



RESEARCH ARTICLE

**REVISED** **Estimating the duration of seropositivity of human seasonal coronaviruses using seroprevalence studies [version 2; peer review: 3 approved]**

Eleanor M. Rees <sup>1,2</sup>, Naomi R. Waterlow <sup>1</sup>,  
Centre for the Mathematical Modelling of Infectious Diseases COVID-19 Working Group,  
Rachel Lowe <sup>1,2</sup>, Adam J. Kucharski<sup>1</sup>

<sup>1</sup>Centre for Mathematical Modelling of Infectious Diseases, London School of Hygiene & Tropical Medicine, London, UK

<sup>2</sup>Centre on Climate Change and Planetary Health, London School of Hygiene & Tropical Medicine, London, UK

**v2** First published: 03 Jun 2021, 6:138  
<https://doi.org/10.12688/wellcomeopenres.16701.1>

Latest published: 22 Nov 2021, 6:138  
<https://doi.org/10.12688/wellcomeopenres.16701.2>

**Abstract**

**Background:** The duration of immunity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is still uncertain, but it is of key clinical and epidemiological importance. Seasonal human coronaviruses (HCoV) have been circulating for longer and, therefore, may offer insights into the long-term dynamics of reinfection for such viruses.

**Methods:** Combining historical seroprevalence data from five studies covering the four circulating HCoVs with an age-structured reverse catalytic model, we estimated the likely duration of seropositivity following seroconversion.

**Results:** We estimated that antibody persistence lasted between 0.9 (95% Credible interval: 0.6 - 1.6) and 3.8 (95% CrI: 2.0 - 7.4) years. Furthermore, we found the force of infection in older children and adults (those over 8.5 [95% CrI: 7.5 - 9.9] years) to be higher compared with young children in the majority of studies.

**Conclusions:** These estimates of endemic HCoV dynamics could provide an indication of the future long-term infection and reinfection patterns of SARS-CoV-2.

**Keywords**

Seasonal coronavirus, Seroprevalence, Catalytic model, waning immunity

**Open Peer Review**

**Reviewer Status**

Invited Reviewers

	1	2	3
<b>version 2</b> (revision) 22 Nov 2021	 report	 report	 report
<b>version 1</b> 03 Jun 2021	 report	 report	 report

1. **Angkana T. Huang** , University of Florida, Gainesville, USA

Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand

2. **Barnaby Flower** , Imperial College London, London, UK

Oxford University Clinical Research Unit, Vietnam, Ho Chi Minh City, Vietnam

3. **Sereina A. Herzog** , Medical University of Graz, Graz, Austria

Any reports and responses or comments on the

.....  
article can be found at the end of the article.

**Corresponding author:** Eleanor M. Rees ([eleanor.rees1@lshtm.ac.uk](mailto:eleanor.rees1@lshtm.ac.uk))

**Author roles:** **Rees EM:** Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Visualization, Writing – Original Draft Preparation; **Waterlow NR:** Formal Analysis, Methodology, Writing – Review & Editing; **Lowe R:** Formal Analysis, Methodology, Supervision, Visualization, Writing – Review & Editing; **Kucharski AJ:** Conceptualization, Formal Analysis, Methodology, Supervision, Visualization, Writing – Review & Editing

**Competing interests:** No competing interests were disclosed.

**Grant information:** AK was supported by Wellcome Trust and the Royal Society (grant Number 206250/Z/17/Z). EMR receives funding from the UK Medical Research Council (MR/N013638/1). NRW receives funding from the UK Medical Research Council (MR/N013638/1). RL was supported by a Royal Society Dorothy Hodgkin Fellowship.

*The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*

**Copyright:** © 2021 Rees EM *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

**How to cite this article:** Rees EM, Waterlow NR, Centre for the Mathematical Modelling of Infectious Diseases COVID-19 Working Group *et al.* **Estimating the duration of seropositivity of human seasonal coronaviruses using seroprevalence studies [version 2; peer review: 3 approved]** Wellcome Open Research 2021, 6:138 <https://doi.org/10.12688/wellcomeopenres.16701.2>

**First published:** 03 Jun 2021, 6:138 <https://doi.org/10.12688/wellcomeopenres.16701.1>

**REVISED Amendments from Version 1**

This article has been updated in response to reviewer comments. We have updated [Figure 3](#) (changed the colours to make it clearer), [Table 1–Table 4](#), and included an additional sensitivity analysis in the Extended data, in which we estimate the duration of seropositivity by assay.

**Any further responses from the reviewers can be found at the end of the article**

**Introduction**

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel beta coronavirus, was first detected in December 2019 and has since spread globally causing high morbidity and mortality. There is evidence of some short-term sterilising immunity (protection against reinfection and symptoms) following infection with SARS-CoV-2<sup>1</sup>, but also some reports of reinfection<sup>2</sup>. However, there is currently limited evidence on the duration of immunity conferred by SARS-CoV-2 infection. Given the limited duration of SARS-CoV-2 circulation to date, the dynamics of antibody responses of seasonal human coronaviruses (HCoV) could provide insights into the possible long-term potential for reinfections<sup>3</sup>. The duration of immunity following infection is of both clinical and epidemiological importance, as it provides information as to how long previously infected individuals may no longer be at risk of infection and disease, as well as influencing the long-term dynamics of epidemics<sup>4</sup> and enabling the interpretation of population-wide serological data<sup>5</sup>.

There are four circulating HCoVs: HCoV-NL63 and HCoV-229E (alpha coronaviruses), HCoV-OC43 and HCoV-HKU1 (beta coronaviruses). HCoV-OC43 and HCoV-229E were first identified in the 1960s, but HCoV-NL63 and HCoV-HKU1 were not identified until 2004 and 2005 respectively<sup>6,7</sup>. Like SARS-CoV-2, these typically cause respiratory tract infections. A small number of human challenge studies have looked at the duration of immunity to these viruses. Callow *et al.*<sup>8</sup> found that six out of nine participants were reinfected when challenged with HCoV-229E again one year later, as measured by a rise in IgG antibodies and viral shedding. However, the period of viral shedding was shorter following the second inoculation, and none of the participants developed symptoms. Reed<sup>9</sup> found that reinfection did not occur when participants were re-inoculated with a homologous strain approximately one year following infection, but participants had partial immunity against reinfection with a heterologous strain. Taken together these results suggest that immunity against infection with a homologous strain could last at least one year<sup>8,9</sup>.

There are also a small number of cohort and community-based surveillance studies which have looked at reinfection of seasonal HCoV. One study looked at HCoV reinfection in a small cohort of ten individuals over 35 years and found the median reinfection times to be 30 months, but with reinfection often occurring at 12 months<sup>10</sup>. A larger study looking at data from Flu Watch, a community cohort study which measures the incidence and transmission of respiratory viruses, found that

between 2006 and 2011, eight subjects were reinfected with a seasonal HCoV (of 216 with confirmed first infection), and the time between reinfection ranged from 7 to 56 weeks. None of these reinfections were with the same strain, providing some evidence of lasting immunity<sup>11</sup>. However, a community surveillance study of 483 participants conducted in Kenya in 2010 over six months found evidence of high numbers of repeat infections of HCoV-NL63 (20.9%), HCoV-OC43 (5.7%), and HCoV-229E (4.0%). The majority of these reinfections showed reduced virus replication in the second infection, and a lower proportion of individuals had symptoms following the second infection<sup>12</sup>. Furthermore, another study conducted in New York City which included 191 participants found that reinfections with the same strain can occur within one year<sup>13</sup>. Care should be taken with the interpretation of these studies since we do not know the background exposure rates, and this will influence the estimates of duration of immunity.

If infections are fully immunising – as is the case for pathogens like measles and varicella zoster – then seroprevalence would be expected to accumulate over time<sup>14</sup>, and hence with age, with little waning of responses. The dynamics can therefore be captured with catalytic models of seroconversion<sup>15</sup>, which enables estimation of the force of infection (FOI, the rate at which susceptible individuals acquire infection and seroconvert). In contrast, when individuals serorevert, i.e. their immunity wanes by the progressive loss of protective antibodies against a disease over time, ‘reverse catalytic models’ can jointly estimate FOI and waning of immunity<sup>16</sup>. Variation in FOI with age may further complicate the dynamics, particularly if a high infection rate in children is followed by a lower rate in adults as well as waning of seroprevalence. To understand how seroconversion, waning and age-variation in infection risk could shape population-level seroprevalence, we combine age-stratified data with age-structured reverse catalytic models, and estimate the likely duration of seropositivity following seroconversion for the four seasonal coronaviruses.

**Methods**

Human seroprevalence from four different human coronavirus strains (229E, HKU1, NL63, and OC43) were identified in a recent systematic review<sup>7</sup>. Studies which did not include estimates for individuals under 10 years old<sup>17</sup> were excluded, as well as studies with which only reported two age groups<sup>18</sup>. A total of six different studies were included, covering the four seasonal HCoVs, with some studies reporting on multiple strains<sup>19–24</sup>. Two studies were reported separately for two different strains, but the overall study population was the same<sup>21,22</sup>. A summary of these studies is presented in [Table 1](#). The different assays used in each study for the different strains is shown, and where the antibody detected was specified this is included in the table. To account for maternal immunity individuals aged  $\leq 1$  year were excluded. The full dataset used for this analysis can be found as underlying data<sup>25</sup>.

To explore the duration of antibody persistence for different seasonal coronaviruses, where detectable antibodies is defined as seropositivity, we developed age-structured reverse catalytic models. The basic reverse catalytic model follows individuals from birth and assumes that there is a constant

**Table 1. Characteristics of studies used to fit the model.**

Strain	Author (year published)	Pubmed ID	Sample size	Country/region	Years sampled	Assay	Antigen	Assay cut-off
HCoV-HKU1	Chan (2009)	19342289	709	Hong Kong	Not specified	ELISA (IgG)	S protein	Mean + 3SD (OD>0.495)
	Zhou (2013) <sup>a</sup>	24040960	789	China	1999 – 2011	IFA (IgG)	S protein	>1:20
HCoV-OC43	Zhou (2013) <sup>a</sup>	24040960	789	China	1999 – 2011	IFA (IgG)	S protein	>1:20
	Monto (1974) <sup>c</sup>	4816305	910	USA	1965 – 1969	CF or HI	Whole virus	<1:8 to >1:8 or 4-fold rise
	Sarateanu (1980)	6248465	3,016	Germany	1974 – 1976	HI	Whole virus	>1:8
HCoV-NL63	Shao (2007) <sup>b</sup>	17889596	243	USA	2003 – 2004	ELISA (IgG)	N protein	OD>0.2 at dilution of 1:80 or greater
	Zhou (2013) <sup>a</sup>	24040960	789	China	1999 – 2011	IFA (IgG)	S protein	>1:20
HCoV-229E	Shao (2007) <sup>b</sup>	17889596	243	USA	2003 – 2004	ELISA (IgG)	N protein	OD>0.2 at dilution of 1:80 or greater
	Zhou (2013) <sup>a</sup>	24040960	789	China	1999 – 2011	IFA (IgG)	S protein	>1:20
	Cavallaro (1970) <sup>c</sup>	5504709	307	USA	1966	Neutralization	Whole virus	>1:4

Human coronavirus (HCoV), Enzyme-linked immunosorbent assays (ELISA), immunofluorescence assays (IFA), complement fixation (CF), hemagglutination inhibition assays (HI), Immunoglobulin G (IgG), standard deviation (SD), optical density (OD). Studies which occurred in the same setting are denoted by the superscripts, a, b and c.

FOI ( $\lambda$ ), which is independent of age ( $a$ ) and calendar year, and that immunity (as measured by serological status) wanes over time, at a rate  $\omega$ . This model also assumes that the mortality rate for susceptible and infectious individuals is the same. The expression for the proportion of individuals age  $a$  who are seropositive,  $z(a)$ , in the reverse catalytic model is as follows:

$$z(a) = \frac{\lambda}{\lambda + \omega} (1 - e^{-a(\lambda + \omega)})$$

where  $\lambda$  is the FOI,  $\omega$  is seropositivity waning rate and  $a$  is age. The duration of antibody persistence was estimated as follows:

$$\text{Duration of antibody persistence} = 1/\omega$$

We then extended the reverse catalytic model to allow for a different FOI by age. The expressions for seroprevalence in the reverse catalytic model with age-varying FOI are as follows:

$$z(a) = \frac{\lambda_1}{\lambda_1 + \omega} (1 - e^{-a(\lambda_1 + \omega)}) \quad \text{when } a < a_0$$

$$z(a) = \left( \frac{\lambda_1}{\lambda_1 + \omega} (1 - e^{-a_0(\lambda_1 + \omega)}) - \frac{\lambda_2}{\lambda_2 + \omega} \right) (e^{-(\lambda_2 + \omega)(a - a_0)}) + \frac{\lambda_2}{\lambda_2 + \omega} \quad \text{when } a \geq a_0$$

$$\lambda_2 = \lambda_1 \alpha$$

Where  $z(a)$  is those who are seropositive at age  $a$ ,  $\lambda_1$  is the FOI in young age groups,  $\lambda_2$  is FOI in the old age group,  $\omega$  is waning,  $a$  is age,  $a_0$  is the age cut-off used to define the young and old group, and the relative change in FOI,  $\alpha$ , is the change in FOI in the older age group. In our analysis, we allowed  $\lambda_1$  to

vary by study and strain, to account for local differences in population-level transmission dynamics, while the average rate of waning within a given individual was assumed to be universal and was jointly estimated across all studies and strains. This means that one overall estimate of waning was obtained. Some of the studies occurred in the same setting, and so the underlying contact patterns were presumed to be the same (in total we identified five settings). Therefore, the relative change in FOI ( $\alpha$ ) and the age at cut-off ( $a_0$ ) were jointly estimated across settings. This model assumes no cross-protection between strains. Annual attack rates were calculated after estimating the FOI using the following expression,

$$\text{Attack rate} = 1 - e^{-\lambda}$$

To reflect uncertainty in current knowledge about the transmission dynamics of HCoVs, weakly informative distributions were chosen as priors for  $\omega$ , the rate of waning over time. Specifically uniform priors from 0 to 5 years. For the FOI, there is little information on the attack rate of HCoVs. However, there have been several systematic reviews and meta-analyses looking at influenza in unvaccinated individuals which have reported the attack rates to range between 15.2% – 22.5% in children and 3.5% – 10.7% in adults<sup>26–28</sup>. Modelling studies using serological influenza data predicted estimates from 20 – 60%<sup>29,30</sup>. Based on the epidemiology of these viruses in children<sup>31</sup>, we expect the attack rate for HCoV may be lower. Therefore, we selected a Gamma distribution, with a mean of 0.3 (shape = 1.2 and scale = 0.25) and this corresponds to an attack rate of 26% and covers a range of plausible values.

For the age at cut-off ( $a_0$ ), uniform priors from 0 to 20 years were chosen as we were interested in the difference in FOI in children and young adults. For the relative change in FOI ( $\alpha$ ) we did not have any prior information. Therefore, we selected a prior with median 1, which presumes no difference between FOI in young compared with FOI in old and allowed for a range of plausible values using a gamma distribution (shape = 5, scale = 0.2).

Several sensitivity analyses were conducted to assess the robustness of these results. First, the choice of priors for the FOI was explored, and a less informed prior was tested (FOI  $\sim$  Normal (mean 0.3, standard deviation 0.5)). Second, waning was estimated by strain, instead of being jointly fitted across all studies. The relative change in FOI ( $\alpha$ ) and age at cut-off ( $a_0$ ) were then held across all studies (instead of allowing them to vary by setting) to explore the impact on the estimate for waning. The impact of excluding the youngest age groups ( $\leq 1$  year) was also explored, and a model was run which

included individuals  $\leq 1$  year. The impact of the assay used in the study on the estimate of waning was also explored, where FOI was allowed to vary by study, alpha and the age at cut-off varied by setting and waning varied by assay (ELISA, IFA, HI and neutralisation). Finally, the primary model (age-varying FOI model) was fitted using only half the data (seroprevalence studies from two strains), to explore whether the results from one study was heavily influencing the results. For this model, waning, the relative change in FOI ( $\alpha$ ) and age at cut-off ( $a_0$ ) were held across all studies. A description of these models is presented in [Table 2](#).

Bayesian inference was used to fit the sero-catalytic models to the seroprevalence data, using Markov chain Monte Carlo (MCMC) with the Gibbs sampling algorithm to estimate model parameters. To do so, we used the following binomial likelihood representing seropositivity by age (a), study (i) and strain (j)

$$y_{ija} \sim \text{Binomial}(P_{ija}, N_{ija}),$$

**Table 2. Description of models explored.**

Model	Priors	Number of parameters
Main model: Reverse catalytic model with age-varying FOI (alpha and cut-off varying across settings) - More informed priors	FOI $\sim$ gamma(shape = 1.2, scale = 0.25) Waning $\sim$ uniform(0,5) Alpha $\sim$ gamma(shape = 5, scale = 0.2) Cut-off $\sim$ uniform(0,20)	21
Reverse catalytic model with age-varying FOI (alpha and cut-off varying across settings) - less informed priors	FOI $\sim$ normal(0.3,0.5) Waning $\sim$ uniform(0,5) Alpha $\sim$ gamma(shape = 5, scale = 0.2) Cut-off $\sim$ uniform(0,20)	21
Reverse catalytic model with age-varying FOI (alpha and cut-off varying across settings, waning varying by strain)	FOI $\sim$ gamma(shape = 1.2, scale = 0.25) Waning $\sim$ uniform(0,5) Alpha $\sim$ gamma(shape = 5, scale = 0.2) Cut-off $\sim$ uniform(0,20)	24
Reverse catalytic model with age-varying FOI (alpha and cut-off held across settings)	FOI $\sim$ gamma(shape = 1.2, scale = 0.25) Waning $\sim$ uniform(0,5) Alpha $\sim$ gamma(shape = 5, scale = 0.2) Cut-off $\sim$ uniform(0,20)	13
Reverse catalytic model with age-varying FOI (alpha and cut-off varying across settings) including data <1 year	FOI $\sim$ gamma(shape = 1.2, scale = 0.25) Waning $\sim$ uniform(0,5) Alpha $\sim$ gamma(shape = 5, scale = 0.2) Cut-off $\sim$ uniform(0,20)	21
Reverse catalytic model with age-varying FOI (alpha and cut-off varying across settings, waning varying by assay)	FOI $\sim$ gamma(shape = 1.2, scale = 0.25) Waning $\sim$ uniform(0,5) Alpha $\sim$ gamma(shape = 5, scale = 0.2) Cut-off $\sim$ uniform(0,20)	24
Reverse catalytic model	FOI $\sim$ gamma(shape = 1.2, scale = 0.25) Waning $\sim$ uniform(0,5)	11

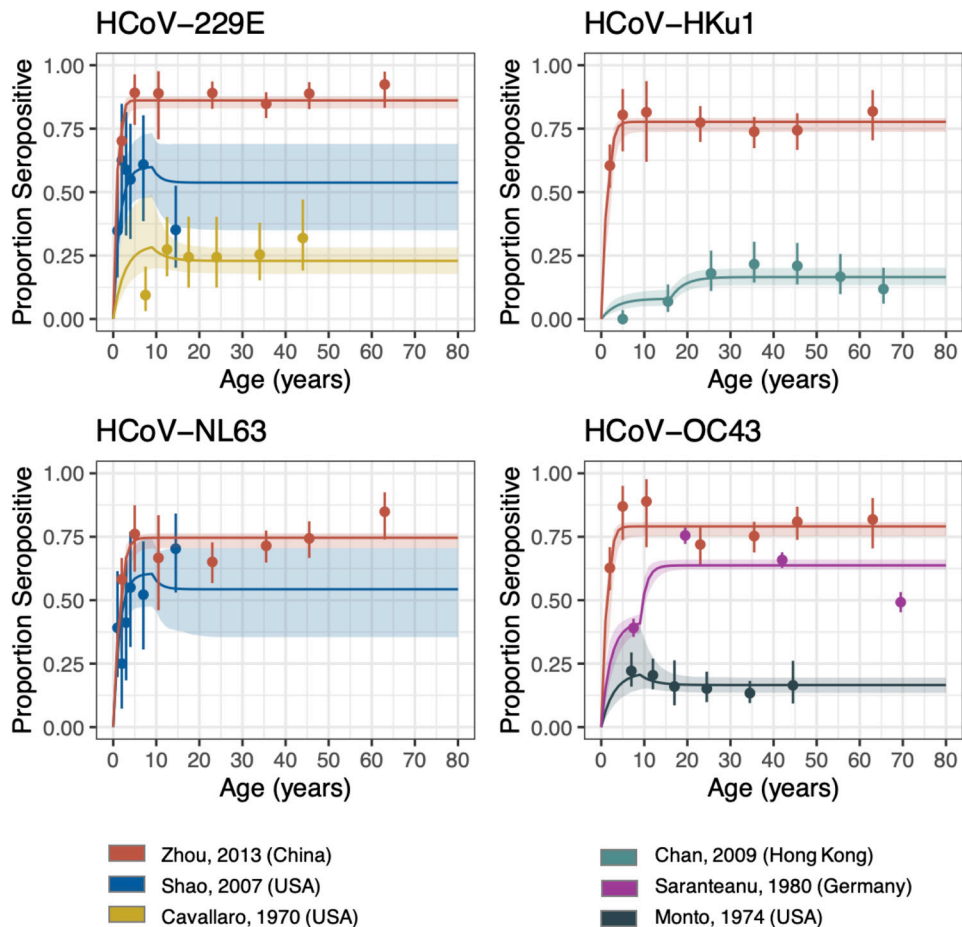
Force of infection (FOI), relative change in FOI (Alpha, $\alpha$ ), age at which the FOI changes (Cut-off).

where  $N_{ija}$  is total number of individuals by age group, strain and study, and  $P_{ija}$  is the proportion of individuals who are seropositive. The inference was implemented in **RJags** (version 4–10)<sup>32</sup>. The Gelman-Rubin statistic was used to evaluate MCMC convergence, and a threshold of <1.1 was chosen. The effective sample size (ESS), which is the estimated number of independent samples accounting for autocorrelations generated by the MCMC run, was checked, and an ESS >200 was used. All analysis and calculations were performed using **R** version 3.6.1. Model selection was based on the lowest value of the deviance information criterion (DIC), the widely applicable information criterion (WAIC) and the leave-one-out cross validation (LOO) using Pareto-smoothed importance sampling<sup>33,34</sup>. WAIC and LOO were estimated using the **R** package **Loo** (version 2.4.1)<sup>34</sup>. All code is available here at [GitHub](#)<sup>25</sup>.

## Results

Using a reverse catalytic model, which allowed the FOI to change in individuals by age, we estimated the duration of

antibody persistence for the four seasonal HCoV.s. Despite having only four parameters by study, our model could capture the overall trends in most studies ([Figure 1](#)). Waning was jointly fitted across all studies and strains to obtain one overall estimate, and the duration of antibody persistence was estimated to be 3.75 (95% credible interval [CrI]: 1.96 - 7.38) years ([Table 3](#)). The FOI across all studies and strains in the young age group ranged from 0.02 (95% CrI: 0.01 - 0.05) to 1.06 (95% CrI: 0.57 - 1.68). The cut-off (age at which the FOI changes) ranged between 2.35 (95% CrI: 0.31 - 17.51) to 16.58 (95% CrI: 7.71 - 19.81) years. The relative change in FOI (Alpha) which measures the relative value of FOI in the young age group compared with the older age group ranged from 0.72 (95% CrI: 0.3 - 1.17) to 2.48 (95% CrI: 1.96 - 2.99). For three of the study settings, the FOI in the older age group was higher ([Figure 2](#)). A sensitivity analysis was conducted using less informative priors for the FOI parameters, where a normal distribution was used (extended data [Figure 1](#), [Table 1](#)<sup>25</sup>). This model estimated a shorter duration of antibody persistence [0.93 (95% CrI: 0.60 - 1.64) years]. The FOI

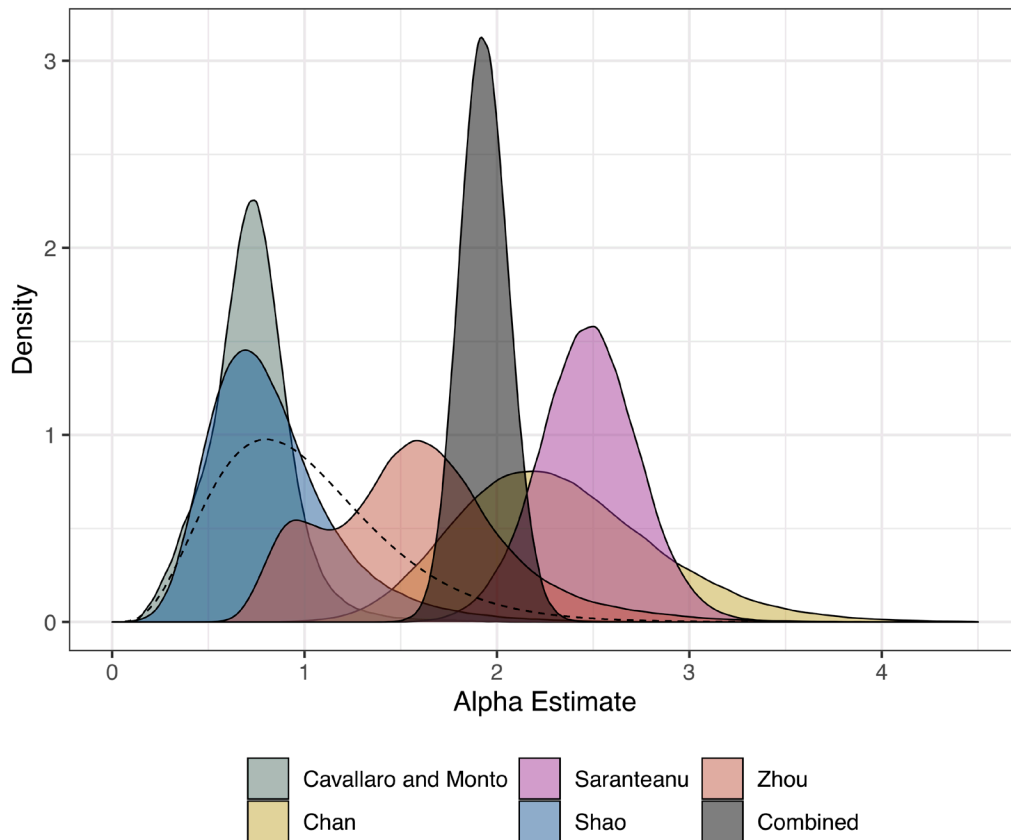


**Figure 1. Reverse catalytic model with age-varying FOI.** The points are the observed proportion of seropositive individuals from each study (with confidence intervals), i.e. the data that was fit to. The lines are the seroprevalence curves, sampled from the fitted model, where the shaded region represents the 95% credible interval of the predictive posterior distribution. FOI was allowed to vary by study, whilst the relative change in FOI (Alpha) and cut-off were allowed to vary by setting. Waning was jointly fit across all studies and strains.

**Table 3. Parameter estimates from the age-varying FOI reverse catalytic model (median [95% CrI]).** FOI was allowed to vary across study, while waning was simultaneously estimated across all studies. The relative change in FOI (Alpha) and the cut-off were allowed to vary across study settings.

Strain	First Author	FOI (youngest age group)	Relative change in FOI (Alpha)	Age at which the FOI changes (cut-off)	Waning
HCoV-229E	Shao	1.06 (0.57 – 1.68)	0.78 (0.35 – 1.68)	9.5 (0.59 – 19.47)	0.27 (0.14 - 0.51)
	Zhou	0.11 (0.06 – 0.3)	1.57 (0.8 – 2.65)	2.35 (0.31 – 17.51)	
	Cavallaro	0.02 (0.01 - 0.05)	0.72 (0.3 - 1.17)	9.14 (0.57 - 19.28)	
HCoV-HKU1	Chan	0.59 (0.32 – 0.89)	2.27 (1.44 – 3.45)	16.58 (7.71 – 19.81)	
	Zhou	0.64 (0.35 – 0.96)	1.57 (0.8 – 2.65)	2.35 (0.31 – 17.51)	
HCoV-OC43	Zhou	0.07 (0.04 – 0.19)	1.57 (0.8 – 2.65)	2.35 (0.31 – 17.51)	
	Monto	0.19 (0.11 – 0.35)	0.72 (0.3 – 1.17)	9.14 (0.57 – 19.28)	
	Saranteanu	0.5 (0.27 – 0.74)	2.48 (1.96 – 2.99)	9.93 (7.34 – 14.84)	
HCoV-NL63	Zhou	0.41 (0.26 – 0.67)	1.57 (0.8 – 2.65)	2.35 (0.31 – 17.51)	
	Shao	1.06 (0.57 – 1.68)	0.78 (0.35 – 1.68)	9.5 (0.59 – 19.47)	

Human coronavirus (HCoV), force of infection (FOI).



**Figure 2. Posterior estimates for the relative change in FOI (alpha) from the age-varying reverse catalytic model for each study setting.** The alpha estimate from the model where alpha and cut-off were simultaneously estimated across studies is shown in grey as “combined”. The prior is shown as a dashed line.

across all studies and strains were higher, ranging from 0.09 (95% CrI: 0.04 - 0.16) to 3.22 (95% CrI: 1.95 - 4.85), with six studies reporting FOI estimates > one, which is equivalent to an attack rate of >63%. The relative change in FOI and cut-off were similar for both models. This model had a lower DIC (476.8 compared with 480.8; with a DIC difference of 4), WAIC (536.2 compared with 546.4), and LOO (546.9 compared with 560.9), which suggests that this model has an improved fit compared with the model with more informed priors. However, the high FOI estimates indicate that this model may be less plausible (Table 4). As an additional sensitivity we allowed the waning estimate to vary by strain (extended data Table 2<sup>35</sup>). This model estimated the duration of antibody persistence to be similar for all strains, ranging from 2.26 (1.06 - 5.07) years for HCoV-OC43 to 4.09 (1.91 - 9.60) years for HCoV-229E.

When the relative change in FOI and cut-off parameters were simultaneously estimated by setting (extended data Figure 2, Table 3<sup>35</sup>) the duration of antibody persistence was estimated to be shorter, 2.20 (95% CrI: 1.57 - 3.08) years, although the confidence intervals overlap with the main model. The FOI ranged from 0.04 (95% CrI: 0.03 - 0.06) to 0.88 (95% CrI: 0.67 - 1.19). The overall model DIC (548.2 compared with 480.8), WAIC (622.0 compared with 546.5) and LOO (633.2 compared with 560.9) were higher, indicating that this model did not have as much support (Table 4).

We also tested a basic reverse catalytic model, where the FOI was not allowed to vary by age, and this model estimated a longer duration of antibody persistence (7.69 [95% CrI: 6.25 - 9.09] years; extended data Table 4, Figure 3<sup>35</sup>). The DIC (608.3), WAIC (716.7) and LOO (718.5) values for the basic reverse catalytic model were higher compared with the other models, indicating that this basic model did not have strong support among the models considered (Table 4).

To explore the effect of excluding the youngest ages ( $\leq 1$  year), a sensitivity analysis was done where these individuals were

included within the analysis. The duration of antibody persistence was found to be slightly shorter (2.04 [95% CrI: 0.128 - 1.476] years) and the FOI was found to be higher for all studies, ranging from 0.04 (95% CrI: 0.02 - 0.07) to 2.92 (95% CrI: 2.08 - 4.01); extended data Table 5, Figure 4<sup>35</sup>). The estimates for the relative change in FOI were found to be very similar to the model which excluded this age group.

As an additional sensitivity analysis, we refit the models using data for only two strains at a time, and estimated the FOI, waning and the relative change in FOI (extended data Table 6<sup>35</sup>). We found that although the results varied, the overall trends were the same, indicating that the model did not rely heavily on one dataset. The duration of antibody persistence varied from 1.80 years (95% CrI: 1.17 - 2.67) to 5.26 years (95% CrI: 2.53 - 13.56).

Finally, we explored the impact of the different assays used in the studies on the waning estimates. We allowed the waning estimate to vary by assay (extended data Table 7, Figure 5<sup>35</sup>), whilst allowing FOI to vary by study, and alpha and cut-off to vary by setting. This model estimated the duration of antibody persistence to be similar for ELISA (2.63 [95% CrI: 0.94-9.09] years), HI (1.08 [95% CrI: 0.44-3.33] years) and neutralisation (1.28 [95% CrI: 0.25-50.0] years) assays, but longer for IFA (7.69 [95% CrI: 3.03-14.29] years). The credible intervals were wide, likely due to the small number of studies by assay.

To demonstrate the relationship between FOI and seropositivity at age 30, we created simulated scenarios under different sero-catalytic models. Using the parameters for the relative change in FOI and waning estimated from the age-varying reverse catalytic model (where the relative change in FOI and the age at cut-off were simultaneously estimated across settings), we simulated the proportion of individuals aged 30 years that would be seropositive using a range of FOI estimates to show how the proportion changes using the different models. The catalytic model, which does not allow for seroreversion,

**Table 4. Comparison of duration of antibody persistence estimates from the different models explored.**

Model	Reverse catalytic model with age-varying FOI (alpha and cut-off varying across settings) - More informed priors	Reverse catalytic model with age-varying FOI (alpha and cut-off varying across settings) - less informed priors	Reverse catalytic model with age-varying FOI (alpha and cut-off held across settings)	Reverse catalytic model
Duration of antibody persistence (years)	3.75 (1.96 - 7.38)	0.93 (0.60 - 1.64)	2.20 (1.57 - 3.08)	7.69 (6.25 - 9.09)
DIC	480.8	476.8	548.2	608.3
WAIC	546.5	536.2	622.0	716.7
LOO	560.9	546.9	633.2	718.5

Force of infection (FOI), relative change in FOI (Alpha), age at which the FOI changes (Cut-off), deviance information criteria (DIC), widely applicable information criterion (WAIC), leave-one-out cross validation (LOO).



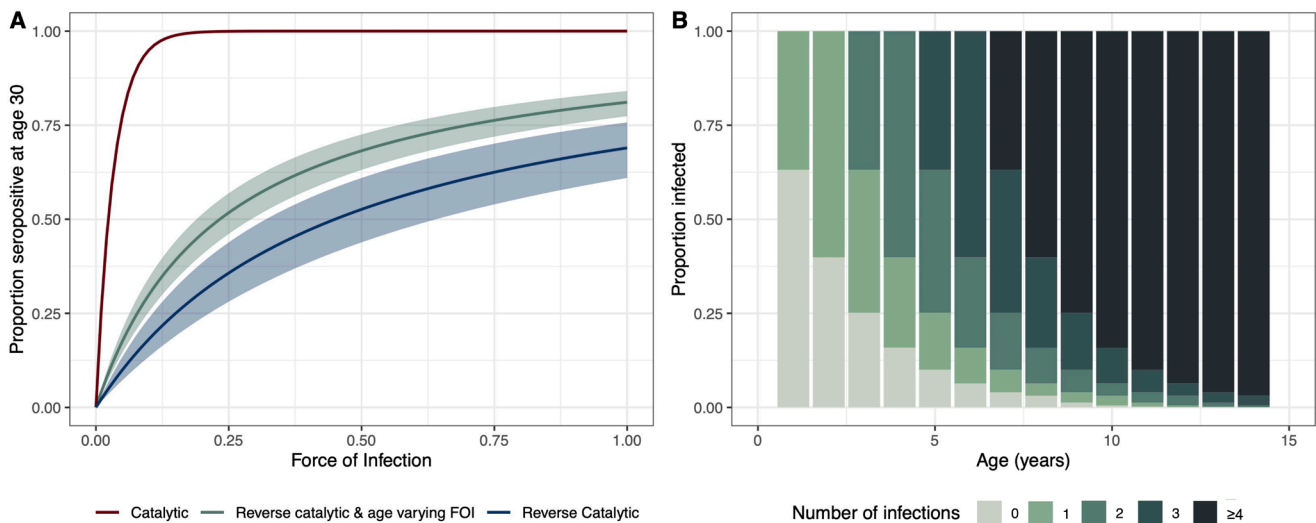
results in the highest estimates of seropositivity at age 30 with increasing FOI. The age-varying FOI model results in higher estimates of seropositivity at age 30 compared with the reverse catalytic model. This is due to the FOI which was estimated to be almost twice as high in the older age group (with age at cut-off 8.49 [7.52 – 9.94] years) in the age-varying FOI model (Figure 3A). We further explored the relationship between FOI, attack rates and the estimated number of infections by age. We used the pooled estimate across all studies of FOI to estimate the proportion exposed at a given age to provide an indication of how many infections we might expect to see by age under our modelling assumptions (Figure 3B). We estimate that by two years, over 50% of the population will have at least one infection, and by age ten over 75% will have had more than four infections.

## Discussion

To date, there has been limited evidence about the duration of immunity to SARS-CoV-2. Given the inevitable right censoring of data during an emerging infectious disease pandemic, understanding the duration of protection following infection with HCoV could help provide insights which will be relevant to SARS-CoV-2. Using an age-varying reverse catalytic model, we estimated the overall duration of immunity, as measured by seropositivity, to be between 0.9 (95% CrI: 0.6 - 1.6) years and 3.8 (95% CrI: 2.0 - 7.4) years for HCoV's. When waning was estimated by strain, we found comparable estimates of the duration of seropositivity, indicating that the assumption that waning is similar across strains holds true. Previous studies have produced varied estimates for the duration of immunity for HCoVs. One study estimated the median duration of immunity to be 2.5 years<sup>10</sup>, and Reed found

immunity lasts at least one year<sup>9</sup>. However, several studies have reported reinfection occurring in less than one year<sup>8,11–13</sup>. Aldridge *et al.*<sup>11</sup> found that reinfection with HCoV did not occur with the same strain, but Kiyuka *et al.*<sup>12</sup> found reinfection frequently occurred with the same strain within a six month period. The reverse catalytic model assumes that waning occurs at a constant rate, however, individuals may become reinfected within a shorter time period than average, and conversely some will take longer. Some evidence also exists for the duration of immunity to SARS-CoV-2. A recent survey of health care workers in Oxford, UK, found that protection against reinfection with SARS-CoV-2 lasts at least six months<sup>36</sup>, whilst another study of health care workers from across the UK conducted by Public Health England found that immunity lasts for at least five months<sup>2</sup>. This seems to align with what is known about reinfection in seasonal HCoVs. However, these studies only followed up individuals for six months and five months respectively, and longer follow-up times are needed. Future studies could also work to untangle the relationship between seroreversion as a result of waning homotypic antibody responses and antigenic evolution leading to a mismatch between prior immunity and circulating viruses<sup>37</sup>.

More informed priors for the FOI based on attack rates for influenza, resulted in higher estimates for the duration of seropositivity. When we used less informed priors for the FOI, a lower estimate of duration of seropositivity was obtained. However, this model produced higher estimates of FOI, with six studies reported FOI estimates in the young age group greater than one (attack rate >63%). There is limited information on the attack rate of seasonal HCoV, however there have been numerous studies looking at influenza. Previous



**Figure 3.** (A) Proportion of individuals age 30 who are seropositive for different estimates of force of infection (FOI). The catalytic model is shown in red, the reverse catalytic model in green, and the reverse catalytic model with age-varying FOI is shown in blue. Model estimates were used for the parameter values (relative change in FOI ( $\alpha$ ), 1.93 [1.69 – 2.19]; waning, 0.45 [0.32 – 0.64]; cut-off, 8.49 [7.52 – 9.94]). (B) Estimated proportion of individuals experiencing infections by age estimated from the age-varying reverse catalytic model (more informed priors) using the pooled median estimate across studies for FOI (0.46), and median estimates for waning (0.45),  $\alpha$  (1.93) and cut-off (8.49).

systematic reviews have estimated the attack rate of influenza to be between 3.5% and 22.5%<sup>26-28</sup>, whilst modelling studies have estimated this to be higher, 20 – 60%<sup>29,30</sup>. Based on reporting rates of seasonal HCoV we would expect the attack rate to be lower than influenza. Therefore, this suggests that the results from the model with less informative priors are less plausible. Maternally derived immunity may also have a role, protecting young infants from infection<sup>38</sup>. We tested this with a model which included individuals  $\leq 1$  year. This resulted in a shorter estimate of the duration of antibody persistence, and a higher FOI, suggesting that maternal immunity may be important.

A wide range of different assays were used in the studies we considered in our analysis, including enzyme-linked immunosorbent assays (ELISA), immunofluorescence assays (IFA), western blots, and complement fixation (CF), hemagglutination inhibition assays (HAI) and neutralisation assays. Neutralisation assays are considered to be the gold standard as they measure the ability of the sera to inhibit viral processes<sup>7,39</sup>. Only Cavallaro and Monto<sup>22</sup> used a neutralisation assay. Other assays, such as ELISA and IFA, do not assess the functionality of the antigen, but instead detect the presence of antibodies in a sample. Zhou *et al.*<sup>19</sup> used IFA to detect levels of IgG antibodies. When we allowed the waning estimate to vary by assay, we found a similar estimates of antibody persistence for ELISA, HI and neutralisation assays, ranging from 1.1 years to 2.6 years, and these are comparable to the estimates from the main model. However, for IFA, we observed a longer estimate of 7.7 years (CrI: 3.0-14.3). Due to the small number of studies, the credible intervals were large, particularly for the IFA and neutralisation assay, which only had one study setting for each assay. This highlights the need for more studies, and better standardisation of assays. A recent study provided evidence that IgG antibodies in SARS-CoV-2 are correlated with neutralising antibodies, and may therefore act as a correlate of sterilising immunity<sup>40</sup>, whilst another study suggested that neutralizing antibodies may be correlated with protection against reinfection<sup>1</sup>. Therefore, although antibody prevalence does not equate to immunity for seasonal HCoVs, prevalence of IgG antibody may be a good correlate of immunity. However, all of these assays only assess humoral immunity, and it is thought that cellular immunity also has a role SARS-CoV-2, and so it is likely to be also important in seasonal HCoVs<sup>41-43</sup>.

The seroprevalence surveys included in this study were conducted in different countries and settings (USA, China, Germany and Hong Kong), as well as in different time-periods (ranging from 1965–2011). It is likely that there are differences in social structure and contact patterns between these settings. Furthermore, individual level data was not available for these studies, and instead aggregated data was used. Finer resolution, particularly for the younger age groups, would have helped to provide more certainty with these estimates. In addition, we did not take into consideration cross-protection between seasonal coronavirus strains. There is some evidence of cross protective immunity between seasonal coronavirus

strains, and in settings where there is co-circulating HCoV strains, this may lead to a higher prevalence. There is also evidence that there is cross-reactivity between different coronaviruses, which may lead to false positive results. A recent systematic review found that there was some cross-reactivity that occurred within alpha (HCoV-229E and HCoV-NL63) and beta (HCoV-OC43 and HCoV-HKU1) coronaviruses, but minimal reactivity between alpha and beta coronaviruses<sup>7</sup>. However, it is not clear whether cross-reactivity equates to cross-protection. False positives due to cross-reactivity would lead to an over-estimation of seroprevalence in a setting. This would lead to a higher plateau in older ages, and therefore generally lead to an over-estimation of both the FOI and the duration of antibody persistence. We also did not account for seasonality within this model, which may have under-estimated our FOI. Ferrari *et al.*<sup>44</sup> found that ignoring seasonality may overemphasize the role of adults in the transmission, however, this was observed in measles in Niger, with outbreak peaks ranging over several orders of magnitude, and long periods between epidemics. The epidemic profile is different for seasonal coronaviruses, and therefore, this is unlikely to apply in this context. Whitaker & Farrington<sup>45</sup> found that accounting for seasonality resulting from past epidemics only had a marginal effect on the estimates, and that regular epidemic dynamics do not strongly bias the catalytic model. The time of year data collection occurred may influence seropositivity estimates, particularly given that the duration of antibody persistence is estimated to range between 0.9 (95% CrI: 0.6 - 1.6) years and 3.8 (95% CrI: 2.0 - 7.4) years. Data collection during high transmission periods would lead to an overestimate of both the FOI and the duration of antibody persistence. All the studies (except for Chan *et al.*<sup>23</sup> who did not report this information), included within this analysis collected data over at least a six-month period. For this reason, the timing of data collection is unlikely to have biased our results. We also assume an overall FOI by age, and we do not account for differences in population susceptibility, for example health care workers or immunocompromised individuals. Despite these limitations, the duration of immunity estimated in this study is in line with literature estimates, suggesting the age-varying reverse catalytic model was able to capture overall dynamics.

Numerous studies have looked at the age pattern of HCoV patients presenting to hospital and healthcare settings, and predominantly found that the burden of disease is higher in younger children and the elderly<sup>46-48</sup>. However, it is likely that these age groups may have more severe symptoms and are therefore more likely to be reported. In contrast, seroprevalence data makes it possible to examine the whole population for evidence of past exposure, and hence can provide a clearer understanding of the underlying transmission dynamics of disease, rather than just the resulting burden.

In this study, when the relative change in FOI and the age of cut-off were simultaneously estimated across studies, we found that the FOI was estimated to be twice as high in the older age group (in this case, those over 8.49 [CrI: 7.52 - 9.94] years), compared with the younger age group. A similar pattern was

observed for three of five settings when the relative change in FOI and the cut-off age were allowed to vary by setting. This suggests that older children and adults may be important for the transmission of seasonal HCoVs in some settings. A previous study looking at social mixing patterns in Europe<sup>49</sup> found that children are expected to have the highest incidence during the initial stages of an epidemic as a result of their social mixing patterns, and this is what is found for some diseases, such as seasonal influenza, where there is evidence young children drive transmission<sup>50,51</sup>. However, a more recent study looking at a large scale dataset of movement and contact patterns in the United Kingdom data found contact intensity was highest in the 18–30 year age group when looking at all types of contacts (conversational, which was defined as face-to-face conversation of three or more words, and physical), although for physical alone, those aged 5–9 years had the highest contact<sup>52</sup>. Therefore, any association between contact intensity and transmission will depend on the contacts considered, particularly if a pathogen is more commonly spread via conversational contacts or via prolonged physical contacts. One possible explanation for the higher FOI we estimate in older age groups is that conversational contacts – which are typically higher in volume but lower in duration and intensity – could be more important for the transmission of seasonal HCoVs.

The results from this study are in accordance with what studies have observed in children during the coronavirus disease 2019 (COVID-19) pandemic, with low numbers of cases reported in young age groups, and several large seroprevalence studies have reported lower seroprevalence in children compared with adults<sup>53,54</sup>. As well as differences in contact structure, this could be explained in part by reduced susceptibility to acquisition of infection; a meta-analysis of contact tracing studies found that children had 56% (31% – 71%) lower odds of becoming an infected contact compared with adults<sup>55</sup>.

The duration of immunity to SARS-CoV-2 is still largely unknown and is of significance for the interpretation of population wide serological data, the understanding of the long-term dynamics of the epidemic, as well as of clinical importance. Given the long-term circulation of seasonal HCoVs, data on these related coronaviruses could provide indications of the possible future dynamics of SARS-CoV-2. With infection likely to become endemic in parts of the world, the duration of antibody-mediated immune responses will be particularly important in shaping transmission patterns in years to come. Using seroprevalence data, in this study we estimated the duration of seropositivity to seasonal HCoVs following seroconversion to be between 0.9 (95% CrI: 0.6 - 1.6) years and 3.8 (95% CrI: 2.0 - 7.4) years. We allowed the FOI to vary by age group and found it to be lower in young children ( $\leq 8.5$  years) compared with older children and adults, which is corroborated with what has been observed in the COVID-19 pandemic. This suggests individuals in settings with endemic HCoVs accumulate multiple infections over the course of their lifetime, punctuated by periods of waning seropositivity against circulating viruses.

## Data availability statement

### Underlying data

Zenodo: erees/seasonalHCoV: First release. <https://doi.org/10.5281/zenodo.5707764><sup>25</sup>

This project contains the following underlying data:

- Data extracted from Huang *et al.*<sup>7</sup> (“41467\_2020\_18450\_MOESM7\_ESM-1.csv”)

GNU General Public License v3.0.

### Extended data

Zenodo: Extended data: Estimating the duration of seropositivity of human seasonal coronaviruses using seroprevalence studies. <https://doi.org/10.5281/zenodo.5705144><sup>35</sup>.

This project contains the following extended data

- SupplementaryMaterial.pdf
  - Sensitivity analysis: Less informed priors for FOI (supplementary Table 1 and Figure 1)
  - Sensitivity analysis: Waning estimated by strain (supplementary Table 2)
  - Sensitivity analysis: Alpha and cut-off jointly simultaneously by study (supplementary Table 3 and Figure 2)
  - Reverse catalytic model (supplementary Figure 3 and Table 4)
  - Sensitivity analysis: Including the youngest age groups (<1 year) (supplementary Table 5 and Figure 4)
  - Sensitivity analysis: Refitting the model using data from only two strains (supplementary Table 6)
  - Sensitivity analysis: Waning estimated by assay (supplementary Table 7 and Figure 5)

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](https://creativecommons.org/licenses/by/4.0/) (CC-BY 4.0).

## Software availability

Source code available from: <https://github.com/erees/seasonalHCoV>

Archived source code at time of publication: <https://doi.org/10.5281/zenodo.5707764><sup>25</sup>

License: GNU General Public License v3.0.

## Acknowledgements

**Members of the Centre for Mathematical Modelling of Infectious Diseases (CMMID) COVID-19 Working Group (random order):**

Hamish P Gibbs, Alicia Rosello, Nicholas G. Davies, Kevin van Zandvoort, Timothy W Russell, Graham Medley, Damien C Tully, Sebastian Funk, Emilie Finch, Kaja Abbas, Fiona Yueqian Sun, Rosanna C Barnard, Matthew Quaife, Oliver Brady, Joel Hellewell, David Hodgson, Carl A B Pearson, W John Edmunds, Simon R Procter, William Waites, Billy J Quilty, Jiayao Lei, James D Munday, Kathleen O'Reilly, Rosalind M Eggo, Christopher I Jarvis, Fabienne Krauer, Mihaly Koltai, Sophie R Meakin, Mark Jit, Anna M Foss, Yalda Jafari, Nikos I Bosse, Emily S Nightingale, Katherine E. Atkins. Thibaut Jombart. Frank G Sandmann, Samuel Clifford, Petra Klepac, Stefan Flasche, C Julian Villabona-Arenas, Yung-Wai Desmond Chan, Yang Liu, Kiesha Prem, Sam Abbott, Akira Endo, Amy Gimma, Gwenan M Knight

#### CMMID COVID-19 working group funding statements:

Hamish P Gibbs (EDCTP2: RIA2020EF-2983-CSIGN, UK DHSC/UK Aid/NIHR: PR-OD-1017-20001), Alicia Rosello (NIHR: PR-OD-1017-20002), Nicholas G. Davies (UKRI Research England, NIHR: NIHR200929, UK MRC: MC\_PC\_19065), Kevin van Zandvoort (Elrha R2HC/UK FCDO/Wellcome Trust/NIHR, FCDO/Wellcome Trust: Epidemic Preparedness Coronavirus research programme 221303/Z/20/Z), Timothy W Russell (Wellcome Trust: 206250/Z/17/Z), Graham Medley (B&MGF: NTD Modelling Consortium OPP1184344), Sebastian Funk, (Wellcome Trust: 210758/Z/18/Z), Emilie Finch (MRC: MR/N013638/1), Kaja Abbas (BMGF: INV-016832; OPP1157270), Fiona Yueqian Sun (NIHR: 16/137/109), Rosanna C Barnard (European Commission: 101003688), Matthew Quaife (ERC Starting Grant: #757699, B&MGF: INV-001754), Oliver Brady (Wellcome Trust: 206471/Z/17/Z), Joel Hellewell (Wellcome Trust: 210758/Z/18/Z), David Hodgson (NIHR: IR01AI141534-01A1), Carl A B Pearson (B&MGF: NTD Modelling Consortium OPP1184344, FCDO/Wellcome Trust:

Epidemic Preparedness Coronavirus research programme 221303/Z/20/Z), W John Edmunds (European Commission: 101003688, UK MRC: MC\_PC\_19065, NIHR: PR-OD-1017-20002), Simon R Procter (B&MGF: INV-016832), William Waites (MRC: MR/V027956/1), Billy J Quilty (NIHR: 16/137/109, NIHR: 16/136/46, B&MGF: OPP1139859), Jiayao Lei (B&MGF: INV-003174), James D Munday (Wellcome Trust: 210758/Z/18/Z), Kathleen O'Reilly (B&MGF: OPP1191821), Rosalind M Eggo (HDR UK: MR/S003975/1, UK MRC: MC\_PC\_19065, NIHR: NIHR200908), Christopher I Jarvis (Global Challenges Research Fund: ES/P010873/1), Fabienne Krauer (Innovation Fund: 01VSF18015, Wellcome Trust: UNS110424), Mihaly Koltai (Wellcome Trust: 221303/Z/20/Z), Sophie R Meakin (Wellcome Trust: 210758/Z/18/Z), Mark Jit (B&MGF: INV-003174, NIHR: 16/137/109, NIHR: NIHR200929, European Commission: 101003688), Yalda Jafari (UKRI: MR/V028456/1), Nikos I Bosse (HPRU: NIHR200908), Emily S Nightingale (B&MGF: OPP1183986), Katherine E. Atkins (ERC: SG 757688),

Thibaut Jombart (Global Challenges Research Fund: ES/P010873/1, UK Public Health Rapid Support Team, NIHR: Health Protection Research Unit for Modelling Methodology HPRU-2012-10096, UK MRC: MC\_PC\_19065), Frank G Sandmann (NIHR: NIHR200929), Samuel Clifford (Wellcome Trust: 208812/Z/17/Z, UK MRC: MC\_PC\_19065), Petra Klepac (Royal Society: RP\EA\180004, European Commission: 101003688), Stefan Flasche (Wellcome Trust: 208812/Z/17/Z), C Julian Villabona-Arenas (ERC: SG 757688), Yang Liu (B&MGF: INV-003174, NIHR: 16/137/109, European Commission: 101003688, UK MRC: MC\_PC\_19065), Kiesha Prem (B&MGF: INV-003174, European Commission: 101003688), Sam Abbott (Wellcome Trust: 210758/Z/18/Z), Akira Endo (Nakajima Foundation), Amy Gimma (European Commission: 101003688), Gwenan M Knight (UK MRC: MR/P014658/1)

## References

1. Addetia A, Crawford KHD, Dingens A, *et al.*: **Neutralizing Antibodies Correlate with Protection from SARS-CoV-2 in Humans during a Fishery Vessel Outbreak with a High Attack Rate.** *J Clin Microbiol.* 2020; **58**(11): e02107–20. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
2. Hall V, Foulkes S, Charlett A, *et al.*: **Do antibody positive healthcare workers have lower SARS-CoV-2 infection rates than antibody negative healthcare workers? Large multi-centre prospective cohort study (the SIREN study), England: June to November 2020.** *medRxiv.* 2021; 2021.01.13.21249642. [Publisher Full Text](#)
3. Guthmiller JJ, Wilson PC: **Remembering seasonal coronaviruses.** *Science.* 2020; **370**(6522): 1272–3. [PubMed Abstract](#) | [Publisher Full Text](#)
4. Saad-Roy CM, Wagner CE, Baker RE, *et al.*: **Immune life history, vaccination, and the dynamics of SARS-CoV-2 over the next 5 years.** *Science.* 2020; **370**(6518): 811–8. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
5. Bobrovitz N, Arora RK, Cao C, *et al.*: **Global seroprevalence of SARS-CoV-2 antibodies: a systematic review and meta-analysis.** *medRxiv.* 2020; 2020.11.17.20233460. [Publisher Full Text](#)
6. Vabret A, Dina J, Gouarin S, *et al.*: **Detection of the New Human Coronavirus HKU1: A Report of 6 Cases.** *Clin Infect Dis.* 2006; **42**(5): 634–9. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
7. Huang AT, Garcia-Carreras B, Hitchings MDT, *et al.*: **A systematic review of antibody mediated immunity to coronaviruses: kinetics, correlates of protection, and association with severity.** *Nat Commun.* 2020; **11**(1): 4704. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
8. Callow KA, Parry HF, Sergeant M, *et al.*: **The time course of the immune response to experimental coronavirus infection of man.** *Epidemiol Infect.* 1990; **105**(2): 435–46. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
9. Reed SE: **The behaviour of recent isolates of human respiratory coronavirus in vitro and in volunteers: Evidence of heterogeneity among 229E-related strains.** *J Med Virol.* 1984; **13**(2): 179–92. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
10. Edridge AWD, Kaczorowska J, Hoste ACR, *et al.*: **Seasonal coronavirus protective immunity is short-lasting.** *Nat Med.* 2020; **26**(11): 1691–3. [PubMed Abstract](#) | [Publisher Full Text](#)
11. Aldridge RW, Lewer D, Beale S, *et al.*: **Seasonality and immunity to laboratory-confirmed seasonal coronaviruses (HCoV-NL63, HCoV-OC43, and HCoV-229E): results from the Flu Watch cohort study [version 2; peer review: 2 approved].** *Wellcome Open Res.* 2020; **5**: 52. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
12. Kiyuka PK, Agoti CN, Munywoki PK, *et al.*: **Human Coronavirus NL63 Molecular Epidemiology and Evolutionary Patterns in Rural Coastal Kenya.** *J Infect Dis.* 2018; **217**(11): 1728–39. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
13. Galanti M, Shaman J: **Direct Observation of Repeated Infections With Endemic Coronaviruses.** *J Infect Dis.* 2021; **223**(3): 409–415. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

14. Antia A, Ahmed H, Handel A, *et al.*: **Heterogeneity and longevity of antibody memory to viruses and vaccines.** *PLoS Biol.* 2018; **16**(8): e2006601. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
15. Melegaro A, Jit M, Gay N, *et al.*: **What types of contacts are important for the spread of infections?: using contact survey data to explore European mixing patterns.** *Epidemics.* 2011; **3**(3-4): 143-51. [PubMed Abstract](#) | [Publisher Full Text](#)
16. Hens N, Aerts M, Faes C, *et al.*: **Seventy-five years of estimating the force of infection from current status data.** *Epidemiol Infect.* 2010; **138**(6): 802-12. [PubMed Abstract](#) | [Publisher Full Text](#)
17. Severance EG, Bossis I, Dickerson FB, *et al.*: **Development of a Nucleocapsid-Based Human Coronavirus Immunoassay and Estimates of Individuals Exposed to Coronavirus in a U.S. Metropolitan Population.** *Clin Vaccine Immunol.* 2008; **15**(12): 1805-10. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
18. Liang FY, Lin LC, Ying TH, *et al.*: **Immunoreactivity characterisation of the three structural regions of the human coronavirus OC43 nucleocapsid protein by Western blot: implications for the diagnosis of coronavirus infection.** *J Virol Methods.* 2013; **187**(2): 413-20. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
19. Zhou W, Wang W, Wang H, *et al.*: **First infection by all four non-severe acute respiratory syndrome human coronaviruses takes place during childhood.** *BMC Infect Dis.* 2013; **13**: 433. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
20. Shao X, Guo X, Esper F, *et al.*: **Seroepidemiology of group I human coronaviruses in children.** *J Clin Virol.* 2007; **40**(3): 207-13. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
21. Monto AS, Lim SK: **The Tecumseh Study of Respiratory Illness. VI. Frequency of and Relationship between Outbreaks of Coronavirus Infection.** *J Infect Dis.* 1974; **129**(3): 271-6. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
22. Cavallaro JJ, Monto AS: **Community-wide outbreak of infection with a 229E-like coronavirus in Tecumseh, Michigan.** *J Infect Dis.* 1970; **122**(4): 272-9. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
23. Chan CM, Tse H, Wong SSY, *et al.*: **Examination of seroprevalence of coronavirus HKU1 infection with S protein-based ELISA and neutralization assay against viral spike pseudotyped virus.** *J Clin Virol.* 2009; **45**(1): 54-60. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
24. Sarateanu DE, Ehrengut W: **A two year serological surveillance of coronavirus infections in Hamburg.** *Infection.* 1980; **8**(2): 70-2. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
25. erees: **erees/seasonalHCoV: Second release (v2.0.0).** *Zenodo.* 2021. <http://www.doi.org/10.5281/zenodo.5707764>
26. Somes MP, Turner RM, Dwyer LJ, *et al.*: **Estimating the annual attack rate of seasonal influenza among unvaccinated individuals: A systematic review and meta-analysis.** *Vaccine.* 2018; **36**(23): 3199-207. [PubMed Abstract](#) | [Publisher Full Text](#)
27. Jayasundara K, Soobiah C, Thommes E, *et al.*: **Natural attack rate of influenza in unvaccinated children and adults: a meta-regression analysis.** *BMC Infect Dis.* 2014; **14**: 670. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
28. Turner D, Wailoo A, Nicholson K, *et al.*: **Systematic review and economic decision modelling for the prevention and treatment of influenza A and B.** *Health Technol Assess.* 2003; **7**(35): iii-iv, xi-xiii, 1-170. [PubMed Abstract](#) | [Publisher Full Text](#)
29. Kucharski AJ, Lessler J, Cummings DAT, *et al.*: **Timescales of influenza A/H3N2 antibody dynamics.** *PLoS Biol.* 2018; **16**(8): e2004974. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
30. Minter A, Hoschler K, Jagne YJ, *et al.*: **Estimation of Seasonal Influenza Attack Rates and Antibody Dynamics in Children Using Cross-Sectional Serological Data.** *J Infect Dis.* 2020; **jiaa338**. [PubMed Abstract](#) | [Publisher Full Text](#)
31. Liu WK, Liu Q, Chen DH, *et al.*: **Epidemiology of Acute Respiratory Infections in Children in Guangzhou: A Three-Year Study.** *PLoS One.* 2014; **9**(5): e96674. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
32. Plummer M, Stukalov A, Denwood M: **rjags: Bayesian Graphical Models using MCMC.** 2019; (accessed 16 Dec 2020). [Reference Source](#)
33. Vehtari A, Gelman A, Gabry J: **Practical Bayesian model evaluation using leave-one-out cross-validation and WAIC.** 2016. [Reference Source](#)
34. Vehtari A, Gabry J, Magnusson M, *et al.*: **loo: Efficient Leave-One-Out Cross-Validation and WAIC for Bayesian Models.** 2020; (accessed 15 Nov 2021). [Reference Source](#)
35. Rees EM, Waterlow NR, Lowe R, *et al.*: **Extended Data: Estimating the duration of seropositivity of human seasonal coronaviruses using seroprevalence studies.** 2021. <http://www.doi.org/10.5281/zenodo.5705144>
36. Lumley SF, O'Donnell D, Stoesser NE, *et al.*: **Antibodies to SARS-CoV-2 are associated with protection against reinfection.** *medRxiv.* 2020; 2020.11.18.20234369. [PubMed Abstract](#) | [Free Full Text](#)
37. Eguia R, Crawford KHD, Stevens-Ayers T, *et al.*: **A human coronavirus evolves antigenically to escape antibody immunity.** *Microbiology.* 2020. [PubMed Abstract](#) | [Free Full Text](#)
38. Dijkman R, Jebbink MF, Bahia el Idrissi N, *et al.*: **Human Coronavirus NL63 and 229E Seroconversion in Children.** *J Clin Microbiol.* 2008; **46**(7): 2368-73. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
39. Kellam P, Barclay W: **The dynamics of humoral immune responses following SARS-CoV-2 infection and the potential for reinfection.** *J Gen Virol.* 2020; **101**(8): 791-7. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
40. Iyer AS, Jones FK, Nodoushani A, *et al.*: **Dynamics and significance of the antibody response to SARS-CoV-2 infection.** *medRxiv.* 2020. [PubMed Abstract](#) | [Free Full Text](#)
41. Dan JM, Mateus J, Kato Y, *et al.*: **Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection.** *Science.* 2021; **371**(6529): eabf4063. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
42. Cox RJ, Brokstad KA: **Not just antibodies: B cells and T cells mediate immunity to COVID-19.** *Nat Rev Immunol.* 2020; **20**(10): 581-2. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
43. Ni L, Ye F, Cheng ML, *et al.*: **Detection of SARS-CoV-2-Specific Humoral and Cellular Immunity in COVID-19 Convalescent Individuals.** *Immunity.* 2020; **52**(6): 971-977.e3. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
44. Ferrari MJ, Djibo A, Grais RF, *et al.*: **Episodic outbreaks bias estimates of age-specific force of infection: a corrected method using measles as an example.** *Epidemiol Infect.* 2010; **138**(1): 108-16. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
45. Whitaker HJ, Farrington CP: **Estimation of infectious disease parameters from serological survey data: the impact of regular epidemics.** *Stat Med.* 2004; **23**(15): 2429-43. [PubMed Abstract](#) | [Publisher Full Text](#)
46. Fischer N, Dauby N, Bossuyt N, *et al.*: **Monitoring of human coronaviruses in Belgian primary care and hospitals, 2015-20: a surveillance study.** *Lancet Microbe.* 2021. [PubMed Abstract](#) | [Free Full Text](#)
47. Zhang SF, Tuo JL, Huang XB, *et al.*: **Epidemiology characteristics of human coronaviruses in patients with respiratory infection symptoms and phylogenetic analysis of HCoV-OC43 during 2010-2015 in Guangzhou.** *PLoS One.* 2018; **13**(1): e0191789. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
48. Fowlkes A, Giorgi A, Erdman D, *et al.*: **Viruses Associated With Acute Respiratory Infections and Influenza-like Illness Among Outpatients From the Influenza Incidence Surveillance Project, 2010-2011.** *J Infect Dis.* 2014; **209**(11): 1715-25. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
49. Mossong J, Hens N, Jit M, *et al.*: **Social Contacts and Mixing Patterns Relevant to the Spread of Infectious Diseases.** *PLoS Med.* 2008; **5**(3): e74. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
50. Baguelin M, Flasche S, Camacho A, *et al.*: **Assessing Optimal Target Populations for Influenza Vaccination Programmes: An Evidence Synthesis and Modelling Study.** *PLoS Med.* 2013; **10**(10): e1001527. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
51. Kissler SM, Viboud C, Grenfell BT, *et al.*: **Symbolic transfer entropy reveals the age structure of pandemic influenza transmission from high-volume influenza-like illness data.** *J R Soc Interface.* 2020; **17**(164): 20190628. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
52. Klepac P, Kucharski AJ, Conlan AJK, *et al.*: **Contacts in context: large-scale setting-specific social mixing matrices from the BBC Pandemic project.** *medRxiv.* Epidemiology. 2020. [PubMed Abstract](#) | [Free Full Text](#)
53. Munro APS, Faust SN: **COVID-19 in children: current evidence and key questions.** *Curr Opin Infect Dis.* 2020; **33**(6): 540-7. [PubMed Abstract](#) | [Publisher Full Text](#)
54. Marks M, Millat-Martinez P, Ouchi D, *et al.*: **Transmission of COVID-19 in 282 clusters in Catalonia, Spain: a cohort study.** *Lancet Infect Dis.* 2021; **21**(5): 629-636. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
55. Viner RM, Mytton OT, Bonell C, *et al.*: **Susceptibility to SARS-CoV-2 infection amongst children and adolescents compared with adults: a systematic review and meta-analysis.** *medRxiv.* Public and Global Health. 2020. [PubMed Abstract](#) | [Free Full Text](#)

# Open Peer Review

Current Peer Review Status:   

---

## Version 2

Reviewer Report 26 November 2021

<https://doi.org/10.21956/wellcomeopenres.19266.r47156>

© 2021 Huang A. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

 **Angkana T. Huang** 

<sup>1</sup> Department of Biology and Emerging Pathogens Institute, University of Florida, Gainesville, FL, USA

<sup>2</sup> Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand

I thank the authors for thoroughly considering and addressing my comments. I only have one minor point to make regarding my suggestion of ELPD but is not meant to hold off the state of the approval. Specifically, it would be great if the authors could also include the 95% CI (in addition to the point estimates of the performance metric) to demonstrate that the superiority was well supported (i.e., whether the intervals were non-overlapping).

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** infectious disease modeling

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

Reviewer Report 23 November 2021

<https://doi.org/10.21956/wellcomeopenres.19266.r47157>

© 2021 Flower B. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

 **Barnaby Flower** 

<sup>1</sup> Department of Infectious Disease, Faculty of Medicine, Imperial College London, London, UK

<sup>2</sup> Oxford University Clinical Research Unit, Vietnam, Ho Chi Minh City, Vietnam

No further comments.

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** SARSCoV2 antibody seroprevalence, SARSCoV2 diagnostics, Hepatitis C Clinical Trialist. No modeling expertise.

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

Reviewer Report 22 November 2021

<https://doi.org/10.21956/wellcomeopenres.19266.r47155>

© 2021 Herzog S. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



**Sereina A. Herzog** 

Institute for Medical Informatics, Statistics and Documentation, Medical University of Graz, Graz, Austria

The authors have addressed the comments I had, and I have no further comments on the revised version.

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Infectious disease modeling, biostatistics

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

---

## Version 1

Reviewer Report 14 October 2021

<https://doi.org/10.21956/wellcomeopenres.18416.r46084>

© 2021 Herzog S. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



**Sereina A. Herzog** 

Institute for Medical Informatics, Statistics and Documentation, Medical University of Graz, Graz, Austria

Rees *et al.* provide estimations for the force of infection (FOI) and seropositivity waning rate regarding four different human coronaviruses (HCoV) strains using reverse catalytic model with age-varying FOI. The limitations of the modelling approach as well as the limitations about the datasets are well discussed.

Some minor points that should be addressed:

1. The authors give in the introduction examples about pathogens which are 'fully immunising' like pertussis. To my knowledge pertussis natural infection protects longer than vaccination but not lifelong (see Wendelboe *et al.*, 2005<sup>1</sup>). Please rephrase the sentence accordingly.
2. Please clarify in the method section what is meant with "[...] were excluded, as well as studies with small number of data points." Is 'small number' referring to number of different age (groups) reported in the study or number of total observations in a study, and what is 'small'?
3. The full dataset used is not available on Zenodo (reference 25) but on GitHub (reference 33) [Method section, 1<sup>st</sup> paragraph, last sentence] – please check throughout the text those two references (e.g. last sentence Method section GitHub is mentioned with reference number 25).
4. In the method section it is stated that for the age at the cut-off time ( $a_0$ ) also uniform priors from 0 to 5 years are also investigated, however, I don't see this prior appearing in the Table 2 with the different models and priors or in the Result section.
5. Can the authors clarify in the discussion why they did not investigate a sensitivity analysis about the different assays used in the studies, e.g. allowing to vary waning according to assays used?
6. It is not clear which model was used to produce Figure 3B and which FOI estimates were used (from the main model, all models?) and how they were pooled. The description and interpretation of Figure 3B should be deepened.

Some minor points which could improve readability:

1. In the 3<sup>rd</sup> paragraph of the introduction, the authors provide the number of observations for the studies mentioned in this paragraph except for the studies conducted in Kenya and in New York. It would help to put the results in perspective to also have the numbers for those two studies.
2. Assay description: Table 1 indicates a very rough description of the assay used in the study. For interested readers it would be helpful to have more information in the supplementary material about the assays like exact assay name, was it qualitative/quantitative, sensitivity/specificity, what cut-off values were used, what is the lower limit of detection (LLOD), what happened with equivocal results (count towards being positive or negative), etc.



3. Referring to tables and figures in the supplementary material: change 'extended data Figure 1, Table 1' to 'Supplementary Figure 1, Table 1' etc.
4. Table 1-4: add the abbreviations used within the table in the table legend (e.g. Table 1 HCoV).
5. Table 2 - 5<sup>th</sup> model: maybe rephrase 'using all data' to 'using also data on <1 year'.
6. Table 3: I would suggest to extend the column titles a bit: "FOI": clarifying that it is the one for the younger age group (i.e. lambda1); "Cut-off": clarifying that this is about splitting observations into two age groups and adding the unit years.
7. Table 4: Why are not all models from Table 2 reappearing in this table?

### References

1. Wendelboe AM, Van Rie A, Salmaso S, Englund JA: Duration of immunity against pertussis after natural infection or vaccination. *Pediatr Infect Dis J*. 2005; **24** (5 Suppl): S58-61 [PubMed Abstract](#) | [Publisher Full Text](#)

### Is the work clearly and accurately presented and does it cite the current literature?

Partly

### Is the study design appropriate and is the work technically sound?

Yes

### Are sufficient details of methods and analysis provided to allow replication by others?

Yes

### If applicable, is the statistical analysis and its interpretation appropriate?

Yes

### Are all the source data underlying the results available to ensure full reproducibility?

Yes

### Are the conclusions drawn adequately supported by the results?

Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Infectious disease modeling, biostatistics

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Author Response 17 Nov 2021

**Eleanor Rees**, London School of Hygiene & Tropical Medicine, London, UK

*Thank you for taking the time to read our article. We have added an additional sensitivity analysis by assay and clarified and amended the technical points you raised. Please see our detailed responses to your comments below.*

Some minor points that should be addressed:

1. The authors give in the introduction examples about pathogens which are 'fully immunising' like pertussis. To my knowledge pertussis natural infection protects longer than vaccination but not lifelong (see Wendelboe *et al.*, 2005<sup>1</sup>). Please rephrase the sentence accordingly.

*Thank you for bringing this to our attention, we have now corrected this.*

2. Please clarify in the method section what is meant with "[...] were excluded, as well as studies with small number of data points." Is 'small number' referring to number of different age (groups) reported in the study or number of total observations in a study, and what is 'small'?

*We excluded Liang *et al.* 2013 since they only reported two age groups (ages 0 and 18-25). This has now been clarified in the text:*

*"Studies which did not include estimates for individuals under 10 years old were excluded, as well as studies with which only reported two age groups."*

3. The full dataset used is not available on Zenodo (reference 25) but on GitHub (reference 33) [Method section, 1<sup>st</sup> paragraph, last sentence] – please check throughout the text those two references (e.g. last sentence Method section GitHub is mentioned with reference number 25).

*Thank you – these references have now been corrected throughout the text.*

4. In the method section it is stated that for the age at the cut-off time ( $a_0$ ) also uniform priors from 0 to 5 years are also investigated, however, I don't see this prior appearing in the Table 2 with the different models and priors or in the Result section.

*This is referred to as "cut-off" in all the tables and text. Uniform priors between 0 and 20 were chosen for the cut-off ( $a_0$ ), and these are stated in Table 2. I have now clarified the description of the priors in the methods and added further information below the table to avoid confusion.*

*Methods:*

*"For the age at cut-off ( $a_0$ ), uniform priors from 0 to 20 years were chosen as we were interested in the difference in FOI in children and young adults."*

5. Can the authors clarify in the discussion why they did not investigate a sensitivity analysis about the different assays used in the studies, e.g. allowing to vary waning according to assays used?

*Following yours and the other reviewers suggestion we have now included an additional sensitivity in the supplementary material, where we estimated the duration of antibody persistence by assay. We found that when we allowed waning to vary by assay (ELISA, IFA, HI and Neutralisation) we estimated the duration of antibody persistence to be between 1.1 years to 2.6 years for ELISA, HI and neutralisation. For IFA we observed a longer estimate of 7.7 (CrI: 3.0-14.3) years. However, we found wide credible intervals, particularly for the neutralisation and IFA which only had one study setting per assay. This highlights the need for more studies looking at the seroprevalence of HCoVs, and for better standardisation of assays.*

**Results:**

*"Finally, we explored the impact of the different assays used in the studies on the waning estimates. We allowed the waning estimate to vary by assay (extended data Table 7, Figure 525), whilst allowing FOI to vary by study, and alpha and cut-off to vary by setting. This model estimated the duration of antibody persistence to be similar for ELISA (2.63 [95% CrI: 0.94-9.09] years), HI (1.08 [95% CrI: 0.44-3.33] years) and neutralisation (1.28 [95% CrI: 0.25-50.0] years) assays, but longer for IFA (7.69 [95% CrI: 3.03-14.29] years). The credible intervals were wide, likely due to the small number of studies by assay."*

**Discussion:**

*"When we allowed the waning estimate to vary by assay, we found a similar estimates of antibody persistence for ELISA, HI and neutralisation assays, ranging from 1.1 years to 2.6 years, and these are comparable to the estimates from the main model. However, for IFA, we observed a longer estimate of 7.7 years (CrI: 3.0-14.3). Due to the small number of studies, the credible intervals were large, particularly for the IFA and neutralisation assay, which only had one study setting for each assay. This highlights the need for more studies, and better standardisation of assays."*

6. It is not clear which model was used to produce Figure 3B and which FOI estimates were used (from the main model, all models?) and how they were pooled. The description and interpretation of Figure 3B should be deepened.

*Thank you for this comment. We have clarified within the figure legend which model was used for Fig 3B. We have also expanded the description and interpretation of the figure within the results section.*

*"To demonstrate the relationship between FOI and seropositivity at age 30, we created simulated scenarios under different sero-catalytic models. Using the parameters for the relative change in FOI and waning estimated from the age-varying reverse catalytic model (where the relative change in FOI and the age at cut-off were simultaneously estimated across settings), we simulated the proportion of individuals aged 30 years that would be seropositive using a range of FOI estimates to show how the proportion changes using the different models. The catalytic model, which does not allow for seroreversion, results in the highest estimates of seropositivity at age 30 with increasing FOI. The age-varying FOI model results in higher estimates of seropositivity at age 30 compared with the reverse catalytic model. This is due to the FOI which was estimated to be almost twice as high in the older age group (with age at cut-off 8.49 [7.52 – 9.94] years) in the age-varying FOI model ( Figure 3A). We further explored the relationship between FOI, attack rates and the estimated number of infections by age. We used the pooled estimate across all studies of FOI to estimate the proportion exposed at a given age to provide an indication of how many infections we might expect to see by age under our modelling*

*assumptions ( Figure 3B). We estimate that by two years, over 50% of the population will have at least one infection, and by age ten over 75% will have had more than four infections.”*

Some minor points which could improve readability:

1. In the 3<sup>rd</sup> paragraph of the introduction, the authors provide the number of observations for the studies mentioned in this paragraph except for the studies conducted in Kenya and in New York. It would help to put the results in perspective to also have the numbers for those two studies.

*This has now been added to the introduction.*

2. Assay description: Table 1 indicates a very rough description of the assay used in the study. For interested readers it would be helpful to have more information in the supplementary material about the assays like exact assay name, was it qualitative/quantitative, sensitivity/specificity, what cut-off values were used, what is the lower limit of detection (LLOD), what happened with equivocal results (count towards being positive or negative), etc.

*Thank you, I have added some further information to Table 1 regarding the assay characteristics (antigen used and assay cut-off used in the study). I have also added an assay-specific sensitivity analysis and added further details regarding different assays in the discussion section. There is limited information in the literature on sensitivity and specificity of these assays, likely because these pathogens aren't tested routinely in the community. Furthermore, given seroprevalence studies include asymptomatic and mildly symptomatic individuals, it is uncertain how these assays perform as validation is usually conducted in acute cases.*

3. Referring to tables and figures in the supplementary material: change 'extended data Figure 1, Table 1' to 'Supplementary Figure 1, Table 1' etc.

*Thank you for your suggestion, however, this is the naming convention chosen by Wellcome Open research.*

4. Table 1-4: add the abbreviations used within the table in the table legend (e.g. Table 1 HCoV).

*These have been added.*

5. Table 2 - 5<sup>th</sup> model: maybe rephrase 'using all data' to 'using also data on <1 year'.

*This has been amended.*

6. Table 3: I would suggest to extend the column titles a bit: "FOI": clarifying that it is the one for the younger age group (i.e.  $\lambda_1$ ); "Cut-off": clarifying that this is about splitting observations into two age groups and adding the unit years.

*Thank you for your suggestion, the table headings have been changed.*

### 7. Table 4: Why are not all models from Table 2 reappearing in this table?

*Since we explored many different models, we chose to focus this table only on the models which we felt were the most relevant, particular since this table is a comparison summary table, and the detailed information for all models is provided elsewhere in the manuscript.*

**Competing Interests:** No competing interests were disclosed.

Reviewer Report 12 October 2021

<https://doi.org/10.21956/wellcomeopenres.18416.r46089>

© 2021 Flower B. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



**Barnaby Flower** 

<sup>1</sup> Department of Infectious Disease, Faculty of Medicine, Imperial College London, London, UK

<sup>2</sup> Oxford University Clinical Research Unit, Vietnam, Ho Chi Minh City, Vietnam

Rees *et al.* provide a timely analysis of duration of natural immunity against seasonal human coronaviruses. They use an age-structured catalytic model which inputs historical seroprevalence data from five studies to estimate likely duration of seropositivity following seroconversion. They estimate HCoV antibodies last between 0.9 and 3.8 years, and find that the rate at which susceptible individuals acquire infection and seroconvert is higher in older children (>8.49 years) and adults than it is in younger children. The duration of seropositivity is consistent with previous estimates by Edridge *et al.* and tallies with emerging data concerning SARSCoV2.

I am not a modeler and defer to my modeling colleague's review regarding aspects of the methodology. However to the non-specialist the methods appear robust and reproducible and they are transparently described in this well-written paper.

As with all models, the outputs are only as good as the inputs, and in this case, data has been extracted from just 5 studies performed between 1965 and 2011 in four countries (Hong Kong, China, USA and Germany). The studies employ different assays, namely: enzyme-linked immunosorbent assays (ELISA), immunofluorescence assays (IFA), western blots, and complement fixation (CF), hemagglutination inhibition assays (HAI) and neutralisation assays which have different sensitivities and specificities, and I suspect this will lead to heterogeneous under-estimation of actual antibody positivity rates, particularly in comparison to current estimates of SARSCoV2 using highly sensitive ELISAs. The study would be strengthened by assay specific sensitivity analysis.

The second limitation regards not accounting for seasonality. The authors point out that other studies have found that ignoring seasonality may overemphasize the role of adults in the transmission. Given that HCoVs are detected at much higher rates in the winter and spring

seasons this makes it difficult to interpret one of the study's major findings of a higher force of infection in adults. This is mentioned in the 4th paragraph of the discussion but not in the context of the finding that the FOI was estimated to be twice as high in the older age group (6th paragraph) and perhaps this should be better tied together.

While these considerations might improve the paper, the limitations are well discussed and the manuscript is well worthy of indexing and dissemination.

One minor point:

In paragraph 4 of the methods it says:

"There is little information on the attack rate of HCoVs, but there have been several systematic reviews and meta-analyses looking at unvaccinated individuals which have reported the attack rate to range between 15.2% – 22.5% in children and 3.5% – 10.7% in adults<sup>26–28</sup>."

This sentence is missing 'influenza'.

**Is the work clearly and accurately presented and does it cite the current literature?**

Yes

**Is the study design appropriate and is the work technically sound?**

Yes

**Are sufficient details of methods and analysis provided to allow replication by others?**

Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**

Yes

**Are all the source data underlying the results available to ensure full reproducibility?**

Yes

**Are the conclusions drawn adequately supported by the results?**

Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** SARSCoV2 antibody seroprevalence, SARSCoV2 diagnostics, Hepatitis C Clinical Trialist. No modeling expertise.

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

Author Response 17 Nov 2021

**Eleanor Rees**, London School of Hygiene & Tropical Medicine, London, UK

*Thank you for your comments on this manuscript. As you suggest, we have added an additional sensitivity analysis by assay and expanded our discussion around seasonality. Please see our*

*detailed responses to your comments below.*

As with all models, the outputs are only as good as the inputs, and in this case, data has been extracted from just 5 studies performed between 1965 and 2011 in four countries (Hong Kong, China, USA and Germany). The studies employ different assays, namely: enzyme-linked immunosorbent assays (ELISA), immunofluorescence assays (IFA), western blots, and complement fixation (CF), hemagglutination inhibition assays (HAI) and neutralisation assays which have different sensitivities and specificities, and I suspect this will lead to heterogeneous under-estimation of actual antibody positivity rates, particularly in comparison to current estimates of SARS-CoV2 using highly sensitive ELISAs. The study would be strengthened by assay specific sensitivity analysis.

*Thank you for this suggestion, we have added an additional sensitivity looking at how the estimates of waning antibody duration change by assay. We found that when we allowed waning to vary by assay (ELISA, IFA, HI and Neutralisation) we estimated the duration of antibody persistence to be between 1.1 years to 2.6 years for ELISA, HI and neutralisation. For IFA we observed a longer estimate of 7.7 (CrI: 3.0-14.3) years. However, we found wide credible intervals, particularly for the neutralisation and IFA which only had one study setting per assay. This highlights the need for more studies looking at the seroprevalence of HCoVs, and for better standardisation of assays.*

**Results:**

*"Finally, we explored the impact of the different assays used in the studies on the waning estimates. We allowed the waning estimate to vary by assay (extended data Table 7, Figure 5<sup>25</sup>), whilst allowing FOI to vary by study, and alpha and cut-off to vary by setting. This model estimated the duration of antibody persistence to be similar for ELISA (2.63 [95% CrI: 0.94-9.09] years), HI (1.08 [95% CrI: 0.44-3.33] years) and neutralisation (1.28 [95% CrI: 0.25-50.0] years) assays, but longer for IFA (7.69 [95% CrI: 3.03-14.29] years). The credible intervals were wide, likely due to the small number of studies by assay."*

**Discussion:**

*"When we allowed the waning estimate to vary by assay, we found a similar estimates of antibody persistence for ELISA, HI and neutralisation assays, ranging from 1.1 years to 2.6 years, and these are comparable to the estimates from the main model. However, for IFA, we observed a longer estimate of 7.7 years (CrI: 3.0-14.3). Due to the small number of studies, the credible intervals were large, particularly for the IFA and neutralisation assay, which only had one study setting for each assay. This highlights the need for more studies, and better standardisation of assays."*

The second limitation regards not accounting for seasonality. The authors point out that other studies have found that ignoring seasonality may overemphasize the role of adults in the transmission. Given that HCoVs are detected at much higher rates in the winter and spring seasons this makes it difficult to interpret one of the study's major findings of a higher force of infection in adults. This is mentioned in the 4th paragraph of the discussion but not in the context of the finding that the FOI was estimated to be twice as high in the older age group (6th paragraph) and perhaps this should be better tied together.

*Thank you for your comment. The seasonality of HCoVs is an important consideration, and we have now expanded this in the discussion:*

*"The time of year data collection occurred may influence our results, particularly given that the duration of antibody persistence is estimated to range between 0.9 (95% CrI: 0.6 - 1.6) years and 3.8 (95% CrI: 2.0 - 7.4) years. Data collection during high transmission periods would lead to an over estimate of both the FOI and the duration of antibody persistence. All the studies (except for Chan et al.<sup>23</sup> who did not report this information), included within this analysis collected data over at least a six-month period. For this reason, the timing of data collection and the seasonality is unlikely to have biased our results."*

*We have also further considered the Ferrari et al. paper in the context of our results. Their paper looked at measles outbreaks in Niger, which have a very different epidemic profile, with erratic outbreaks that vary by orders of magnitude, and large periods between epidemics. The epidemic profile is different for seasonal coronaviruses and we think that regular cyclic outbreaks do not strongly bias the model, as found by Whitaker & Farrington. We have expanded this within the discussion:*

*"We also did not account for seasonality within this model, which may have under-estimated our FOI. Ferrari et al.<sup>42</sup> found that ignoring seasonality may overemphasize the role of adults in the transmission, however, this was observed in measles in Niger, with outbreak peaks ranging over several orders of magnitude, and long periods between epidemics. The epidemic profile is different for seasonal coronaviruses, and therefore, this is unlikely to apply in this context."*

While these considerations might improve the paper, the limitations are well discussed and the manuscript is well worthy of indexing and dissemination.

One minor point:

In paragraph 4 of the methods it says:

"There is little information on the attack rate of HCoVs, but there have been several systematic reviews and meta-analyses looking at unvaccinated individuals which have reported the attack rate to range between 15.2% – 22.5% in children and 3.5% – 10.7% in adults<sup>26-28</sup>."

This sentence is missing 'influenza'.

*Thank you, this has now been corrected.*

**Competing Interests:** No competing interests were disclosed.

Reviewer Report 28 June 2021

<https://doi.org/10.21956/wellcomeopenres.18416.r44311>



© 2021 Huang A. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



**Angkana T. Huang** 

<sup>1</sup> Department of Biology and Emerging Pathogens Institute, University of Florida, Gainesville, FL, USA

<sup>2</sup> Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand

Leveraging data on other human coronaviruses (HCoV) that have been circulating for longer, the authors estimated a range of antibody waning rates that might apply to SARS-CoV-2. They performed multiple sensitivity analyses to assess the robustness of their estimates. Their results also pointed towards transmission being higher in older individuals.

The authors provided ample background to understand the motivation and the approach of their work. Below are some minor points that I view should be addressed.

**1)** Please consider using the term 'seropositivity waning rate' instead of 'immunity waning rate' for  $\omega$  as many of the assays in the dataset are binding assays which may not directly translate to protection, though correlated.

**2)** I appreciate that the authors included multiple sensitivity analyses in their study. I would like to suggest one more where waning rates are assay specific. The assays measure different functional aspects of the antibodies which may involve different subsets of the induced repertoires. Some hints exist in the authors' results. Shao (2007) and Chan (2009) used IgG ELISA while Monto (1974) and Sarateanu (1980) were HI based. Looking at plots of the observed data, these tend to exhibit more prominent wanes. In Table S6, Model 1, 5, and 6 where Monto (1974) and Sarateanu (1980) were included, the estimated waning rates were much higher than the others. It could be that these were specific to HCoV-OC43, but looking at Table S2, the estimates for -NL63 and -HKU1 were similar to -OC43 (considering both the point estimates and credible intervals). Posterior density plots from code provided by the authors showed that combined cutoff of the Cavallaro (1970) and the Monto (1974) study in the main model, though converged, is bimodal. I wonder if this resulted from the model trying to accommodate the enforced single waning rate between studies which used different assays. This assessment will likely help the field reconcile discrepancies in serosurveys that were measured using different assays.

**3)** As the authors pointed out, data for some strains were from the same settings. This is evidence for co-circulation. The cross-reactivity between strains, specifically within alpha- and beta-CoVs, would affect the seropositivity. I acknowledge that literature is slim on what the degree of cross-reactivity is and the limited data may make it hard to infer from the data. Anyhow, please consider adding some discussion around how this would change the estimated waning rate as it will help readers adjust their expectations on what the true waning rates could be. One way to gain such intuition may involve extending the models to include cross-reactivity in studies with known co-circulation, imposing different sets of informative priors to the cross-reactivity rate, and assess how those affect the inferred waning rates. It is optional whether the authors would take on this path.

- 4) The authors may consider additional metrics of model performance, for instance, the expected log predictive density (ELPD) which is based on approximate leave-one-out cross-validation, <https://doi.org/10.1007/s11222-016-9696-4>. The measure provides uncertainties around the performance estimates which may help determine the superiority among the suite of models, especially for ones where DIC were very similar.
- 5) It would be helpful to provide an equation to explicitly show the link between the estimated waning rates and the duration of antibody persistence which were reported throughout the paper, and is the main finding of the study.
- 6) In contrast to the previous point, the authors provided an equation linking the FOI to the attack rates but barely touched upon this topic in the paper except for one occurrence in the Discussion. May there be ideas that the authors wished to discuss but were not fully expressed in the text?
- 7) It is unclear what the motivation for the analysis which led to Figure 3 was. Providing some context, especially how that would better our projections on SARS-CoV-2 would be helpful.
- 8) Lastly, there are some truncated sentences or missing/inconsistent information in the paper that needs to be fixed. For example:
- In the Methods, “The different assays used in each study for the different strains is shown, and where the antibody detected was specified this is included in the table.”
  - In the Results, “When the relative change in FOI and cut-off parameters were simultaneously estimated by setting (extended data Figure 2, Table 3) the duration of antibody persistence was estimated to be shorter, ...”.
  - According to the captions, it occurs to me that the pairings are as follows: Table S1 with Figure S1, Table S3 with Figure S2, Table S5 with Figure S4. The pair of Table S2 is not obvious. It is unclear for Figure S3 which analysis this belongs to. Please also double check that the Extended data section in the main text matches the materials provided in the supplement.
  - “The inference was impleented in RJags...”
  - The figure legend of Figure 3A says “reverse catalytic & age varying FOI” while the caption says “reverse catalytic model with time-varying FOI”. The colors also do not seem to match the legend (blue vs green vs grey). May be helpful to choose colors that are more different, especially that the lines in the legend keys are quite thin.
  - It is unclear which model was used to generate Figure 3B. I am guessing the “reverse catalytic model” from its matching color but explicit statements would be helpful to the readers.
  - Please consider breaking this portion in the Discussion into a new sentence, “... and a meta-analysis of contact tracing studies found that children had 56% (31% – 71%) lower odds of becoming an infected contact compared with adults<sup>52</sup>.”

**Is the work clearly and accurately presented and does it cite the current literature?**

Partly

**Is the study design appropriate and is the work technically sound?**

Yes

**Are sufficient details of methods and analysis provided to allow replication by others?**

Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**

Yes

**Are all the source data underlying the results available to ensure full reproducibility?**

Yes

**Are the conclusions drawn adequately supported by the results?**

Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** infectious disease modeling

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Author Response 17 Nov 2021

**Eleanor Rees**, London School of Hygiene & Tropical Medicine, London, UK

Thank you for taking the time to review our article. We have added an additional sensitivity analysis by assay and technical details to the manuscript, as you suggest. Please see our detailed responses to your comments below.

**1)** Please consider using the term 'seropositivity waning rate' instead of 'immunity waning rate' for  $\omega$  as many of the assays in the dataset are binding assays which may not directly translate to protection, though correlated.

*Thank you for this comment. We agree with the point you raise, and have amended "immunity waning rate" to "seropositivity waning rate" as suggested.*

**2)** I appreciate that the authors included multiple sensitivity analyses in their study. I would like to suggest one more where waning rates are assay specific. The assays measure different functional aspects of the antibodies which may involve different subsets of the induced repertoires. Some hints exist in the authors' results. Shao (2007) and Chan (2009) used IgG ELISA while Monto (1974) and Sarateanu (1980) were HI based. Looking at plots of the observed data, these tend to exhibit more prominent wanes. In Table S6, Model 1, 5, and 6 where Monto (1974) and Sarateanu (1980) were included, the estimated waning rates

were much higher than the others. It could be that these were specific to HCoV-OC43, but looking at Table S2, the estimates for -NL63 and -HKU1 were similar to -OC43 (considering both the point estimates and credible intervals). Posterior density plots from code provided by the authors showed that combined cutoff of the Cavallaro (1970) and the Monto (1974) study in the main model, though converged, is bimodal. I wonder if this resulted from the model trying to accommodate the enforced single waning rate between studies which used different assays. This assessment will likely help the field reconcile discrepancies in serosurveys that were measured using different assays.

*Thank you for this suggestion, we have added an additional sensitivity looking at how the estimates of waning antibody duration change by assay. We found that when we allowed waning to vary by assay (ELISA, IFA, HI and Neutralisation) we estimated the duration of antibody persistence to be between 1.1 years to 2.6 years for ELISA, HI and neutralisation. For IFA we observed a longer estimate of 7.7 (CrI: 3.0-14.3) years (See Extended data Figure 5 and Table 7). However, we found wide credible intervals, particularly for the neutralisation and IFA which only had one study setting per assay. This highlights the need for more studies looking at the seroprevalence of HCoVs, and for better standardisation of assays.*

**Results:**

*"Finally, we explored the impact of the different assays used in the studies on the waning estimates. We allowed the waning estimate to vary by assay (extended data Table 7, Figure 5<sup>25</sup>), whilst allowing FOI to vary by study, and alpha and cut-off to vary by setting. This model estimated the duration of antibody persistence to be similar for ELISA (2.63 [95% CrI: 0.94-9.09] years), HI (1.08 [95% CrI: 0.44-3.33] years) and neutralisation (1.28 [95% CrI: 0.25-50.0] years) assays, but longer for IFA (7.69 [95% CrI: 3.03-14.29] years). The credible intervals were wide, likely due to the small number of studies by assay."*

**Discussion:**

*"When we allowed the waning estimate to vary by assay, we found a similar estimates of antibody persistence for ELISA, HI and neutralisation assays, ranging from 1.1 years to 2.6 years, and these are comparable to the estimates from the main model. However, for IFA, we observed a longer estimate of 7.7 years (CrI: 3.0-14.3). Due to the small number of studies, the credible intervals were large, particularly for the IFA and neutralisation assay, which only had one study setting for each assay. This highlights the need for more studies, and better standardisation of assays."*

**3)** As the authors pointed out, data for some strains were from the same settings. This is evidence for co-circulation. The cross-reactivity between strains, specifically within alpha and beta-CoVs, would affect the seropositivity. I acknowledge that literature is slim on what the degree of cross-reactivity is and the limited data may make it hard to infer from the data. Anyhow, please consider adding some discussion around how this would change the estimated waning rate as it will help readers adjust their expectations on what the true waning rates could be. One way to gain such intuition may involve extending the models to include cross-reactivity in studies with known co-circulation, imposing different sets of informative priors to the cross-reactivity rate, and assess how those affect the inferred waning rates. It is optional whether the authors would take on this path.

*Thank you for this comment. We have added some additional discussion surrounding cross-*

reactivity and cross-protection to the discussion and explored how this might have impacted our results. Since we only have a limited number of datasets and data points, we don't feel that we have sufficient data to include cross-reactivity within this analysis.

*Discussion:*

*"In addition, we did not take into consideration cross-protection between seasonal coronavirus strains. There is some evidence of cross protective immunity between seasonal coronavirus strains, and in settings where there is co-circulating HCoV strains, this may lead to a higher prevalence. There is also evidence that there is cross-reactivity between different coronaviruses, which may lead to false positive results. A recent systematic review found that there was some cross-reactivity that occurred within alpha (HCoV-229E and HCoV-NL63) and beta (HCoV-OC43 and HCoV-HKU1) coronaviruses, but minimal reactivity between alpha and beta coronaviruses<sup>7</sup>. However, it is not clear whether cross-reactivity equates to cross-protection. False positives due to cross-reactivity would lead to an over-estimation of seroprevalence in a setting. This would lead to a higher plateau in older ages, and therefore would generally lead to an over-estimation of both the FOI and the duration of antibody persistence."*

**4)** The authors may consider additional metrics of model performance, for instance, the (ELPD) which is based on approximate leave-one-out cross-validation, <https://doi.org/10.1007/s11222-016-9696-4>. The measure provides uncertainties around the performance estimates which may help determine the superiority among the suite of models, especially for ones where DIC were very similar.

*Thank you for the suggestion. We agree that DIC as a metric has limitations for model selection, particularly given our DIC estimates were so similar, which is why in the main results and abstract we chose to report a range of estimates from the different models, rather than focussing simply on just one model. We have now added leave-one-out cross validation (LOO) to estimate the out of sample prediction ability. Additionally, we have added WAIC, which offers advantages over the DIC for Bayesian models, since it uses the entire posterior distribution. We have reported these for all models, and found the same general trends as observed using DIC.*

*"A sensitivity analysis was conducted using less informative priors for the FOI parameters, where a normal distribution was used (extended data Figure 1, Table 1<sup>25</sup>). This model estimated a shorter duration of antibody persistence [0.93 (95% CrI: 0.60 - 1.64) years]. The FOI across all studies and strains were higher, ranging from 0.09 (95% CrI: 0.04 - 0.16) to 3.22 (95% CrI: 1.95 - 4.85), with six studies reporting FOI estimates > one, which is equivalent to an attack rate of >63%. The relative change in FOI and cut-off were similar for both models. This model had a lower DIC (476.8 compared with 480.8; with a DIC difference of 4), WAIC (536.2 compared with 546.4), and LOO (546.9 compared with 560.9), which suggests that this model has an improved fit compared with the model with more informed priors. However, the high FOI estimates indicate that this model may be less plausible ( Table 4)."*

*"When the relative change in FOI and cut-off parameters were simultaneously estimated by setting (extended data Figure 2, Table 3<sup>25</sup>) the duration of antibody persistence was estimated to be shorter, 2.20 (95% CrI: 1.57 - 3.08) years, although the confidence intervals overlap with the*

*main model. The FOI ranged from 0.04 (95% CrI: 0.03 - 0.06) to 0.88 (95% CrI: 0.67 - 1.19). The overall model DIC (548.2 compared with 480.8), WAIC (622.0 compared with 546.5) and LOO (633.2 compared with 560.9) were higher, indicating that this model did not have as much support (Table 4)."*

**5)** It would be helpful to provide an equation to explicitly show the link between the estimated waning rates and the duration of antibody persistence which were reported throughout the paper, and is the main finding of the study.

*The duration of antibody persistence was estimated a 1/seropositivity waning rate. I have now included this as an equation in the text.*

*"The duration of antibody persistence was estimated as follows:*

*Duration of antibody persistence =  $1/\omega$ "*

**6)** In contrast to the previous point, the authors provided an equation linking the FOI to the attack rates but barely touched upon this topic in the paper except for one occurrence in the Discussion. May there be ideas that the authors wished to discuss but were not fully expressed in the text?

*Our primary motivation for exploring attack rates was to inform our priors for the FOI estimates using attack rates from influenza (reported on in the methods). We realise we could have been clearer, so we have clarified this in the methods. We also compare the attack rates estimated for seasonal HCoV with influenza in the results and discussion to ensure that model parameter estimates were within plausible ranges.*

*Methods:*

*"For the FOI, there is little information on the attack rate of HCoVs. However, there have been several systematic reviews and meta-analyses looking at influenza in unvaccinated individuals which have reported the attack rates to range between 15.2% – 22.5% in children and 3.5% – 10.7% in adults<sup>26-28</sup>. Modelling studies using serological influenza data predicted estimates from 20 – 60%<sup>29,30</sup>. Based on the epidemiology of these viruses in children<sup>31</sup>, we expect the attack rate for HCoV may be lower. Therefore, we selected a Gamma distribution, with a mean of 0.3 (shape = 1.2 and scale = 0.25) and this corresponds to an attack rate of 26% and covers a range of plausible values. For the age at cut-off ( $a_{\rho}$ ), uniform priors from 0 to 20 years were chosen as we were interested in the difference in FOI in children and young adults."*

*Results:*

*"A sensitivity analysis was conducted using less informative priors for the FOI parameters, where a normal distribution was used (extended data Figure 1, Table 1<sup>25</sup>). This model estimated a shorter duration of antibody persistence [0.93 (95% CrI: 0.60 - 1.64) years]. The FOI across all studies and strains were higher, ranging from 0.09 (95% CrI: 0.04 - 0.16) to 3.22 (95% CrI: 1.95 - 4.85), with six studies reporting FOI estimates > one, which is equivalent to an attack rate of >63%. The relative change in FOI and cut-off were similar for both models. This model had a lower DIC (476.8 compared with 480.8; with a DIC difference of 4), WAIC (536.2 compared with 546.4), and LOO (546.9 compared with 560.9), which suggests that this model has an improved fit*

*compared with the model with more informed priors. However, the high FOI estimates indicate that this model may be less plausible ( Table 4)."*

*Discussion:*

*"When we used less informed priors for the FOI, a lower estimate of duration of seropositivity was obtained. However, this model produced higher estimates of FOI, with six studies reported FOI estimates in the young age group greater than one (attack rate >63%). There is limited information on the attack rate of seasonal HCoV, however there have been numerous studies looking at influenza. Previous systematic reviews have estimated the attack rate of influenza to be between 3.5% and 22.5%<sup>26-28</sup>, whilst modelling studies have estimated this to be higher, 20 – 60%<sup>29, 30</sup>. Based on reporting rates of seasonal HCoV we would expect the attack rate to be lower than influenza. Therefore, this suggests that the results from the model with less informative priors are less plausible."*

**7)** It is unclear what the motivation for the analysis which led to Figure 3 was. Providing some context, especially how that would better our projections on SARS-CoV-2 would be helpful.

*Thank you for this comment. Our motivation for this figure was to look at the relationship between FOI, attack rates, and the number of infections you might expect to observe in younger ages. As you suggest, we have expanded the interpretation of this figure in the last paragraph of the results:*

*"To demonstrate the relationship between FOI and seropositivity at age 30, we created simulated scenarios under different sero-catalytic models. Using the parameters for the relative change in FOI and waning estimated from the age-varying reverse catalytic model (where the relative change in FOI and the age at cut-off were simultaneously estimated across settings), we simulated the proportion of individuals aged 30 years that would be seropositive using a range of FOI estimates to show how the proportion changes using the different models. The catalytic model, which does not allow for seroreversion, results in the highest estimates of seropositivity at age 30 with increasing FOI. The age-varying FOI model results in higher estimates of seropositivity at age 30 compared with the reverse catalytic model. This is due to the FOI which was estimated to be almost twice as high in the older age group (with age at cut-off 8.49 [7.52 – 9.94] years) in the age-varying FOI model ( Figure 3A). We further explored the relationship between FOI, attack rates and the estimated number of infections by age. We used the pooled estimate across all studies of FOI to estimate the proportion exposed at a given age to provide an indication of how many infections we might expect to see by age under our modelling assumptions ( Figure 3B). We estimate that by two years, over 50% of the population will have at least one infection, and by age ten over 75% will have had more than four infections."*

**8)** Lastly, there are some truncated sentences or missing/inconsistent information in the paper that needs to be fixed. For example:

*Thank you for highlighting these, these have all been fixed.*

- o In the Methods, "The different assays used in each study for the different strains is*

shown, and where the antibody detected was specified this is included in the table.”  
*This has been amended.*

- In the Results, “When the relative change in FOI and cut-off parameters were simultaneously estimated by setting (extended data Figure 2, Table 3) the duration of antibody persistence was estimated to be shorter, ...”.

*This has been amended.*

- According to the captions, it occurs to me that the pairings are as follows: Table S1 with Figure S1, Table S3 with Figure S2, Table S5 with Figure S4. The pair of Table S2 is not obvious. It is unclear for Figure S3 which analysis this belongs to. Please also double check that the Extended data section in the main text matches the materials provided in the supplement.

*The contents of the extended data can be found at the end of the manuscript under the “extended data” section:*

*The supplementary contains the following:*

- ○ • *Sensitivity analysis: Less informed priors for FOI (supplementary Table 1 and Figure 1)*
- ○ • *Sensitivity analysis: Waning estimated by strain (supplementary Table 2)*
- ○ • *Sensitivity analysis: Alpha and cut-off jointly simultaneously by study (supplementary Table 3 and Figure 2)*
- ○ • *Reverse catalytic model (supplementary Figure 3 and Table 4)*
- ○ • *Sensitivity analysis: Including the youngest age groups (<1 year) (supplementary Table 5 and Figure 4)*
- ○ • *Sensitivity analysis: Refitting the model using data from only two strains (supplementary Table 6)*
- ○ • *Sensitivity analysis: Waning estimated by assay (supplementary Table 7 and Figure 5)*

*We have also included subheadings within the supplementary material to make it easier to follow.*

- “The inference was impleented in RJags...”

*This has been amended.*

- The figure legend of Figure 3A says “reverse catalytic & age varying FOI” while the caption says “reverse catalytic model with time-varying FOI”. The colors also do not seem to match the legend (blue vs green vs grey). May be helpful to choose colors that are more different, especially that the lines in the legend keys are quite thin.

*I have updated the figure caption to clarify the models used to create Figure 3. I have changed the colours to allow for a clearer distinction between the models.*

- It is unclear which model was used to generate Figure 3B. I am guessing the “reverse catalytic model” from its matching color but explicit statements would be helpful to the readers.

*I have updated the figure caption to clarify the model used to create Fig 3b.*

*“Figure 3. ( A ) Proportion of individuals age 30 who are seropositive for different estimates of force of infection (FOI). The catalytic model is shown in red, the reverse catalytic model in green,*



and the reverse catalytic model with age-varying FOI is shown in blue. Model estimates were used for the parameter values (relative change in FOI ( $\alpha$ ), 1.93 [1.69 – 2.19]; waning, 0.45 [0.32 – 0.64]; cut-off, 8.49 [7.52 – 9.94]). ( **B** ) Estimated proportion of individuals experiencing infections by age estimated from the age-varying reverse catalytic model (more informed priors) using the pooled median estimate across studies for FOI (0.46), and median estimates for waning (0.45),  $\alpha$  (1.93) and cut-off (8.49)."

- Please consider breaking this portion in the Discussion into a new sentence, "... and a meta-analysis of contact tracing studies found that children had 56% (31% – 71%) lower odds of becoming an infected contact compared with adults<sup>52</sup>."

*This has been amended.*

**Competing Interests:** No competing interests were disclosed.