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LETTERS

Reply letter to "Immunogenicity and safety of a quadrivalent high-dose inactivated influenza vaccine compared with a standard-dose quadrivalent influenza vaccine in healthy people aged 60 years or older: a randomized Phase III trial"

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ABSTRACT

A recent study reported that the high-dose quadrivalent influenza vaccine provided superior immunogenicity and efficacy versus the standard-dose quadrivalent vaccine in the elderly. However, we need to view these results in terms of public health benefits as well. The Number Needed to Vaccinate (NNV) is an important tool to measure the benefit of a given vaccine. Further, NNV evaluates the benefits of a vaccine in preventing and controlling communicable diseases. Considering the target of vaccination and coverage of 75% not met in the elderly in Europe, it is important not to prioritize one vaccine over the other, but rather to increase the vaccine coverage with all the available vaccines.

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Dear editor,

We read with interest the article from Pepin et al.[1] demonstrating that quadrivalent high-dose inactivated influenza vaccine (IIV4HD) generated superior immunogenicity to a standard-dose quadrivalent vaccine (IIV4SD) and was well tolerated with no major safety concerns in adults ≥60 years of age. However, we had a few comments on some of the extrapolated conclusions put forward in the publication.

First, the author correlated the results with an earlier study where the high-dose trivalent influenza vaccine (IIV3HD) showed superior clinical efficacy relative to the standard-dose trivalent influenza vaccine (IIV3SD).[2] The earlier study showed a relative efficacy of 24.2% in favor of the IIV3HD in terms of laboratory-confirmed influenza and concluded that among persons 65 years of age or older, IIV3-HD induced significantly higher antibody responses and provided better protection against laboratory-confirmed influenza illness than the IIV3-SD.[2]

The Pepin et al.[1] study focused on immunogenicity, which may be considered an indicative biomarker of vaccine efficacy,[3] but the author extrapolated the clinical and health economic benefits highlighted in the real-world setting for the IIV3-HD to the newer IIV4HD vaccine.

Vaccine efficacy is usually expressed as relative risk reduction (RRR), which is the measure of the reduced risk of infection in the vaccinated group compared to the control group who did not receive the vaccine (or received a placebo). Absolute risk reduction (ARR), another measure of vaccine efficacy, is the disease risk difference between the control group and the group receiving the vaccine. RRR considers only the clinical trial participants who could benefit from the vaccine, whereas ARR considers all participants (with and without vaccine). Studies omitting ARR and considering only RRR can overestimate the vaccine efficacy and cause reporting bias. For example, the reported RRR rates of Covid-19 vaccines were 95% for the Pfizer–BioNTech, 94% for the Moderna, 91% for the Gamaleya, 67% for the J&J/Janssen, and 67% for the AstraZeneca–Oxford vaccines. Now, looking at the ARR rates for these vaccines, it is 1.3% for the AstraZeneca–Oxford, 1.2% for the Moderna, 1.2% for the J&J/Janssen, 0.93% for the Gamaleya, and 0.84% for the Pfizer–BioNTech vaccines.[4] ARR is usually ignored because it gives a less impressive effect size than RRR. Also, the health care professionals overestimate the efficacy of an intervention when the results are expressed in terms of RRR rather than ARR. In fact, ARR is probably a more useful tool, and reporting the efficacy in terms of ARR is a must.[5]

ARR also helps in deriving the Number Needed to Vaccinate (NNV), a simple summary calculation that evaluates the possible benefits of immunization programs in preventing and controlling communicable diseases. It is defined as the number of persons needed to vaccinate to prevent one outcome, and it combines both vaccine effectiveness (VE) and the background incidence of disease in the population. Generally, the NNV is calculated as NNV = 1/(annual incidence of event in the unvaccinated × VE). This is equivalent to the reciprocal of the ARR.[6] The NNV is a more relevant tool when assessing vaccines in a real-world setting because it allows us to measure the effectiveness of the vaccine in the context of the public health

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Table 1. Number needed to vaccinate in High dose influenza vaccine vs Standard dose influenza vaccine.

	Laboratory Confirmed Influenza cases/Total participants	ARR (from 7.2% background rate)	NNV (1/ARR)
High Dose Vaccine- Influenza Incidence Rate	228/ 15,990 = 0.01426	0.072–0.01426 = 0.05574	1/0.05574 = **18**
Standard Dose Vaccine- Influenza Incidence Rate	301/ 15,993 = 0.01882	0.072–0.01882 = 0.05318	1/0.05318= **19**

ARR, Absolute risk reduction; NNV, Number Needed To Vaccinate.

utility, and not in the limited and controlled context of clinical trials. Further, the NNV (and ARR) is sensitive to background risk. The higher the risk, the higher the effectiveness.

Understanding the context of vaccine efficacy in terms of ARR and NNV is important when communicating about the public health decisions such as vaccine choice, purchase, and distribution.[4] Therefore, we believe that the benefits of influenza immunization need to be promoted using simple and intuitive measures like NNV, that enable a fair comparison between the available vaccine options.

We calculated the NNV for the IIV4HD and IIV4SD influenza vaccines from the DiazGranados et al.[2] in subjects aged ≥65 years with a 7.2% background annual attack rate[7] of seasonal influenza among unvaccinated individuals. The calculation showed a NNV of 18 with the high-dose influenza vaccine and 19 with the standard-dose vaccine (Table 1).

As can be seen from Table 1, the NNV between the IIV4HD and IIV4SD vaccines is similar. Hence, when communicating about vaccine efficacy, especially for public health decisions, having a complete picture of the data is important, and looking at just one summary measure is not good practice. In line with the extrapolation of superior vaccine efficacy of IIV4HD vaccine vs IIV4SD based on trivalent data as anticipated by Pepin et al.[1] similarly, limited differences in NNV numbers may be expected considering IIV4SD vs IIV4HD.

Second, seasonal influenza infects nearly 10 to 30% of Europe's population. It poses a severe economic impact by causing hundreds of thousands of hospitalizations across Europe each year. Especially, the vulnerable populations such as the elderly, young children, and people with chronic conditions suffer the most. Nevertheless, everyone is at risk of developing serious complications that may result in death.[8]

In particular, people older than 65 years are at higher risk of developing the severe disease than any other age group. They constitute over 90% of all influenza-associated deaths, take a long time to recover, and are more likely to be hospitalized. Therefore, WHO recommends that at least 75% of older people should be vaccinated every year against influenza infection before the season starts. Vaccine uptake targets ensure sufficient direct and indirect protection within the population and help ensure the protection of members of society who are unable to be vaccinated or are most likely to suffer influenza-associated morbidity and mortality. Many European countries have incorporated WHO recommendations in their influenza vaccination programs, targeting to reach this level of vaccination coverage. However, the most recent survey showed that only 1 out of 3 elderly get vaccinated in half of the countries in the European region, none of the countries met the targeted coverage, and only one almost achieved the 75% target.[9] The results of this survey have shown that achieving high vaccine coverage for those who are at risk of developing severe complications due to influenza infection remains a serious public health challenge and there is still a lot to do to improve vaccine coverage.[10]

Based on published data and extrapolated superior VE in elderly patients, the recommendations to prioritize the high dose vaccine in this subgroup, have been included in a few guidelines such as the German's STIKO[11] and UK's JCVI.[12] This appears to be misaligned with the WHO mandate to improve vaccine coverage. Shortages of vaccines have also been reported as an increasing concern in Europe[13] in addition to the risk of limitation of vaccine supply. Thus, efforts should be made to increase vaccine coverage for the elderly by making use of all age-appropriate vaccines available on the market.

In addition to providing appropriate vaccine protection for the elderly, it is also important to ensure adequate vaccine coverage in children. Children are important targets for vaccination because their susceptibility to infection is high, which makes them an important route of transmission of influenza.[14] Increased vaccination coverage in children reduced all-cause mortality from pneumonia and influenza in the elderly in Japan, also protecting themselves from death.[15] A study by Cohen et al.[16] reported that vaccinating children against influenza reduced the burden of pneumonia and influenza in the elderly. Another study by Sandmann et al.[14] suggested that mass vaccinating the pediatric population can result in the reduction of infections across all age groups, especially in the elderly population. These results recommend that increasing the vaccination coverage in children induces herd immunity, which in turn reduces the chances of infection in the elderly population.

Third, the ongoing coronavirus disease (Covid-19) has led to a major step back globally in all areas of health. A recent study showed that a hospitalized patient coinfected with influenza has an increased odds of receiving invasive mechanical ventilation compared with a Covid-19 mono-infected hospitalized patient. The coinfection was also significantly associated with increased odds of death.[17] The current season showed a lower incidence of flu (because of non-pharmacological preventive measures), with a different pattern with respect to the past, but flu is still there and still harmful.[18] Almost, all public health restrictions have now been lifted and this could increase the likelihood of more respiratory virus co-infections during future winters, substantially straining the available healthcare resources.[19,20] Interestingly, it is reported that influenza vaccination may be

associated with a reduced risk of SARS-CoV-2 infection.[21] These results lend support to the importance of continuing vaccinating against Covid-19 as well as against Influenza.

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