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 have 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 (ARR), 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. ARR 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
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. 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. in subjects aged ≥65 years with a 7.2% background annual attack rate 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., 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.

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. 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.

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 and UK’s JCVI. 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 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. Increased vaccination coverage in children reduced all-cause mortality from pneumonia and influenza in the elderly in Japan, also protecting themselves from death. A study by Cohen et al. reported that vaccinating children against influenza reduced the burden of pneumonia and influenza in the elderly. Another study by Sandmann et al. 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 coinfectcd 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. 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. 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. Interestingly, it is reported that influenza vaccination may be
associated with a reduced risk of SARS-CoV-2 infection. These results lend support to the importance of continuing vaccinating against Covid-19 as well as against Influenza.

Disclosure statement
No potential conflict of interest was reported by the author(s).

Funding
The author(s) reported there is no funding associated with the work featured in this article.

References
1. Pepin S, Nicolas JF, Szymanski H, Leroux-Roels I, Schaum T, Bonten M, Icardi G, Shrestha A, Tabar C. QHD00011 study team. 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. Hum Vaccines Immunother. 2021;17(12):5475–5486. Epub 2021 Oct 29. PMID: 34714720; PMCID: PMC8903946. doi:10.1080/21645515.2021.1983387.

2. DiazGranados CA, Dunning AJ, Kimmel M, Kirby D, Treanor J, Collins A, Pollak R, Christoff J, Earl J, Landolf V, et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. N Engl J Med. 2014;371(7):635–645. PMID: 25119609. doi:10.1056/NEJMoA1315727.

3. Van Tilbeurgh M, Lemdani K, Beignon AS, Chapon C, Tchitchek N, Cheraitia I, Marcos Lopez E, Pascal Q, Le Grand R, Maisonnasse P, et al. Predictive markers of immunogenicity and efficacy for human vaccines. Vaccines (Basel). 2021;9(6):579. PMID: 34205932; PMCID: PMC8226531. doi:10.3390/vaccines9060579.

4. Oliaro P, Torreele E, Vaillant M. COVID-19 vaccine efficacy and effectiveness—the elephant (not) in the room. Lancet Microbe. 2021;2(7):e279–e280. Epub 2021 Apr 20. PMID: 33899038; PMCID: PMC8057721. doi:10.1016/S2666-5247(21)00069-0.

5. Ranganathan P, Premash CS, Aggarwal R. Common pitfalls in statistical analysis: absolute risk reduction, relative risk reduction, and number needed to treat. Perspect Clin Res. 2016;7(1):51–53. PMID: 26952180; PMCID: PMC4763559. doi:10.4103/2229-4385.173773.

6. Hashim A, Dang V, Bolotin S, Crowcroft NS. How and why researchers use the number needed to vaccinate to inform decision making—a systematic review. Vaccine. 2015;33(6):753–758. doi:10.1016/j.vaccine.2014.12.033.

7. Somes MP, Turner RM, Dwyer LJ, Newall AT. Estimating the annual attack rate of seasonal influenza among unvaccinated individuals: a systematic review and meta-analysis. Vaccine. 2018;36(23):3199–3207. Epub 2018 Apr 30. PMID: 29716771. doi:10.1016/j.vaccine.2018.04.063.

8. European Centre for Disease Prevention and Control. Seasonal influenza; 2022. [accessed 2022 Apr 21]. Seasonal influenza (europa.eu)

9. World Health Organization. Giving influenza vaccination a boost among older people; 2022; [accessed 2022 Apr 21]. WHO/Europe | Giving influenza vaccination a boost among older people.

10. European Centre for Disease Prevention and Control. Seasonal influenza vaccination and antiviral use in EU/EEA Member States – Overview of vaccine recommendations for 2017–2018 and vaccination coverage rates for 2015–2016 and 2016–2017 influenza seasons; 2018 [accessed 2022 May 10]. Seasonal influenza vaccination and antiviral use in EU/EEA Member States europa.eu

11. Epidemiologisches Bulletin. Robert Koch institute. Epidemiologisches Bulletin 32/33 2020 [rki.De]; 2020. [accessed 2022 Apr 19]. Epidemiologisches Bulletin 32/33 2020 [rki.de]

12. Advice on influenza vaccines for 2022/23. Joint committee on vaccination and immunisation; 2021 [accessed 2022 Apr 19]. JCVI Statement on Influenza Vaccines 2022-23. pdftitl-resource.org

13. PASTÉ M, STOFFEL M, BARDONE C, BARON-PAPILLON F, CZWARNO A, GABRAITH H, GASTINEAU T, GERMAY O, GONZO D, JUVIN P, et al. Addressing vaccine supply challenges in Europe: expert industry perspective and recommendations. Health Policy (New York). 2022;126(1):35–42. Epub 2021 Nov 28. doi:10.1016/j.healthpol.2021.11.006.

14. Sandmann FG, van Leeuwen E, Bernard-Stoecklin S, Casado I, CASTILLA J, DOMEGAN L, GHERASIM A, HOOIVELD M, KISLAYA I, LARRAURI A, et al. Health and economic impact of seasonal influenza mass vaccination strategies in European settings: a mathematical modelling and cost-effectiveness analysis. Vaccine. 2022;40(9):1306–1315. Epub 2022 Jan 31. PMID: 35109968; PMCID: PMC8861572. doi:10.1016/j.vaccine.2022.01.015.

15. Reichert TA, Sugaya N, Fedson DS, Glezen WP, Simonsen L, TASHIRO M. The Japanese experience with vaccinating schoolchildren against influenza. N Engl J Med. 2001;344(12):889–896. PMID: 11259722. doi:10.1056/NEJM200103234220420.

16. Cohen SA, Chui KK, NAUNOVA EN. Influenza vaccination in young children reduces influenza-associated hospitalizations in older adults, 2002-2006. J Am Geriatr Soc. 2011;59(2):327–332. Epub 2011 Jan 28. PMID: 21275932; PMCID: PMC3111961. doi:10.1111/j.1532-5415.2010.03271.x.

17. Swets MC, Russell CD, Harrison EM, Docherty AB, Lone N, Girvan M, Hardwick HE, Visser LG, Openshaw PJM, Groenevel GH, et al. SARS-CoV-2 co-infection with influenza viruses, respiratory syncytial virus, or adenoviruses. Lancet. 2022;399(10334):1463–1464. Epub 2022 Mar 25. PMID: 35344735; PMCID: PMC8956294. doi:10.1016/S0140-6736(22)00383-X.

18. Early influenza cases indicate the possibility of severe upcoming season for elderly. European Centre for Disease Prevention and Control; 2021 [accessed 2022 April 19]. Early influenza cases indicate the possibility of severe upcoming season for the elderly (europa.eu).

19. López Montesinos I, Arrieta-Aldea I, Dicastaillo A, Zuccarino F, Sorli L, Guerri-Fernández R, Arnau-Barrés I, Milagro Montero M, Siverio-Parès of and vaccination coverage rates for 2015–2016 and 2016–2017 influenza seasons; 2018 [accessed 2022 May 10]. Seasonal influenza vaccination and antiviral use in EU/EEA Member States europa.eu

20. Ashraf M, Rajaram S, English PM. How the COVID 19 pandemic will shape influenza public health initiatives: the UK experience. Hum Vaccin Immunother. 2022;18(1):1–8. Epub ahead of print. PMID: 35435806. doi:10.1080/21645515.2022.2056399.

21. Su W, Wang H, Sun C, Li N, Guo X, Song Q, Liang Q, Liang M, Ding X, Sun Y. The association between previous influenza vaccination and COVID-19 Infection risk and severity: a systematic review and meta-analysis. Am J Prev Med. 2022;80(4):3797(22):00131–3. Epub ahead of print. PMID: 35410774; PMCID: PMC8920881. doi:10.1016/j.amepre.2022.02.008.