Clinical Infectious Diseases

EDITORIAL COMMENTARY

Vaccination of Older Adults Against Respiratory Syncytial Virus: The Final Pieces of the Puzzle

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Keywords. elderly vaccination; mathematical modelling; duration of vaccine protection.

With an estimated 186 000–614 000 older adults hospitalized annually as a result of respiratory syncytial virus (RSV) infection and with no effective treatment, there is an unmet need to prevent these infections, many of which lead to death [1]. Fortunately, we are in a golden age of RSV vaccine development with 5 formulations targeting older adults currently emerging from phase 3 trials [2]. With favorable trial results appearing, policy makers are now asking crucial questions about how we will use these new pharmaceuticals to improve the health of our elderly populations: Which vaccine product should we use? Should our vaccine campaign be seasonal? Do we need annual boosters? Which age groups should be eligible?

Answers to these questions will rely in part on mathematical models that can predict the population impact of each vaccine. Consequently, mathematical models have become an indispensable part of the policy maker's evidence toolkit. Indeed, one of the benefits of mathematical models is that they can capture the considerable uncertainty in both the epidemiology of RSV disease and the protection afforded by potential vaccines.

In this issue of *Clinical Infectious Diseases*, van Effelterre et al [3] use a mathematical model of RSV transmission to capture this uncertainty to predict the impact of an RSV vaccination program targeted at adults aged ≥60 years in the United States. The study uses a Bayesian framework to incorporate existing knowledge on the epidemiology of RSV. The mathematical model itself is an adaptation of a previously published model that captures the uptick in older adult RSV incidence by assuming an elevated risk of disease and clinical outcomes [4]. The van Effelterre et al study uses scenario analyses to predict the impact of potential vaccination programs with varied assumptions around vaccine protection. Specifically, the authors assume that vaccine efficacy against acute respiratory infection (ARI) varies between 50% and 70%, that vaccine efficacy against onward transmission varies between 0% and 50%, and that the duration of vaccine protection is either 3 or 5 years. Here we look at whether the uncertainty in these 3 components of vaccine protection reflects true gaps in our knowledge about the current suite of RSV vaccines, and, importantly, if this uncertainty matters when considering whether to introduce a vaccination program.

First, and surprisingly, the efficacies for each of the 4 vaccines aimed at older adults are remarkably consistent against trial endpoints, including ARI and the more severe lower respiratory tract infection (LRTI) [5–10]. Specifically, the midpoint estimates range from 62%–71% against RSV-associated ARI to 80%–86% for RSV-associated LRTI, consistent with what was assumed in van Effelterre et al. Notwithstanding the rather wide confidence intervals (CIs) around these estimates, these trials offer the first promise of reducing the considerable burden of severe respiratory disease in the elderly population. What is less known is the vaccine efficacy against very severe disease and death, with only 1 trial suggesting that efficacy against severe disease is higher at 94% (95% CI, 62%–100%) [5]. Thus, for studies such as van Effelterre et al that want to predict the impact of a vaccine program on hospitalizations and death, we may have to wait for more information on the full range of clinical benefits from these vaccines. However, if these early indications are correct and consistent across all vaccines, the predicted reduction in hospitalizations and deaths by van Effelterre et al would underestimate the vaccine impact, all else being equal.

Second, the completed trials do not give us any indication on how vaccines prevent onward transmission, instead measuring disease endpoints rather

Received 10 March 2023; editorial decision 15 March 2023; accepted 17 March 2023; published online 23 March 2023

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https://doi.org/10.1093/cid/ciad162

than infection or infectiousness (although see [11]). However, consistent with many studies describing vaccination of the elderly population, van Effelterre and colleagues' work concludes that assumptions about the infectiousness of vaccinated individuals who become infected matter little to the impact of any vaccination program. This invariance arises because the model assumes few opportunities for pathogen transmission between older adults and other individuals, consistent with studies in the United States and elsewhere [12, 13]. Consequently, despite vaccine efficacy against infection or infectiousness being unknown, this is unlikely to significantly influence vaccine impact and the cost-effectiveness of these older adult programs.

Finally, there is an important knowledge gap around the duration of protection of these vaccines, because all completed trials that report results are powered to evaluate efficacy up to 1 year after vaccination. While van Effelterre et al simply assume booster vaccines are given prior to any vaccine waning, thus maintaining the considerable reduction in disease burden over time, the implications of this uncertainty are of crucial importance to the efficiency and affordability of widespread vaccine rollout. Van Effelterre et al calculate the "number needed to vaccinate," which is a measure of efficiency of the vaccine program and equivalent to the number of administered doses necessary to prevent 1 RSV-associated ARI. When the model assumed that vaccine immunity duration dropped from 5 years to 3 years, there was, unsurprisingly, a proportional increase in the number needed to vaccinate, from 6–12 to 10–20. Although van Effelterre et al did not calculate this explicitly, to achieve the same clinical impact as the base case predictions if a booster were to be needed every year—as it is the case with influenza—the number needed to vaccinate would increase 5-fold, as would the total cost of the vaccine program. Consequently, van Effelterre et al implicitly highlight the importance of evaluating multiseason vaccine efficacy before any decisions about widespread rollout are made.

While van Effelterre et al strengthen the consensus that vaccination of older adults against RSV has the potential to significantly reduce RSV seasonal burden, it simply highlights, but does not fill, the pressing knowledge gaps that need resolution. With a large and growing older adult population, these vaccines will, rightly, come under intense scrutiny about their affordability and cost-effectiveness. And with little to distinguish each vaccine product's efficacy against acute respiratory infection, the decision to implement a vaccine program—and which vaccine to choose—will likely rest on the vaccine's duration of disease protection, its protection against very severe outcomes and death, and ultimately, its price.

Notes

Financial support. D. H. gratefully acknowledges funding from the National Institutes of Health (grant number 1R01AI141534-01A1) for this work. Outside this work, K. E. A. reports receipt of a European Research Council Starting Grant (grant number 757688), a program grant from the Wellcome Trust (219798/Z/19/Z), and the Wellcome Trust institutional translational partnership award (paid to institution);

Potential conflicts of interest. K. E. A. reports honoraria from the Institute for Global Health University College London as an External Examiner, and unpaid participation on a grant selection committee and travel support for meetings from the Wellcome Trust. D. H. reports no potential conflicts.

Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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