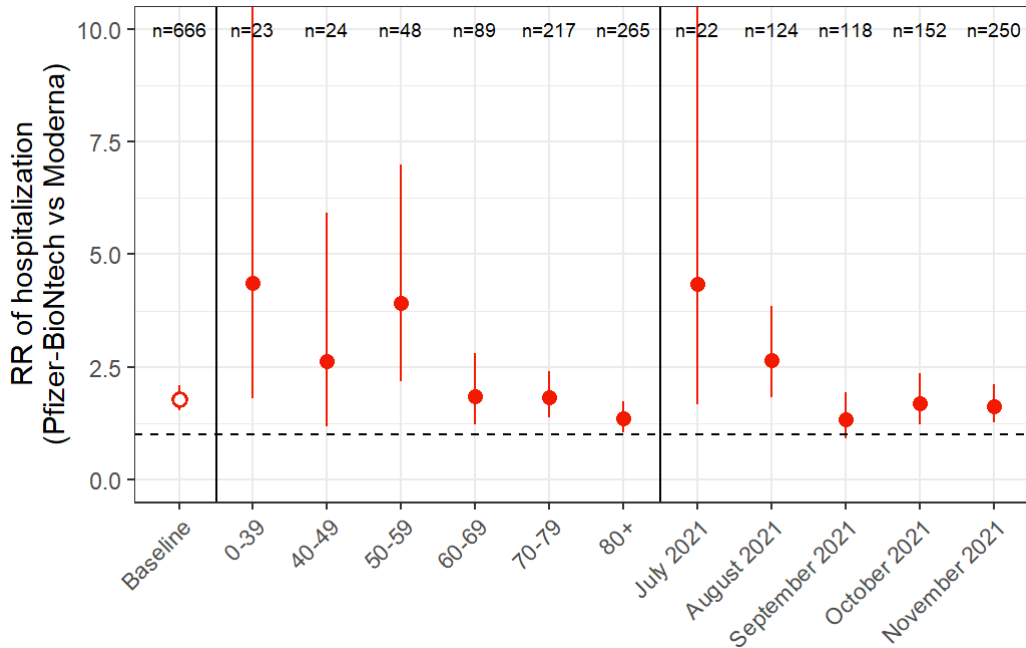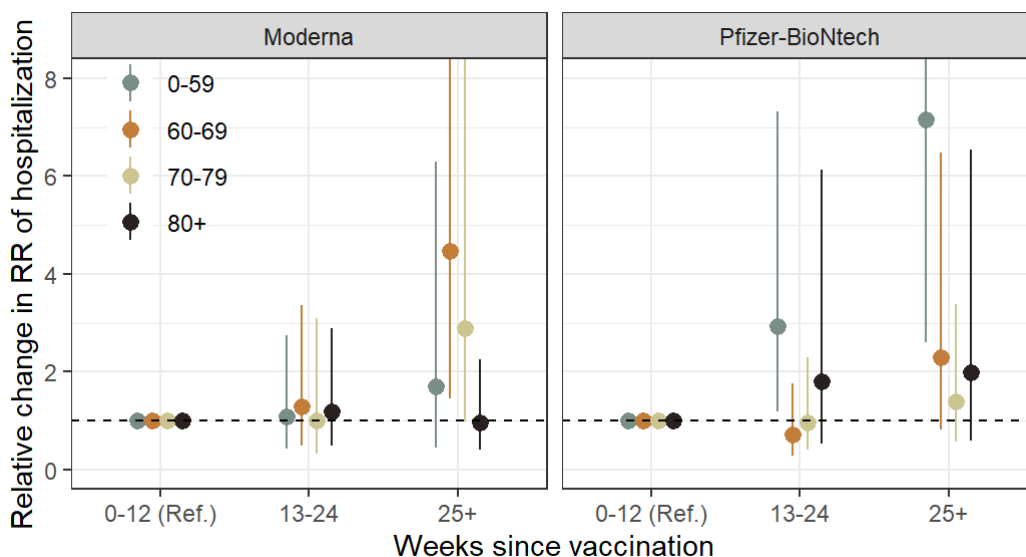

Figure S4. Relative change in the RR of hospitalization for individuals fully-vaccinated with Pfizer-BioNtech compared to individuals fully-vaccinated with Moderna, overall, by age group, and by month.

2.6 Waning by vaccine type and age group

Figure S5. Relative change in the RR of hospitalization for individuals fully-vaccinated with Pfizer-BioNtech compared to individuals fully-vaccinated with Moderna, overall, by age group, and by month.

3 Simulation study

3.1 Simulate vaccination coverage

We start by simulating vaccination coverage for a year following a typical vaccination campaign. We consider 5 age groups, and assume that the coverage will be higher in older age groups. We also assume that the number of daily vaccinations starts high and decreases with time, and scale the coverage so that it ends at 95% in the oldest age group.

```
WEEKS = 1:52
AGE_GROUPS = 1:5
COV_MAX = .95
coveragedata = expand_grid(week=WEEKS, age_group=AGE_GROUPS) %>%
  mutate(coverage=rpois(length(WEEKS)*length(AGE_GROUPS),10*1/week*age_group)) %
       >%
  group_by(age_group) %>%
  mutate(coverage=cumsum(coverage),
         coverage=age_group*coverage/max(coverage)/max(AGE_GROUPS)*COV_MAX)
```

```
ggplot(coveragedata) +
  geom_line(aes(x=week,y=coverage,colour=factor(age_group))) +
  labs(colour="age_group") +
  scale_y_continuous(labels=scales::percent,limits=c(0,1))
```
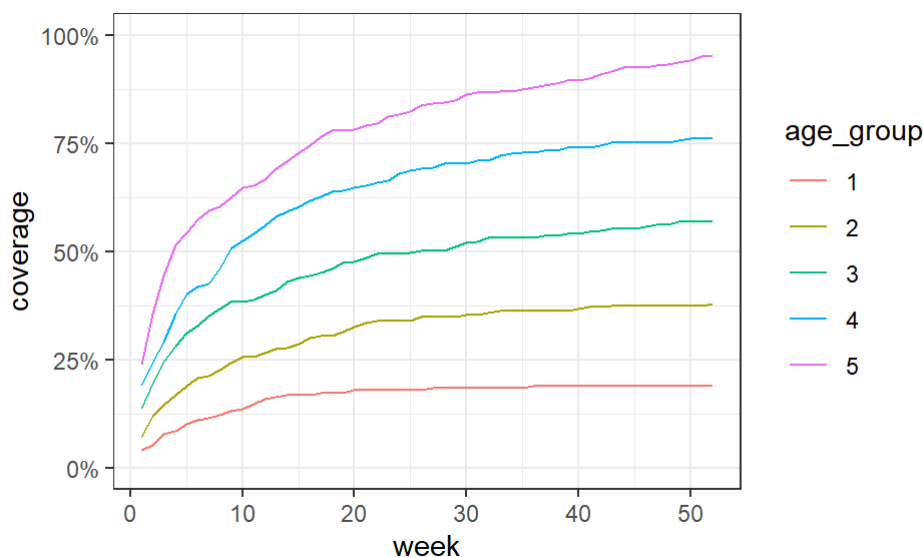

Figure S6. Simulated vaccination coverage in time by age group.

3.2 Simulate vaccination status among hospitalized

```
N = 5000
CHOSEN_RR = 10
```

We simulate typical surveillance data on hospitalized patients. We generate 5000 patients and attribute to each a week of hospitalization and an age group uniformly. Using the coverage data, we link each patient with the vaccination coverage at the corresponding time in the corresponding age group.

```
survdata = tibble(id=1:N,
                  week=sample(WEEKS,N,replace=TRUE),
                  age_group=sample(AGE_GROUPS,N,replace=TRUE)) %>%
   left_join(coveragedata,by=c("week","age_group"))
```

We now simulate the expected probability that each patient is vaccinated or not depending on (1) vaccination coverage and (2) a relative risk of hospitalization among non-vaccinated compared to vaccinated of 10. For that we use the following equation:

$$\Pr(V|H) = \frac{\Pr(V)}{\Pr(V) + RR \times (1 - \Pr(V))}$$

where $\Pr(V|H)$ is the probability of being vaccinated given hospitalization, $\Pr(V)$ is the probability of being vaccinated in the population (i.e. coverage), and RR is relative risk of hospitalization among non-vaccinated compared to vaccinated ($RR = 10$). We then draw the actual vaccination status of each individual (`0` for not vaccinated, `1` for vaccinated) from a Bernoulli distribution.

```
survdata = survdata %>%
   mutate(expected_vacc=coverage/(coverage+CHOSEN_RR*(1-coverage)),
          vacc=rbinom(N,size=1,prob=expected_vacc))
survdata
```

```
## # A tibble: 5,000 x 6
##       id  week age_group coverage expected_vacc  vacc
##    <int> <int>     <int>    <dbl>         <dbl> <int>
## 1      1    43         2    0.376        0.0567     0
## 2      2    13         3    0.410        0.0649     1
## 3      3    17         4    0.626        0.143      0
## 4      4    37         5    0.883        0.430      1
## 5      5    39         5    0.896        0.462      0
## 6      6    35         2    0.362        0.0538     0
## 7      7    14         5    0.707        0.195      1
## 8      8    50         1    0.19         0.0229     0
## 9      9    43         1    0.19         0.0229     0
## 10    10     3         2    0.146        0.0168     0
## # ... with 4,990 more rows
```

Aggregating over time, this results in an increasing trend in the proportion of vaccinated among hospitalized cases.

```
survdata %>%
  dplyr::group_by(week) %>%
  dplyr::summarise(prop_vaccinated=mean(vacc)) %>%
  ggplot() +
  geom_line(aes(x=week,y=prop_vaccinated))+
  scale_y_continuous(labels=scales::percent)
```
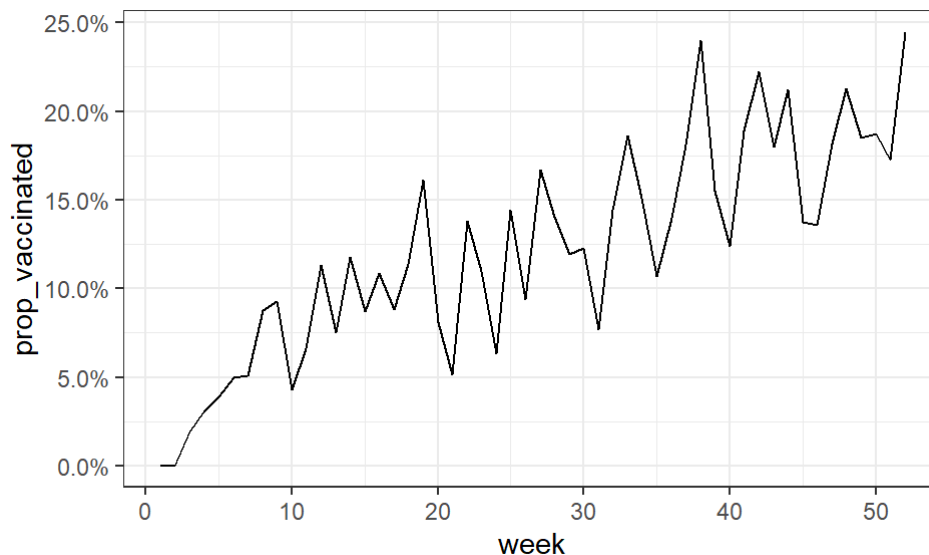

Figure S7. Simulated proportion of vaccinated among hospitalized patients.

3.3 Estimate vaccine effectiveness

We can then apply the function `estimate_rr()` and directly estimate the RR of hospitalization among non-vaccinated compared to vaccinated from individual data on the vaccination status of hospitalized patients and the vaccine coverage corresponding to each patient.

```
EST_RR = estimate_rr(vacc=survdata$vacc, coverage=survdata$coverage)
```

We find a maximum likelihood estimate of 10.8839744 with a 95% confidence interval of 9.9218687 to 11.9393738. This can be compared to the value of 10 used to simulate the data.

```
as_tibble(EST_RR) %>%
  ggplot() +
  geom_pointrange(aes(x="Estimate",y=rr,ymin=rr_lower,ymax=rr_upper)) +
  geom_point(aes(x="Chosen value",y=CHOSEN_RR),colour="firebrick") +
  scale_y_continuous(limits=c(0,CHOSEN_RR*1.2)) +
  labs(x=NULL)
```
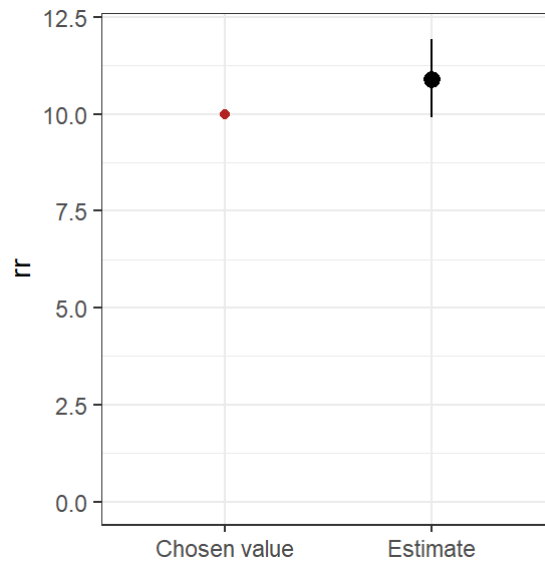
Figure S8. Estimated value of the relative risk of hospitalization among non-vaccinated compared to vaccinated compared to the value chosen to simulate the data.

We can transform the RR into a relative risk reduction with $1 - 1/RR$, resulting in estimates of 90.8121798% with a 95% confidence interval of 89.9212534% to 91.6243514%. With the assumption that the differences between the vaccinated and non-vaccinated groups (e.g. in terms of exposure or risk of hospitalization) only come from the vaccination status, this relative risk reduction can be interpreted as vaccine effectiveness.

3.4 Extensions

The function `estimate_rr()` allows the estimation of the overall RR of hospitalization for non-vaccinated compared to vaccinated. It can be applied to other outcomes, e.g. the RR of death or the RR of confirmed case, provided that individual data with vaccination status is reliably collected.

If there are reasons to believe that the RR varies according to individual characteristics (e.g. age or sex), it is possible to estimate the variation in RR according to covariates with function `estimate_rr_covariates()`. Note that it is necessary to provide the covariates in matrix form.

If vaccination status includes 3 possibilities instead of 2 (e.g. including several vaccine types or vaccination by time since vaccination), then it is possible to estimate the RR for different possibilities with function `estimate_rr_3groups()`. It uses an extension of the equation of $\Pr(V|H)$ to obtain $\Pr(V_1|H), \Pr(V_2|H)$ and $\Pr(V_3|H)$ and a categorical distribution instead of Bernoulli (see supplementary appendix). The 3 groups can be for instance not vaccinated, vaccinated with vaccine 1 and vaccinated with vaccine 2. Or, restricting only to vaccinated people, the 3 groups can be vaccinated for fewer than 3 months, 3-6 months and more than 6 months.