A methodological framework for assessing the benefit of SARS-CoV-2 vaccination following previous infection: case study of five to eleven year olds

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Abstract

Vaccination rates against SARS-CoV-2 in children aged five to 11 years remain low in many countries. The current benefit of vaccination in this age group has been questioned given that the large majority of children have now experienced at least one SARS-CoV-2 infection. However, protection from infection, vaccination or both wanes over time. National decisions on offering vaccines to this age group have tended to be made without considering time since infection.

There is an urgent need to evaluate the additional benefits of vaccination in previously infected children and under what circumstances those benefits accrue. We present a novel methodological framework for estimating the potential benefits of COVID-19 vaccination in previously infected children aged five to 11, accounting for waning. We apply this framework to the UK context and for two adverse outcomes: hospitalisation related to SARS-CoV-2 infection and Long Covid.

We show that the most important drivers of benefit are: the degree of protection provided by previous infection; the protection provided by vaccination; the time since previous infection; and future attack rates. Vaccination can be very beneficial for previously infected children if future attack rates are high and several months have elapsed since the previous major wave in this group. Benefits are generally larger for Long Covid than hospitalisation, because Long Covid is both more common than hospitalisation and previous infection offers less protection against it.

Our framework provides a structure for policy makers to explore the additional benefit of vaccination across a range of adverse outcomes and different parameter assumptions. It can be easily updated as new evidence emerges.

Introduction

The Pfizer-BioNTech paediatric COVID-19 vaccine for five to eleven year olds has been approved in the US, EU and UK since late 2021.

Before Omicron emerged at the end of 2021, when most children had not yet been infected and the vaccine displayed excellent efficacy [1–3], roll-out in the US [4], Israel and European countries was motivated by a desire to prevent adverse outcomes in children infected with COVID-19 for the first time. The Omicron SARS-CoV-2 variant proved both more transmissible and more immune evasive, with more rapid waning of protection from previous infection or vaccination [2,5–14], and a much higher incidence of reinfections [15]. Protection against new infection and subsequent hospitalisation has been shown to be highest in children who had both vaccination and previous infection [3,9,10]. Protection against adverse outcomes can be very high shortly after infection, but as protection wanes over the following months and years, adding further protection through vaccination might provide significant benefit. The question is then: how much benefit and when would vaccination (with respect to previous exposure) maximise any benefit?

In England, three large Omicron waves from January to July 2022 resulted in a very high number of infections in children [16]. Population antibody surveys estimated that 82% of primary school children had antibodies to SARS-CoV-2 in March 2022 [17], and almost all of these antibodies will have been as a result of exposure to SARS-CoV-2 and not vaccination (as general roll out did not begin until April 2022). Not all children seroconvert and some will serorevert over time [18]. As such, given continued infections since then (including a large July 2022 wave in five to 11 year olds), 82% is likely a significant underestimate as of February 2023. Estimates of incidence from the UK Office for National Statistics (ONS) Coronavirus (COVID-19) Infection Survey [19] show that the highest number of new infections over the whole of the pandemic is in children aged two to 11 [up to November 2022] and cumulative incidence in two to 11 year olds was 98% over the first two Omicron waves (December 2021 to June 2022) [20] .

While most high-income countries offered COVID-19 vaccination to children aged five to 11 [21–24], uptake remains low. In England, vaccines were offered to five to 11 year olds from April 2022 but COVID-19 vaccination for five to 11 year olds with no underlying health conditions will end from June 2023 [25]. As of April 2023, only 10% of five to 11 year olds have received at least one dose [26]. The vaccination coverage in this age group will decrease every year as under-fives (who have no access to the vaccine in the UK) and vaccinated 11 year olds grow older, entering and leaving this age group respectively. As protection from previous infection wanes, should this decision to stop primary vaccination for five to 11 year olds be revisited?

A revised assessment of vaccine benefit for five to 11 year olds is required to reflect the current situation, namely the *added benefit* of a vaccine dose over the protection provided as a consequence of previous infection. The wording of “a vaccine dose” is deliberate: while the efficacy of a vaccine dose wanes relatively rapidly in children in the context of the Omicron variant (particularly against infection), protection can be increased again through subsequent doses, whether that is a second dose [7,12,13,27] or a booster dose [9,13]. We must consider waning from vaccination and infection in combination with population infection dynamics to determine not just whether to vaccinate but also when.

Current mathematical models for estimating vaccine benefit typically do not take waning into account (see Box 1). Waning is complicated by the fact that the extent and duration of immunity against Omicron reinfection depends on which variant, or sub-variant, caused the initial infection and when that infection occurred [28]. With a soup of new, more immune evasive, Omicron variants continuing to emerge [29,30] and national prevalence fluctuating between 1.5-8% since January 2022 [16], it seems likely that Omicron variants and waning immunity will continue to keep prevalence above 1.5% in the near future [31,32].

Whilst protection against serious outcomes such as hospitalisation and death persists for longer than protection against infection, avoidance of reinfection remains important in view of emerging evidence on the association between number of reinfections and burden of acute and post-acute COVID-19 sequelae (albeit most relevant studies pertain only to adults) [33] and the ONS Infection Survey data reporting no evidence of reduction in reported Long Covid in children on reinfection compared to first infection (albeit in a relatively small sample) [34].

In this paper, we present a simple but flexible framework for determining likely additional benefit of a vaccine dose in children aged five to 11 with previous infection, accounting for waning of immunity. We illustrate the framework in the UK context using current best evidence for averting hospital admissions related to SARS-CoV-2 infection and new cases of Long Covid.

BOX 1: Existing models for risk/benefit of vaccination against SARS–CoV-2 in 5-11 year olds

When the US Centers for Disease Control and Prevention (CDC) carried out its risk-benefit assessment in November 2021 [4], it based its calculations on the projected different levels of incidence into the future, and estimated new infections, hospitalisations and cases of Multisystem Inflammatory Syndrome in Children (MIS-C) prevented. The CDC assessment acknowledged that at that point, 38% of the age group had had at least one infection, but considered that infection would not provide 100% protection and it waned with time. The CDC (necessarily) used efficacy estimates for the vaccine against Delta and assumed no new variants.

Hawkes and Good [35] modelled the roll-out of the five to 11 year old vaccine in Canada, using a deterministic susceptible-infected-recovered (SIR) model and found modest clinical benefit to children at essentially zero risk. However, their model assumed that immunity from either vaccination or infection did not wane and their SIR models do not allow for reinfection.

Keeling and Moore have also modelled impact of vaccination in five to 11 year olds in England [36]. Their most recent reported run of the model was in November 2021 (prior to Omicron), with the results informing the decision-making of the UK approval body, the Joint Committee for Vaccination and Immunisation (JCVI). They showed modest clinical benefit across a range of uptake estimates, assuming that roll out would begin in March 2022. Protection from the vaccine or previous infection is assumed constant (no waning) [37,38], meaning little benefit of vaccination is *intrinsically* possible after large waves of infection because children are assumed to already be protected.

The JCVI had not approved the five to 11 vaccine for this age group in February 2022, by which time a large proportion of five to 11 year olds had been infected in the January 2022 wave. Thus, for its February 2022 deliberations, the JCVI commissioned mathematical models of two future wave scenarios: a more serious or less serious variant, with different attack rates (33% and 27% respectively) and hospitalisation rates (0.064% and 0.023% respectively). The models additionally assumed that 80-90% of children had been previously infected and that previous infection

provided 50-70% additional protection against disease outcomes. No waning was considered from either vaccination or past infection, and vaccine effectiveness was considered the same whether previously infected or not (i.e. no benefit ascribed to hybrid immunity) [39]. On the basis of the results of these models, in February 2022, the JCVI assessed that the benefit of the vaccine did outweigh the risks, but that any benefit was marginal, with between 78 (less severe variant) and 450 hospital admissions (more severe variant) prevented if all children without an underlying health condition were vaccinated [39].

Methods

In the below analysis, we assume all children have been previously infected (note that this underestimates vaccine benefit, since benefit will be larger in the absence of previous infection). The timeline that frames our analysis is shown in Figure 1. We also assume, consistent with the evidence, that vaccination after infection can never reduce protection against adverse outcomes from subsequent reinfection. Notation used is summarised in Table 1.

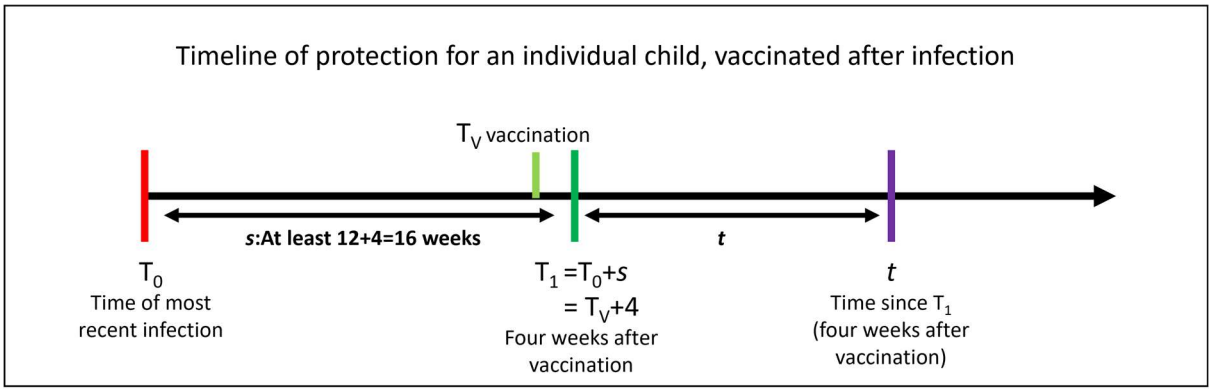

Figure 1 – Timeline showing sequence of events for vaccination following prior infection. Note we use four weeks to allow for maximal vaccine efficacy following Lin et al. [7].

Quantifying the additional benefit of vaccination for an individual previously infected child

At time $t + s$ since infection, the probability of an unvaccinated child experiencing an adverse outcome of type A if reinfected can be expressed as:

$$r_A(1 - X_A(t + s)) \quad (1)$$

where r_A is the probability of adverse outcome A in an unvaccinated child infected for the first time and X_A is the degree of protection afforded by previous infection at time $t + s$. Protection (X_A) can range from 0 (no protection) to 1 (complete protection).

If a child is vaccinated at time T_V (i.e., T_0 + s -4 weeks = $T_1 - 4$ weeks; see Figure 1), then the probability of that child experiencing an adverse outcome of type A if (re)infected at time t can be expressed as:

$$r_A(1 - Y_A(t)) \leq r_A(1 - X_A(t + s)) \quad (2)$$

where Y_A is the degree of protection afforded by vaccination against adverse outcome of type A at time $t + 4$ weeks after vaccination in a previously infected child. Again, protection can range from 0 (no protection) to 1 (complete protection) but is (consistent with evidence) assumed at least as high

as $X_A(t+s)$. The key (reasonable) assumption here is that protection of vaccination following previous infection **only** depends on time since vaccination and does not depend on the interval between previous infection and vaccination. Note we use four weeks to allow for maximal vaccine efficacy following Lin et al. [7].

Therefore, the additional benefit (reduction in adverse event probability) offered by vaccination to a child infected *t+s* months ago can be expressed as:

$$r_A\big(1 - X_A(s+t)\big) - r_A\big(1 - Y_A(t)\big) = r_A(Y_A(t) - X_A(t+s)) \quad (3)$$

Incorporating waning

For both vaccination and infection, efficacy wanes over time. The functional form of waning is currently uncertain but Lin et al. [7] provide tables for waning efficacy of vaccination and previous infection against reinfection, and waning efficacy of vaccination against hospitalisation (not broken down by previous infection status) in children aged five to 11. While Lin et al. show good vaccine effectiveness by two weeks, maximal efficacy is at four weeks, after which waning begins. For both protection against reinfection and hospitalisation upon reinfection, waning from week four post-vaccination can be approximated by a linear relationship over a time frame of a few months (up to the end of the available data). Lin et al. also provide tables of effectiveness of previous infection alone against reinfection and hospitalisation upon reinfection, which we have plotted in Figure 2 [7]. While the waning over time is not linear, as a first approximation and on the timescale of several months, it is adequate for our use case. Waning is clearly much faster for protection against reinfection than it is for protection from serious illness as measured by hospitalisation upon reinfection. We assume that we can also use a linear approximation for waning following vaccination with previous infection.

Let c and d represent the rate of waning following infection alone and vaccination after infection respectively, then a linear relationship implies the following:

$$Y_A(t) = \max(0, (Y_A(0) - dt) \text{ and } X_A(t) = \max(0, X_A(s) - ct) = \max(0, X_A(0) - cs - ct) \quad (4)$$

It is reasonable to suppose that the rate of waning from vaccination following previous infection *cannot be faster than* waning from previous infection alone. So, a *conservative* estimate of additional vaccine benefit is to assume that the rate of waning from vaccination following previous infection is equal to that of infection alone, i.e. $d = c$ in equation 4.

Substituting equations from (4) into equation (3) then gives the following additional benefit to a child in reducing the probability of adverse event of type *A*:

$$\begin{cases} r_A(Y_A(0) - ct - X_A(0) + ct + cs) = r_A(Y_A(0) - X_A(0) + cs), & Y_A(t) > 0 \text{ and } X_A(s+t) > 0 \quad (5a) \\ r_A(Y_A(0) - ct), & Y_A(t) > 0 \text{ and } X_A(s+t) = 0 \quad (5b) \\ 0, & Y_A(t) = 0 \text{ and } X_A(s+t) = 0 \quad (5c) \end{cases}$$

Equation parts 5b and 5c simply say that benefit is just the full vaccine benefit if protection from previous infection has waned to zero (5b), or the benefit is zero if we are sufficiently far in the future for benefit from both infection and vaccination to have waned to zero (5c).

Notation

Table 1 – Notation used to set up the new framework

Variable	Description
A	Adverse outcome of type A due to infection
VA	Adverse outcome of type A due to vaccination
T_0	Time of a child's most recent infection
T_V	Time of vaccination
$T_1 = T_v + 4$	Time of maximal vaccination efficacy in weeks (while Lin et al show good effectiveness by two weeks, their reported maximal efficacy is at four weeks, after which waning begins [7])
s	Time between last infection and four weeks after vaccination ($T_1 - T_0$), where this is at least 16 weeks (allowing 12 weeks between infection and vaccination, as per current UK guidance)
t	Time since four weeks after vaccination
$X_A(s+t), \quad 0 \leq X_A(s+t) \leq 1$	The degree of protection afforded by previous infection against adverse outcome of type A at time $s+t$ after infection in an unvaccinated child. Protection can range from 0 (no protection) to 1 (complete protection)
$Y_A(t), 0 \leq X_A(s+t) \leq Y_A(t) \leq 1$	The degree of protection afforded by vaccination *after previous infection* against adverse outcome of type A at time t after administration + four weeks (to allow for maximum efficacy). Protection can range from $X_A(s+t)$ (same as previous infection alone) to 1 (complete protection)
r_A	Probability of adverse event of type A for a child infected *for the first time*
r_{VA}	Probability of adverse event of type A due to the vaccine
N_{VA}	The number of adverse events of type A caused by the vaccine if the whole population of children were vaccinated
$N_A = r_A N$	Number of adverse events of type A across the whole population of N children, if all infected *for the first time*
$N_{VA} = r_{VA} N$	Number of adverse events of type A across the whole population of N children, if all vaccinated
$p, 0 \leq p \leq 1$	The proportion of children infected (again) in the future, over some time period, where the proportion can range from 0 (no new infections) to 1 (all children reinfected)
c, d	The rate of waning of protection following infection or vaccination following infection respectively

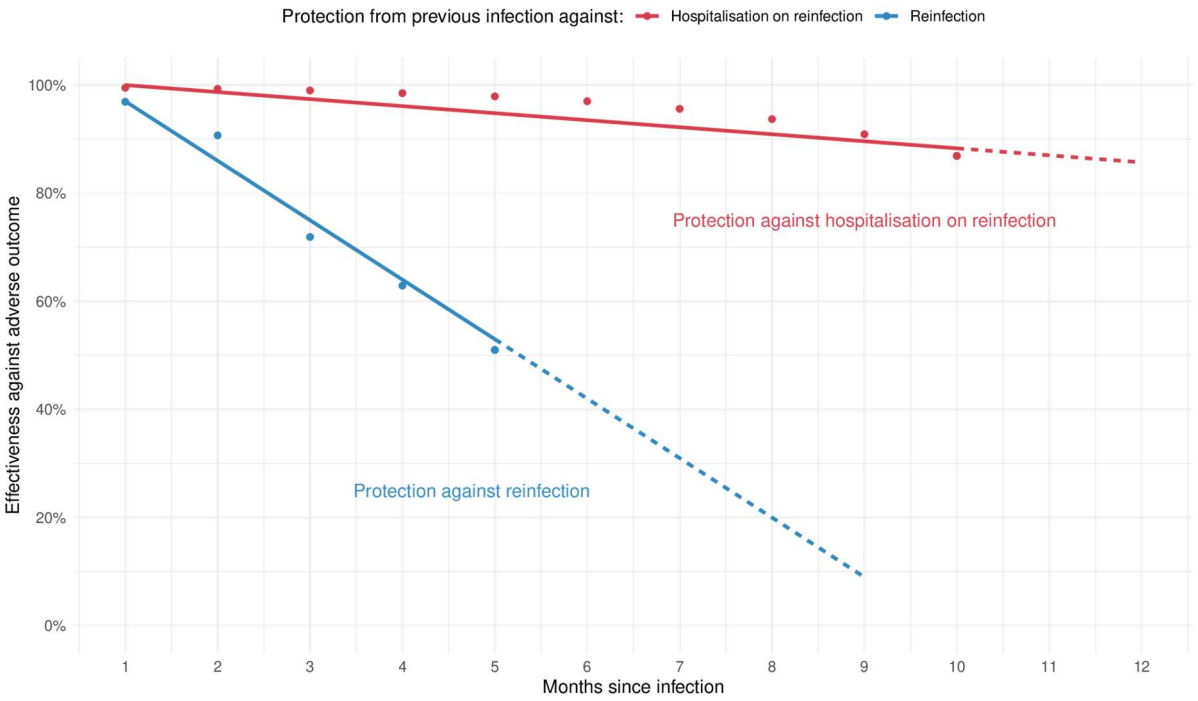

Figure 2 –– Charts showing the approximate linear relationship of waning of protection from previous infection (without vaccination) vs reinfection (blue) and hospitalisation on reinfection (red). Data taken from the supplemental material from Lin et al. [7]. Linear fits are shown as solid lines, with dashed lines showing the linear extrapolation.

As long as equation 5a holds, the **time since vaccination** does not make a difference to the **additional** benefit from vaccination for children previously infected. Instead, the benefit depends only on the difference between maximum protection of vaccination after prior infection ($Y_A(0)$), maximum protection after infection ($X_A(0)$) and time between last infection and 4 weeks after vaccination, s. For severe outcomes from reinfection, protection from previous infection is likely to be non-zero over long time periods (so equation 5a holds). Protection against reinfection will wane more quickly but we note that since the benefit provided by equation 5b is strictly greater than that provided by 5a, considering only equation 5a will provide a lower bound of benefit even once protection from previous infection has dropped to zero (for long intervals $s+t$).

<u>Estimating additional benefit for the six months post vaccination following previous infection with linear-approximated waning</u>

We consider a timescale of six months for vaccine benefit as a plausible minimum interval between vaccine boosters and/or before the pandemic context might change from a new variant or an updated vaccine (so equation 5c does not apply). We consider a maximum time window of 15 months between infection and 4 weeks after vaccination (s).

Over the whole population, the time since previous infection, s, varies, but given the linearity in equation (5a) we can simply take expectations such that the expected reduction in the number of adverse events of type A for attack rate p is given by:

$$pN_A\big(Y_A(0) - E(X_A(s)\big) = pN_A(Y_A(0) - X_A(0) + cE(s)) \qquad (6)$$

We also need to consider the possibility of adverse events from the vaccine. Thus, assuming all children vaccinated, the final expected reduction in the number of adverse events of type A is given by:

$$pN_A\big(Y_A(0) - X_A(0) + cE(s)\big) - N_{VA} \quad (7)$$

The key is that as long as we have a reasonable estimate for N_A (number of adverse events following *first* infection if *all* children infected) and reasonable estimates for maximal vaccine effectiveness for children with previous infection, $Y_A(0)$, then we can quantify the additional benefit of vaccination across a range of estimates for effectiveness of protection of infection after several weeks and months ($X_A(0) - cE(s)$) and the proportion of children infected in the future. This framework can be applied to the child population as a whole, or to sub-cohorts (such as children with and without underlying health conditions).

Parameterising the framework and depicting plausible benefit

Plausible estimates drawn from the literature for the relevant parameters are given in the following sections. The UK Office for National Statistics (ONS) Coronavirus (COVID-19) Infection Survey has released estimates of the cumulative incidence by age group by variant up to November 2022. Among two to 11 year olds, it estimates a cumulative incidence of 48% over the seven-month Delta period; 60% over the three-month Omicron BA.1 period and 38% over the four-month Omicron BA.2 wave (98% over seven months) [20]. Autumn 2022 saw much smaller waves in two to 11 year olds, but nonetheless ONS reports a cumulative incidence of 26% in two to 11 years olds from June to November 2022 [20]. We thus consider a full range of future attack rates over six months from 0% to 100%.

By using a plausible estimate for maximum effectiveness of the vaccine following previous infection ($Y_A(0)$) and previous infection alone ($X_A(0)$) and using a plausible estimate for the waning rate, c, we can assess the possible additional benefit from vaccination across possible future attack rates and a range of plausible intervals, *E(s)*, between infection and 4 weeks after vaccination from 4 months (the minimum) to 15 months using contour plots.

For a given estimate of average time from last infection to four weeks post vaccination, *E(s),* we can also estimate maximum and minimum additional benefit of vaccination for maximum and minimum parameter estimates and plot the plausible range across all values of future attack rates, *p*.

We now illustrate this framework with two important adverse outcomes. Firstly, the most commonly considered adverse outcome where there is also excellent real-world data: hospital admissions related to a SARS-CoV-2 infection, stratified by the presence of an underlying health condition. Secondly, we consider Long Covid, where estimates are far more uncertain, but the number of children affected is potentially much larger. Other models of vaccine benefit have typically not taken Long Covid into account due to uncertainties involved, so it provides an opportunity for demonstrating the utility of our simple framework.

We note that we do not explicitly consider new cases of paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS or MIS-C in the US) within the hospitalisation adverse outcome. PMS-TS is a severe adverse outcome of SARS-CoV-2 infection in children occurring typically 4 to 6 weeks post infection [40]. While there is evidence that vaccination reduces rates of PIMS-TS [6,41], the extent to which previous infection or hybrid immunity protect

against PIMS-TS is very uncertain. Thankfully, rates of PIMS-TS are also much lower than hospitalisation rates. Thus, in this paper, we use overall hospitalisations related to SARS-CoV-2 infection as an adverse outcome of interest, which will include PIMS-TS admissions. As more evidence emerges on PIMS-TS following reinfection (with or without vaccination), the framework could also be applied explicitly to PIMS-TS as an outcome.

Results

Hospital admissions averted

Table 2 gives the parameters used for applying the model to hospital admissions averted for children with and without an underlying health condition (UHC). Further detail on the parameterisation is given in the appendix. We note that we explicitly exclude incidental hospitalisations with SARS-CoV-2 infection from our parameter estimates, using new analysis from Wilde et al. (under review) [42].

Table 2 - main parameters used to quantify hospital admissions averted in children with and without an underlying health condition (UHC) aged 5-11.

Parameter for children aged 5 to11	Value for those with UHC	Value for those with no UHC	Comment (further detail provided in the Appendix)
Number in population resident in England	687,935	4,036,891	We use 2021 UK Office for National Statistics (ONS) estimates for overall population of 5-11 year olds [43]. We derive a UHC rate of 14.6% based on the proportion of medical records for all of the five to 11 year olds in the NHS Digital Trusted Research Environment where there was evidence of a health condition linked to greater vulnerability to severe disease with SARS-CoV-2 infection by the JCVI [25] as per the method described in Wilde et al (under review) [42]. This rate is then applied to the overall ONS population estimate.
Proportion infected at least once by March 2022	82%		We use the UK Office for National Statistics (ONS) Schools Infection Survey antibody study for primary school children from early 2022, reporting 82% of primary school age children had antibodies. The actual proportion infected is likely to be much higher (ONS infection survey estimates cumulative incidence of 123% by March 2022 [20]), so this is a conservative estimate. We assume the same proportion for children with UHC and those without UHC since we do not have a reliable way of estimating difference in infection likelihood between the two populations.
Number of hospital admissions directly associated with first ascertained SARS-CoV-2	3,375	3,465	We use the number reported in Wilde et al. (under review) [42] for first hospital admissions associated with first ascertained SARS-CoV-2 infection in children aged five to 11 and excluding admissions that are incidental to SARS-CoV-2

infection July 2020 to end February 2022			infection (see Wilde et al for details), from July 2020 to end of February 2022 in England. NOTE: this will be an underestimate of the total number since it excludes individuals that had an admission prior to July 2020. This means that the benefit of vaccination would be greater than estimated here.
Number of hospital admissions expected *if whole population had been infected for the first time* (N_A)	4,120	4,230	Obtained by dividing the number observed by the proportion of children infected in each group as given in row 2 above, to 3 significant figures.
Maximum protection of previous infection against hospitalisation from reinfection ($Y_A(0)$)	99.5%		Lin et al. [7] give an estimate of 99.5% efficacy at 1 month post infection against hospitalisation.
Maximum protection of vaccination in children with previous infection (at least 16 weeks after infection and 4 weeks after vaccination) ($X_A(0)$)	100%		Lin et al. [7] do not provide estimates for additional protection from vaccination but just say that it is higher than vaccination or infection alone. Bobrovitz et al [9] give an efficacy of over 95% at both three and 12 months after two or three doses of vaccine following infection.
The waning rate of protection from either vaccination following infection or infection alone (c)	1.3 percentage points per month (minimum 0.6 and maximum 1.7)		Estimated using the data in the supplemental material for Lin et al. [7] for protection from previous Omicron infection only. See appendix for fits for maximum and minimum ranges and Figure 2 for the central estimate.
The number of hospitalisations due to vaccine adverse events *if all children were vaccinated* (N_{VA})	1	7	A systematic review of vaccination for 5-11 year olds reported a myocarditis rate of 1.3-1.8/million vaccinations given [44]. Extrapolating this rate to the five to 11 year old population in UK (5 million) and conservatively assuming all would be hospitalised gives a central estimate of 8 hospital admissions due to the vaccine, which we split across UHC and non UHC children 1:7. We note that Watanabe et al. report no vaccine-caused deaths among 16.6 million injections [44].

The benefits across a range of possible intervals between previous infection and vaccination and all possible 6 month future attack rates are shown as contour plots in Figure 3 for children with (right panel) and without underlying health conditions (left panel) for a mid-range estimate of efficacy, assuming $Y_A(0) = 100\%$, $X_A(0) = 99.5\%$ and a waning rate $c = 1.3\%$ points/month (see Table 2).

The largest additional benefit is when a large proportion of children are infected (high attack rate) *and* the last significant wave of infection in children was a long time ago (over a year) (right hand top corner). Conversely, there is little added benefit when future attack rates are low *or* infection is relatively recent. This is because protection against hospitalisation from new infection is very high (99.5%) shortly after previous infection and there is little room for improvement from vaccination even at high attack rates.

Children with underlying health conditions are more vulnerable to severe disease (as shown by Wilde et al (under review) [42]) and the estimated number of hospitalisations averted with vaccination is slightly higher than in children with none of the specified types of these conditions [25], but at the cost of far fewer vaccinations required (0.7 million).[45]

Many children aged five to 11 years in England are now approximately a year out from their previous infection (two very large waves in January and March 2022 and a smaller wave in July 2022 [16]). Whilst previous infection is very protective against hospitalisation on reinfection in the months immediately following first infection, this protection does wane with time. Lin et al [7] estimate an efficacy of 86.7% at 10 months post infection. Our central, minimum, and maximum waning rates (see Table 2) provide a range of efficacy at 1 year of 84% (79% - 92%) from previous infection alone. Vaccinating at a year would (under our framework) restore efficacy to 100% immediately after vaccination (regardless of how much protection from previous infection has waned) which then wanes slowly over the following 6 months. As we are assuming waning happens at the same rate for vaccination following infection and from infection alone (a conservative estimate), the added benefit of vaccination over infection alone is simply the difference in efficacy immediately after vaccination. Vaccination an average of a year after previous infection thus adds between 8% (= 100% - 92%) and 21% (= 100% - 79%) protection. An illustrative range of potential benefit in terms of averted hospitalisations on reinfection for different 6-month future attack rates is shown in Table 3.

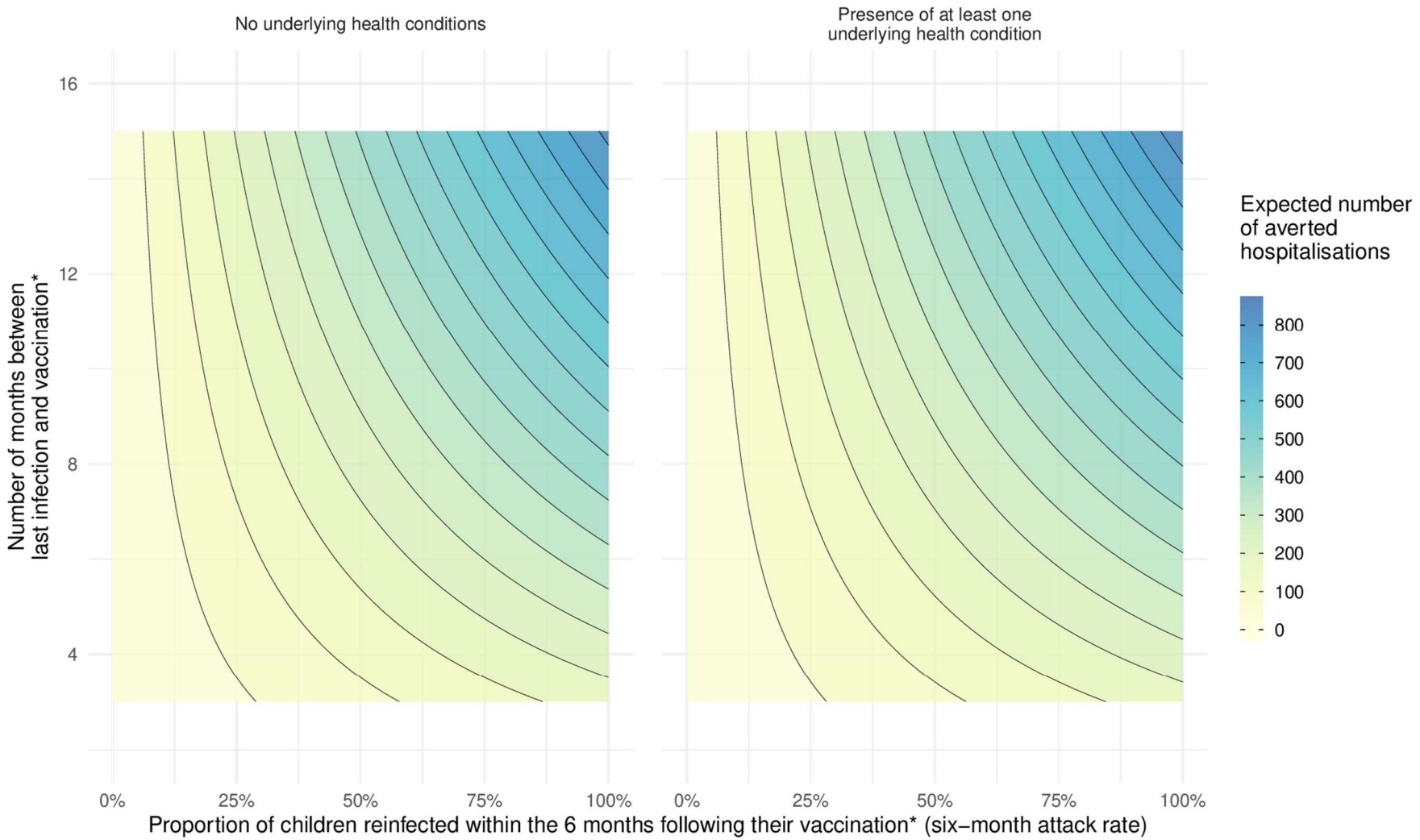

*Figure 3 – This figure shows the potential impact of vaccination amongst 5 - 11 year old children in terms of the number of hospital admissions that can be averted across a range of months since previous infection, to show the increasing impact of vaccination as both time since last infection and the six-month attack rate increase. *We define vaccination as the point in time at which 4 weeks have passed since the administration of a dose, to allow for effectiveness to peak and begin to wane [7].*

Table 3 – illustration of plausible range of benefit in terms of hospitalisations and new cases of Long Covid averted for vaccination an average of a year after previous infection for a range of attack rates in the 6 months following vaccination. All numbers rounded to reduce impression of precision and with plausible minimum and maximum estimates of efficacy (see Table 2 and Table 4).

Attack rate (proportion of children reinfected in the 6 months post vaccination)	Estimated number of **hospitalisations** averted on reinfection if all 4 million children without underlying health conditions (UHC) were vaccinated on average a year after previous infection.	Estimated number of new cases of **Long Covid** averted on reinfection if all 4.7 million children were vaccinated on average a year after previous infection.
5%	25 (10-35)	3,500 (800 – 6,500)
25%	160 (75 – 215)	18,000 (4,000 – 32,000)
40%	265 (120 – 350)	29,000 (6,500 – 51,000)
50% (ONS estimate an incidence rate of 45% in two to 11 year olds July - December 2022)	330 (160 – 440)	36,500 (8,000 – 64,000)
60%	400 (190 – 520)	43,500 (9,500 – 76,500)
75%	500 (240 – 660)	54,500 (12,000 – 96,000)
95% (ONS estimate an incidence rate of 98% in two to 11 year olds, Dec 2021 to June 2022)	640 (300 – 830)	69,000 (15,000 – 121,500)

Thus, the size of anticipated benefit on SARS-CoV-2-related hospitalisation at attack rates of about 50% (in the few hundreds) is considerably lower, but not negligible, than the over 2,000 hospitalisations expected if 50% of children were infected for the first time, even an average of a year after previous infection. This is because previous infection alone is very protective against new hospitalisation and that protection wanes relatively slowly. That said, as the time since previous infection increases there is benefit to a "top-up" vaccination and this will only increase further as more time elapses without new significant waves of infection in this age group.

Cases of Long Covid averted

Given the greater uncertainty in Long Covid parameters, we illustrate the range of benefit expected at a given average interval between infection and 4 weeks after vaccination, namely 1 year ($E(s) = 12$). We thus wish to parameterise equation 7 at *E(s)*=12 for cases averted: $pN_A(Y_A(0) - X_A(12)) - N_{VA}$.

Table 4 gives the parameters used for applying the model to cases of Long Covid averted. Further detail on the parameterisation is given in the appendix.

Table 4 -main parameters used to quantify Long Covid cases averted in children aged 5-11.

Parameter for children aged five to 11	**Value**	**Comment**
Number in population resident in England	4,724,826	We use 2021 UK Office for National Statistics (ONS) estimates for overall population of five to 11 year olds [43]
Incidence of Long Covid (ongoing symptoms lasting at least 3 months following first infection)	3.5%	A central estimate from recent studies and the American Academy of Pediatrics [46–49]
Number of children experiencing Long Covid if whole population had been infected for the first time (N_A)	165,000	Rounded to 3 significant figures
(Infection only): Protection of previous infection against new Omicron infection at *1 year* post infection (representing $X_A(0) - 12c$)	16%-36%	Bobrovitz et al [9] give an efficacy of 24.7% at 12 months with CI 16.4% to 35.5%.
(Hybrid): Maximum protection against reinfection of vaccination in children following previous infection. We are interested in efficacy *just after vaccination ($Y_A(0)$)*	59%-78%	Bobrovitz et al [9] give an efficacy of 69.0% at 3 months with CI 58.9% to 77.5%, and we use this as a conservative estimate of maximum vaccine benefit following previous infection. Note also that Dowell et al. [50] show that antibodies to SARS-CoV-2 are increased greatly in children with vaccination on top of previous immunity (from Omicron).
(Infection only): Minimum and maximum protection of previous infection against Long Covid once reinfected at least 1 year later	0%-40%	There is a great deal of uncertainty in the protection afforded by previous infection once reinfected. The UK ONS reports no significant difference in reporting Long Covid in two to 11 year olds 20 weeks after reinfection vs 20 weeks after first infection [34]. We choose a range of 0-40% as a plausible range.
(Hybrid): Maximum protection of vaccination following previous infection against Long Covid once reinfected	30%-70%	There is a great deal of uncertainty in the protection afforded by hybrid immunity once reinfected. Protection from vaccination alone is thought to be somewhere between 15%-50% [51]. A recent systematic review reported great uncertainty in the scale but likely definite benefit of vaccination in preventing Long Covid [52]. Assuming hybrid protection is better than vaccination alone, we choose a range of 30%-70%
Overall effectiveness of previous infection 1 year earlier against new Long Covid on reinfection.	16%-62%	Combining minimum and maximum ranges of respective protections above.
Overall effectiveness of vaccination after previous infection against new Long Covid on reinfection.	71%-93%	Combining minimum and maximum ranges of respective protections above.
The number of Long Covid cases due to vaccination if all children were vaccinated	0	There is no mechanism by which vaccination can cause Long Covid.

Figure 4 illustrates the expected number of additional cases of Long Covid over six months that could be averted by vaccination assuming an average time since infection of one year across the range of plausible benefit in children for a range of the proportion of children reinfected over that time period (attack rates). Note that for this example, we need to use estimates of protection from infection alone a year later and from vaccination shortly after vaccination (to get the benefit of vaccination a year after infection). Specific estimates at given future attack rates are also provided in Table 3 (essentially cross sections through Figure 4).

Firstly, while the pattern of increasing benefit is the same as for hospitalisations, the potential scale of cases averted is far higher (potentially 10,000 – 75,000 Long Covid cases averted in a medium 6-month wave with attack rates of 50-60%, if average time between previous infection and vaccination is a year). Secondly the plausible range of benefit is very wide, reflecting the large uncertainty in the evidence around the protection that vaccination and/or previous infection provide in preventing both infection and Long Covid once (re)infected. Given the potential scale of benefit, this highlights the urgency of understanding the protection from previous infection and hybrid immunity against Long Covid.

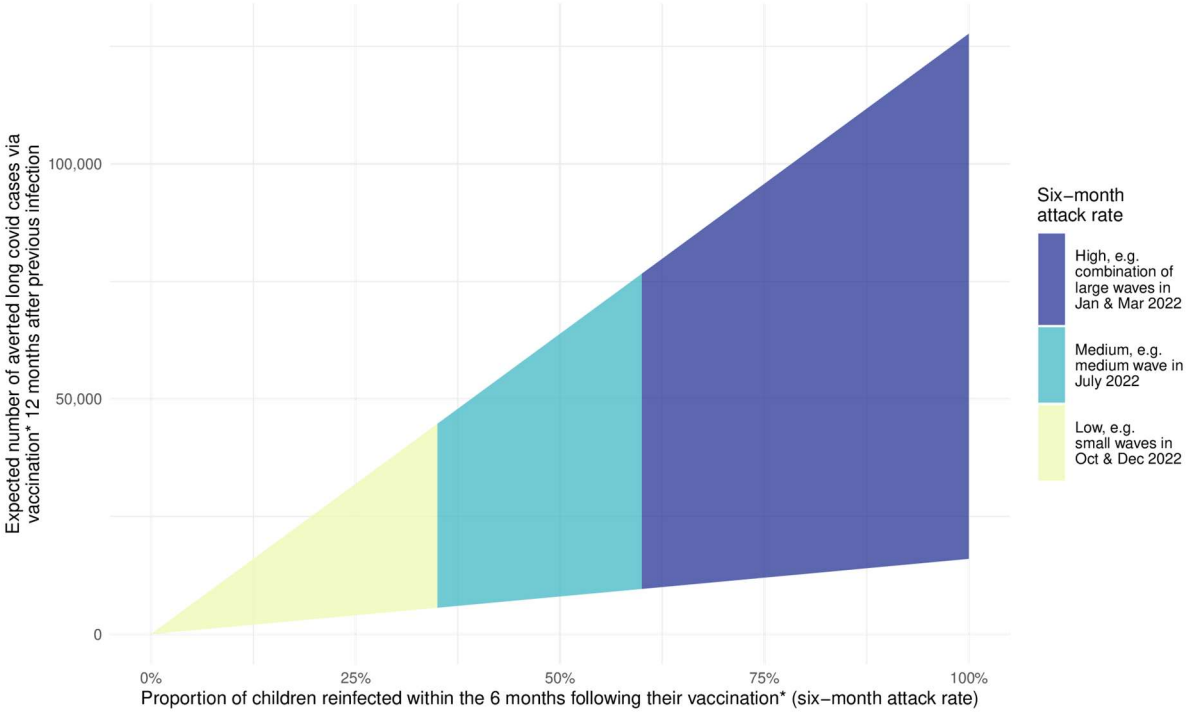

Figure 4 - This figure shows the potential impact of vaccination amongst 5 - 11 year-old children in terms of the number of new Long Covid cases that can be averted under varying attack rate scenarios in the six months following vaccination. We represent the uncertainty in infection and vaccination protection to show an example range of outcomes for the case where 12 months separate previous infection and receipt of a vaccine dose before allowing for a further month to reach vaccination as defined above (equation 8).*

**We define vaccination as the point in time at which 4 weeks have passed since the administration of a dose, to allow for effectiveness to peak and begin to wane [7].).*

Discussion

The benefit of vaccination in preventing adverse outcomes on new infection for children previously infected will be lower than its benefit for infection naïve children [12]. Extrapolating the UK's experience [26], it is likely that almost all children aged five to 11 in many countries will have experienced at least one SARS-CoV-2 infection. Thus, given vaccine uptake in this age group remains much lower than for adults, it is important to try to quantify what the additional benefit of vaccination is in previously infectedF children, especially as primary vaccination in healthy children is due to be withdrawn in the UK from the summer of 2023. In this paper, we have suggested a new framework for understanding the potential value of COVID-19 vaccination, incorporating waning and providing a robust and efficient method for illustrating both the range and the magnitude of possible benefit and the extent of uncertainty in those estimates given a set of modifiable parameters (e.g., duration since prior exposure, waning of immunity from previous infection and vaccination, vaccine side effects).

Applying this framework to the case of five to 11 year olds in England for a future moderate sized 6-month attack rate of about 50% [20] illustrates that there might plausibly be a relatively modest but important benefit with regards to hospitalisation risk from vaccinating all children without a UHC of around 400 averted hospitalisations in a population of 4.6 million. This benefit is much higher now than it was in spring 2022 (when vaccination was first offered) since many more five to 11 year old children are now a year or more out from their most recent infection [16,20]. There would be a similarly sized benefit from vaccinating all of the much lower number (~700,000) of children with any evidence of an underlying health condition placing them at increased risk of severe disease [25]. The potential benefit in preventing Long Covid is potentially much greater (tens of thousands of Long Covid cases averted) but the true figure is much harder to ascertain given the large uncertainty. We note that even if most cases of Long Covid in children resolve within a few months [53], those months still represent significant disruption to a child's education and life more broadly.

In essence, we illustrate that there is robust evidence for net benefit from continued vaccination of the five to 11 year old cohort, even after previous infection with SARS-CoV-2, where the scale of benefit depends most strongly on the future attack rate and the time since last infection. This extends the work of Keeling and Moore [36], showing that accounting for meaningful waning is possible (albeit in a very simple way) and in doing so, illustrates the importance of considering timing of vaccination (with reference to previous infection). In essence, the question that this framework exposes as being critical to an evidence-based policy is: at what point since previous infection would it be beneficial to *add* the immunity from the vaccine, given we know that both vaccine-related and infection-related immunity wane?

As we learn more about the risks of adverse outcomes from third or more infections and the efficacy of vaccination in those with many previous infections, the parameters can be updated accordingly without changing the framework.

Strengths and limitations

The key strength of this study is that the underlying modelling framework is flexible, allowing for a range of future scenarios (e.g. one can lower or increase range of efficacy to model new variants, more waning or better vaccines). Moreover, the framework incorporates adverse effects from the vaccines (equation 7). Finally, the framework can be easily extended to adults or any other sub-

population of interest to explore the benefits of further vaccine doses given previous infection or updated with more accurate parameter estimates as data become available, as long as the assumptions made are reasonable in that population.

However, there are four key limitations of the current framework. First, several assumptions were made in the model of benefit. Critically, we assumed that waning of protection occurs in a linear fashion based on available data [15], but this assumption is very likely to fail for longer time scales. Second, we assumed that the rate of waning protection from prior infection versus vaccination following infection were identical, which is also likely to be false (although, if anything, waning of hybrid immunity will be slower than from infection alone, thus this assumption would underestimate the benefit of vaccination post infection). Third, the parameter estimates around waning and protection offered by vaccination or infection against Long Covid are still very uncertain. Fourth, the framework itself only considers the direct benefits of individual protection from preventing hospitalisation and Long Covid.

There are number of indirect benefits as well which we have not considered. For example, a vaccinated cohort is less conducive to community transmission/spread, since hybrid immunity has been consistently shown to be higher and longer lasting than immunity from infection alone [7,10,50]. This would not only have knock-on benefits to other children, thereby further reducing risk of infection and adverse events, but would also break transmission chains which could result in older or otherwise vulnerable individuals contracting COVID-19, for whom there is a much higher risk of severe outcomes [54]. Furthermore, there are additional indirect benefits to the vaccinated individuals that have not been considered, including shorter or less severe Long Covid if it occurs [55] and reduced school-related absenteeism [56] as a consequence of reduced infection and Long Covid rates, that can have longer term health-related and socio-economic impacts [57].

On the other hand, we have also not considered potential indirect negative consequences such as missing school due to short-lived vaccine side effects or any impact on uptake of other childhood vaccines [39]. And finally, certain logistical assumptions have been made, e.g., assuming all vaccination happens instantaneously at a given timepoint or that all children will be vaccinated, which is not realistic. In light of these limitations, it is worth noting that this framework is not meant to replace a formal health economic analysis, but rather to move the debate about childhood vaccination forward acknowledging both widespread previous infection and waning protection from infection and vaccination.

Future Research

More research is clearly required to evaluate the societal and health economic case for vaccination in the 5-to-11-year-old population in the presence of widespread previous infection. Use of this framework highlighted where there are several key gaps in knowledge, which unless addressed will continue to limit the ability of policy makers and practitioners to fully understand the value of vaccination in this sub-population and others. For instance, more evidence is needed on how long protection from previous infection lasts, how long hybrid immunity lasts, and how this varies based on the type of vaccine or variant of initial (and increasingly, subsequent) infections.

Conclusions

We present a framework for visualising the additional benefit of vaccination in children given high levels of previous infection. The framework provides a way to estimate plausible ranges of benefit as

well as identifying where important research gaps remain. The framework allows for a synthesis of real-world evidence, modelling and projected scenarios to inform policy discussion. While our example is centred on the UK context, the basic framework is applicable to any country or region with appropriately defined parameters.

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Appendix

Parameterising the framework for hospital admissions averted

Previous work led by author Brown undertook detailed analysis of all child hospital admissions with COVID-19 in England, conducted as part of the British Heart Foundation Data Science Centre's COVID-IMPACT consortium [58].

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This analysis provided high quality data on the number of overall hospital admissions where SARS-CoV-2 was a contributing factor in children aged five to 11 associated with their first confirmed infection from July 2020 up to the end of February 2022, separated out by whether a child had evidence of an underlying health condition (UHC). For this estimate, a UHC was an underlying health condition recognised as placing the child at potentially having higher risk of severe disease in the UK Green Book [25]. The analysis also provided estimates of the number of children with and without an UHC in the overall population. For details of the methods in that study please see Wilde et al. (under review) [42].

The UK Office for National Statistics Schools Infection Survey reported that 82% of primary school pupils in England tested positive for SARS-CoV-2 antibodies by March 2022, and an incidence of 98% from mid December 2021 to mid June 2022 among 2 to 11 year olds, denoting high levels of exposure to SARS-CoV-2 as vaccination roll out did not begin until April 2022 [17,20].

Estimates for the range of protection provided against hospitalisation provided by previous infection alone and previous infection plus vaccination are taken from Lin et al. and Bobrovitz et al. [7,9] and assumed the same for children with and without UHC.

For estimating the bounds on a linear waning rate for protection against hospitalisation on reinfection, we used a minimum and maximum waning rate of 0.6 and 1.7 percentage points each month informed by the fits shown in Figure A1 below.

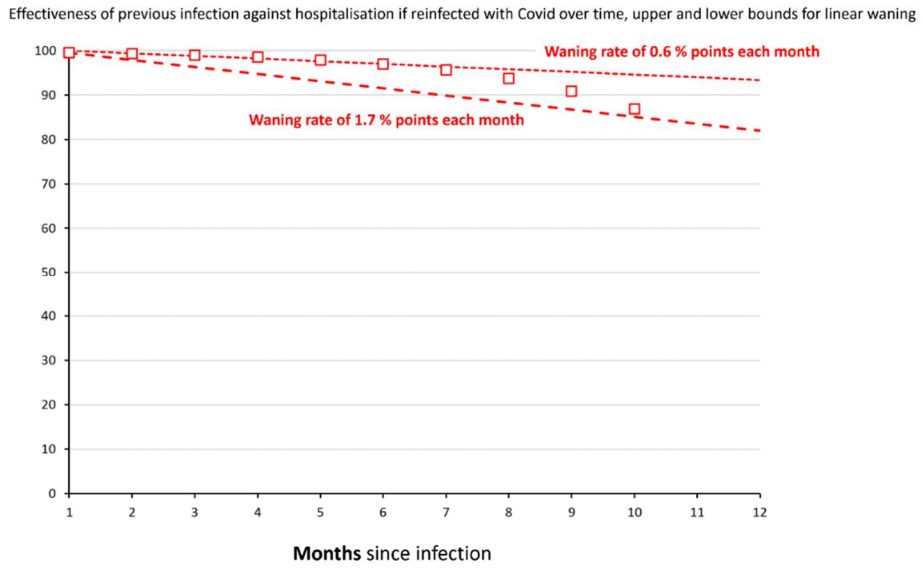

Figure A1 – fits of maximum and minimum linear waning to protection of previous infection against hospitalisation on new infection.

Parameterising the framework for Long Covid cases averted

For this analysis, we consider children as a whole group since reliable estimates for parameterising by underlying health condition do not exist to our knowledge.

There exist a wide range estimates of the incidence of Long Covid in children from 1.8% to 14% [59–61], using different cohorts, different definitions of Long Covid and different analysis methods. Three recent studies, all with some sort of control group (albeit with remaining significant limitations), put the percentage of children experiencing symptoms longer than two to three months (different studies use different definitions) following a SARS-CoV-2 infection at between 1.6% and 5% [46,47,49]. Recent guidance (September 2022) from the American Academy of Pediatrics gives a range of 2-5% of children experiencing ongoing symptoms after 3 months [48]. We use a central estimate of 3.5%, giving an N_A of 200,000 children in England (out of 5.7 million) who would have experienced Long Covid if all had been infected for the first time.

Vaccination and previous infection can reduce new incidence of Long Covid in two ways: firstly by preventing reinfection in the first place and secondly by reducing the chance of developing Long Covid once infected [51]. If z is the effectiveness in preventing infection and v the effectiveness of preventing Long Covid once infected, then the overall effectiveness, w, in preventing Long Covid is given by: $w=1-(1-z)(1-v)$, where z and v can vary for protection from infection or hybrid immunity.

Estimates for the range of protection provided against reinfection provided by previous infection along and previous infection and vaccination are taken from Bobrovitz et al. [9] and assumed the same for children with and without the specified underlying health conditions.