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Short communication

Importance of COVID-19 vaccine efficacy in older age groups

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ABSTRACT

Importance: An effective vaccine against SARS-CoV-2 will reduce morbidity and mortality and allow substantial relaxation of physical distancing policies. However, the ability of a vaccine to prevent infection or disease depends critically on protecting older individuals, who are at highest risk of severe disease.
Objective: We quantitatively estimated the relative benefits of COVID-19 vaccines, in terms of preventing infection and death, with a particular focus on effectiveness in elderly people.
Design: We applied compartmental mathematical modelling to determine the relative effects of vaccines that block infection and onward transmission, and those that prevent severe disease. We assumed that vaccines showing high efficacy in adults would be deployed, and examined the effects of lower vaccine efficacy among the elderly population.
Setting and participants: Our mathematical model was calibrated to simulate the course of an epidemic among the entire population of British Columbia, Canada. Within our model, the population was structured by age and levels of contact.
Main outcome(s) and measure(s): We assessed the effectiveness of possible vaccines in terms of the predicted number of infections within the entire population, and deaths among people aged 65 years and over.
Results: In order to reduce the overall rate of infections in the population, high rates of deployment to all age groups will be critical. However, to substantially reduce mortality among people aged 65 years and over, a vaccine must directly protect a high proportion of people in that group.
Conclusions and relevance: Effective vaccines deployed to a large fraction of the population are projected to substantially reduce infection in an otherwise susceptible population. However, even if transmission were blocked highly effectively by vaccination of children and younger adults, overall mortality would not be substantially reduced unless the vaccine is also directly protective in elderly people. We strongly recommend: (i) the inclusion of people aged 65 years and over in future trials of COVID-19 vaccine candidates; (ii) careful monitoring of vaccine efficacy in older age groups following vaccination.

1. Introduction

At the time of writing, there have been over 100 million detected cases of coronavirus disease 2019 (COVID-19), resulting in over two million deaths worldwide. The socioeconomic costs related to restrictions on work, school, and travel required to slow the spread of the causative virus (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2), are enormous. It is widely accepted that multiple effective COVID-19 vaccines will be required to control the pandemic. The pace of COVID-19 vaccine development has been unprecedented[1]; there are >140 candidates in development, representing a wide range of platforms and strategies. Importantly, however, the majority of vaccine

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efficacy trials – including the Pfizer and Moderna vaccines approved in Canada and many other countries – have reported limited results related to efficacy among people over 70 years and data on people over 80 years is almost completely lacking [2,3]. In contrast, the risks of COVID-19 hospitalization and death are strikingly higher among the elderly and individuals with medical comorbidities; the case-fatality rates among those aged <50 years are typically <0.5%, compared with >10% in people >70 years [4]. In British Columbia, Canada, the median age of death from COVID-19 disease is 86 and the case-fatality rate for people over 80 years exceeds 30% [5]. Other demographic factors, including co-morbid medical conditions, African descent, and male sex, have also been reported as important risk factors for severe COVID-19[6,7].

The goal of a vaccine is typically prevention of infection (i.e., sterilizing immunity). However, the true value of an effective vaccine is prevention of the disease caused by that infection. This may be achieved directly in the vaccinated person, or indirectly by reducing transmission through the population. High rates of sterilizing immunity to SARS-CoV-2 may be difficult to achieve given that natural immunity from infection with other common CoVs (e.g., 229E) is incomplete, and neutralizing antibodies to SARS-CoV-1, Middle East respiratory syndrome CoV, and SARS-CoV-2 are not always induced by infection, and may wane rapidly [8]. Clinical trial results reported to date do not address these questions around vaccine-induced prevention of onward transmission [2,3].

Furthermore, COVID-19 vaccination may be less protective against disease in elderly people than in younger adults, as is seen for example with some influenza vaccines [9,10,11]. Recent reports of Phase 3 trials delivered encouraging but inconclusive results on protection for elderly people. Both mRNA vaccine trials reported overall protection against symptomatic infection results for subjects over 65 that were similar to those for younger adults. However, there were limited data for people over 75 years, and people over 85 years were excluded from both trials. In the Pfizer trial, among subjects over 75 years, there were zero symptomatic infections in the vaccine group compared to 5 symptomatic infections in the placebo group (the groups contained approximately 775 people each) [2]. Results for the Moderna trial were very similar: there were zero symptomatic infections in the over-75 vaccine group versus three symptomatic infections in the corresponding placebo group (the groups contained approximately 650 people each) [3].

Here, we apply mathematical modelling to examine possible outcomes of different vaccination scenarios, distinguishing between protection against infection, onward transmission, and disease, and focusing on differential protective effects in the elderly. Mathematical models have a long track record of use as tools to examine vaccination policy and are currently being applied extensively during the Covid-19 epidemic, for example to propose age-structured vaccine delivery strategies [12].

2. Methods

In order to quantify the benefits of a COVID-19 vaccine, we modified an established age- and activity-structured mathematical model originally designed to study vaccination against pandemic influenza [13]. Briefly, the population was divided into age compartments, with people aged 65 years and over further divided into individuals living in the community and those in care. Within each age group, individuals were further stratified into five compartments with different contact rates. Infectious contact rates within and between individuals in all compartments were defined to mimic interactions in British Columbia, Canada. Full details of the contact structure are given in the original model publication [13]. Children (17 years old and under) were assumed to be 40% as susceptible to infection as adults [14,15], and we started simulations with 0.01% of the population in an infectious class. Within each compartment, infection followed a susceptible-exposed-infected-recovered (SEIR) model with two exposed and two infectious compartments. Parameters were chosen so that there was a characteristic delay of 5 days from exposure to infectiousness and an average infectious period of 6 days. The probability of infection per contact was set so that the baseline reproductive number (R_0) for the model was 3.5, broadly reflecting estimates established for SARS-CoV-2. We estimated aggregate infection-fatality-ratios of 1% among people aged at least 65 years old living independently, and 15% among those living in care facilities[16]. We then examined vaccination scenarios distinguishing between protection against infection, onward transmission, and disease and allowing for differential vaccine efficacy in people aged 65 years and over. In these scenarios, we looked at a first-wave epidemic occurring concurrently with vaccination in a population that is otherwise entirely susceptible to the disease.

3. Results

We first assumed that the vaccine was administered to 60% of people aged 18–64 and 80% of people 65 years and older. We allowed the vaccine to be delivered uniformly in time, over a period of 10 weeks, concurrent with the COVID-19 epidemic. In different simulations, we distinguished between a sterilizing vaccine that prevents infection (and therefore onward transmission) and a disease-attenuating vaccine that prevents mortality but only partially blocks onward transmission. In the sterilizing vaccine scenario, we supposed that the efficacy of the vaccine was 90% among people aged 18–64, but considered different levels of efficacy from 25% to 100% among people aged 65 years and older. In the attenuating vaccine scenario, we supposed that the vaccine prevents 40% of onward transmission from people 18–64, while also preventing mortality with an efficacy of between 25% and 100%. For consistency, the attenuating vaccines were taken to reduce transmission from people 65 years and older by an amount equal to the baseline of 40% multiplied by the attenuation factor (the percentage reduction in mortality due to that vaccine). Fig. 1 shows the time-course of infections across the whole population, and predicted mortality among people aged 65 years and older. We observe that the sterilizing vaccines considered are more effective in reducing overall infections than the attenuating vaccines. We also observe that transmission-blocking among people aged 65 years and older is not an important effect in terms of reducing overall infection. However, the ability of a vaccine to reduce mortality was strongly influenced by its direct effectiveness in elderly people (Fig. 1b). The transmission-reducing effect of vaccinating people younger than 65 (sometimes called a "shielding" effect [17]) reduced mortality from 4% (no vaccine scenario) to below 3% (either scenario at the level of 25% vaccine effectiveness among older groups), but in our model, further reductions required high levels of direct protection in people aged 65 years and older. The sterilizing vaccines generated a greater reduction in mortality than the corresponding attenuating vaccines, as a result of being considerably more effective in reducing overall infections. This effect was due to the modeled ability of the sterilizing vaccines to reduce infections. Nonetheless, both vaccines strongly reduced mortality when their efficacy was high in the older groups.

Next, we examined the effect of prioritizing vaccination of older people. In Fig. 2, we show contour diagrams showing aggregate population infections, and deaths among people aged ≥65 years, for vaccines that are (2a,b) 90% effective for all ages, and (2c,d)

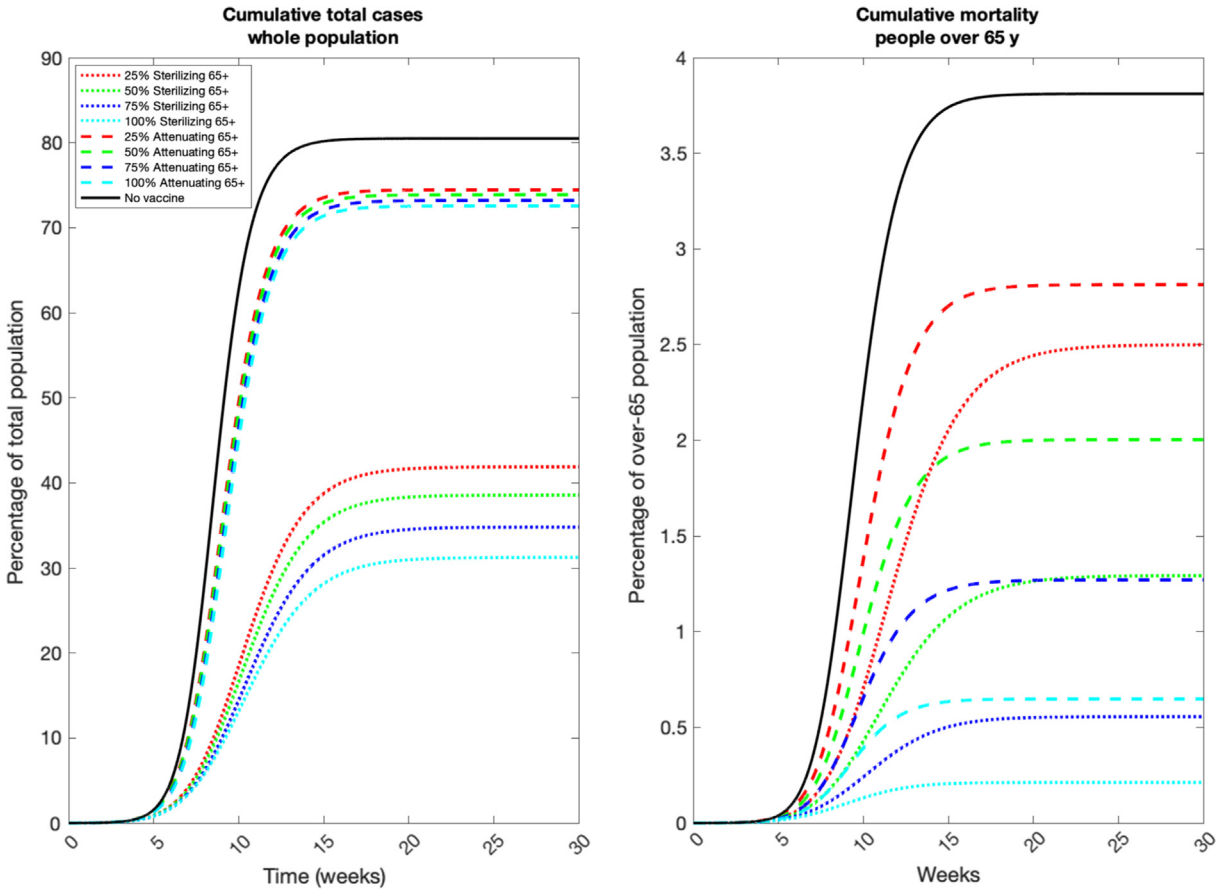

Fig. 1. Epidemic time courses under varying vaccine efficacy. Left: Cumulative time-course of total infections across the entire population, assuming fixed efficacy of 90% among people 3–64 and different levels of vaccine effectiveness in people aged ≥65 years. Right: Corresponding time-course of cumulative mortality among elderly people. Solid line: epidemic model with no vaccination. Dotted lines: sterilizing vaccine that prevents infection. Dashed lines: infection-attenuating vaccine that reduces transmission and mortality as described in the text.

90% effective in people 18–64 and 50% effective in people aged ≥65 years. Contours are drawn across vaccine uptake fractions. We assume that the vaccine is delivered at a uniform rate, reaching the indicated vaccine uptake levels after 10 weeks, and that this process is concurrent with the epidemic. We show results only for a sterilizing vaccine. In both scenarios, the overall infection rate is primarily determined by the uptake of vaccination among people 18–64 years old. However, prevention of mortality in the elderly is strongly determined by vaccination rates among people aged 65 years and older, as well as vaccine efficacy in this group (compare Fig. 2b,d). Finally, we looked at inclusion of vaccination of children (17 years old and under), in whom current vaccines have not been tested or recommended to date. We found that this factor did not contribute substantially to prevention of overall mortality in any of the scenarios shown in Figs. 1 and 2 (data not shown).

4. Discussion

Given the astronomical COVID-19 fatality rate among elderly and other high-risk groups, the development of an effective vaccine has been a global imperative. Although vaccines have been licensed based on preventing symptomatic disease, we posit that the most important goal of a vaccine is prevention of severe disease and death. Recently published trial results show remarkable COVID-19 vaccine efficacy. However, it remains possible that, despite being protective among adults up to age 75, the efficacy of a COVID-19 vaccine among the elderly will be substantially lower. This will substantially undermine the population-level benefits of vaccination with respect to hospitalization, ventilator use, and deaths.

Trial designs that include sufficiently large numbers of high-risk participants to evaluate outcomes of greatest clinical and public health importance are feasible. For example, influenza vaccine trials have been successfully conducted specifically to assess efficacy in elderly residents of nursing homes [18]. Immune responses to vaccination tend to be higher in females[19], and so sex is important to evaluate in COVID-19 vaccine trials [7]. Individuals with diabetes, chronic kidney disease, or other conditions associated with impaired immunity, are at high risk for severe COVID-19 and may also produce suboptimal vaccine responses. Further, availability of licensed vaccines is likely to be limited, at least initially, resulting in prioritization of people at highest risk of severe COVID-19, as well as health care workers and other essential service providers[20]. In this scenario, high-risk populations are more likely to benefit from direct vaccination than from indirect protection by vaccination of lower-risk groups, underscoring the need to ensure efficacy in the elderly and other vulnerable groups.

Our results strongly underline the importance of accurately measuring vaccine efficacy in elderly populations. It is imperative, in our view, to establish the efficacy of new vaccines in preventing infection, disease and transmission among elderly people, given that the preponderance of COVID-19-related deaths occurs in exactly this population. This should be prioritized as vaccines are rolled out into these populations. The next wave of COVID-19 vaccine efficacy studies and trials should seek to establish the parameters of vaccine-induced protection among exactly these vulnerable groups.

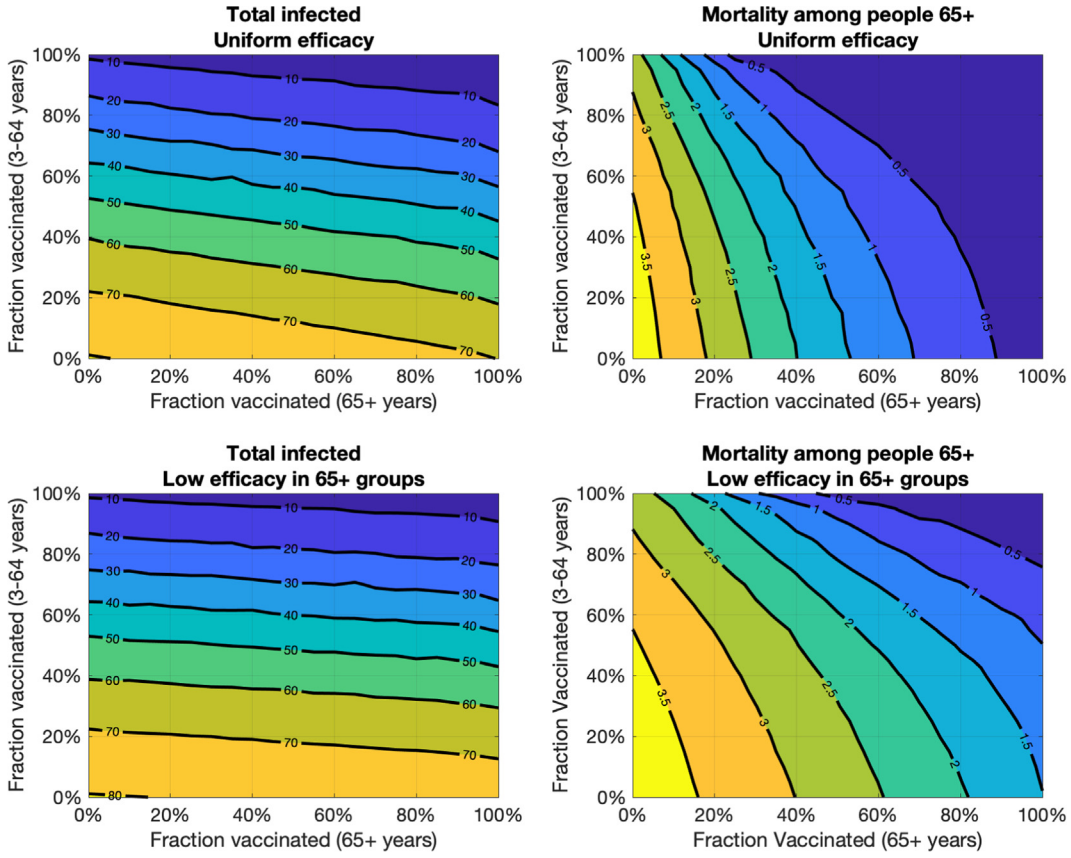

Fig. 2. Infections and mortality under different (sterilizing) vaccine uptake rates. Contour plots indicate (a,c) total percentage of the population that becomes infected and (b, d) estimated mortality among people aged ≥65 years old. Two scenarios are shown: (a,b) constant vaccine efficacy of 90% across the whole population aged 3 and above; (c,d) vaccine efficacy of 90% among people aged 3–64 and 20% among people aged ≥65 years.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] Lurie N, Saville M, Hatchett R, Halton J. Developing Covid-19 Vaccines at Pandemic Speed. N Engl J Med 2020.
[2] Polack FP et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med 2020;383:2603–15.
[3] FDA Briefing Document: Moderna COVID-19 Vaccine. https://www.fda.gov/media/144434/download.
[4] Canada Government. Coronavirus disease 2019 (COVID-19): Epidemiology update; 2021. https://health-infobase.canada.ca/covid-19/epidemiological-summary-covid-19-cases.html.
[5] British Columbia Centre for Disease Control. British Columbia COVID-19 Situation Report; 2021. http://www.bccdc.ca/Health-Info-Site/Documents/COVID_sitrep/Week_3_2021_BC_COVID-19_Situation_Report.pdf.
[6] Yancy CW. COVID-19 and African Americans. JAMA 2020.
[7] Jordan RE, Adab P, Cheng KK. Covid-19: risk factors for severe disease and death. BMJ 2020;368:m1198.
[8] Huang AT, Garcia-Carreras B, Hitchings MDT, et al. A systematic review of antibody mediated immunity to coronaviruses: antibody kinetics, correlates of protection, and association of antibody responses with severity of disease. medRxiv. 2020.
[9] Andrew MK, Bowles SK, Pawelec G, et al. Influenza Vaccination in Older Adults: Recent Innovations and Practical Applications. Drugs Aging 2019;36(1):29–37.
[10] Dhakal S, Klein SL. Host Factors Impact Vaccine Efficacy: Implications for Seasonal and Universal Influenza Vaccine Programs. J Virol 2019;93(21).
[11] Rolfes MA, Flannery B, Chung JR, et al. Effects of Influenza Vaccination in the United States During the 2017–2018 Influenza Season. Clin Infect Dis 2019;69(11):1845–53.
[12] Bubar KM, Reinholt K, Kissler SM, Lipsitch M, Cobey S, Grad YH, et al. Model-informed COVID-19 vaccine prioritization strategies by age and serostatus. Science 2021. https://doi.org/10.1126/science.abe6959.
[13] Conway JM, Tuite AR, Fisman DN, et al. Vaccination against 2009 pandemic H1N1 in a population dynamical model of Vancouver, Canada: timing is everything. BMC Public Health 2011;11:932.
[14] Davies NG, Klepac P, Liu Y, et al. Age-dependent effects in the transmission and control of COVID-19 epidemics. Nat Med 2020.
[15] Viner RM, Russell SJ, Croker H, et al. School closure and management practices during coronavirus outbreaks including COVID-19: a rapid systematic review. Lancet Child Adolesc Health 2020;4(5):397–404.
[16] Ghisolfi S, Almas I, Sandefur J, von Carnap T, Heitner J, Bold T. Predicted COVID-19 fatality rates based on age, sex, comorbidities, and health system capacity. medRxiv 2020.
[17] Weitz JS, Beckett SJ, Coenen AR, et al. Modeling shield immunity to reduce COVID-19 epidemic spread. Nat Med 2020;26:849–54. https://doi.org/10.1038/s41591-020-0895-3.
[18] Gravenstein S, Davidson HE, Han LF, et al. Feasibility of a cluster-randomized influenza vaccination trial in U.S. nursing homes: Lessons learned. Hum Vaccin Immunother 2018;14(3):736–43.
[19] Klein SL, Flanagan KL. Sex differences in immune responses. Nat Rev Immunol 2016;16(10):626–38.
[20] World Health Organization. Ethics and COVID-19: resource allocation and priority-setting; 2020. https://www.who.int/ethics/publications/ethics-covid-19-resource-allocation.pdf?ua=1 [accessed June 19, 2020].