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*Published in:*  
Human vaccines & immunotherapeutics

*DOI:*  
[10.1080/21645515.2022.2106749](https://doi.org/10.1080/21645515.2022.2106749)

**IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.**

*Document Version*  
Publisher's PDF, also known as Version of record

*Publication date:*  
2022

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Yin, J. K., Pepin, S., van Aalst, R., Loiacono, M. M., & Samson, S. I. (2022). Reply to letter to editor by Hadigal et al. regarding the immunogenicity and safety trial of high-dose influenza vaccine in adults aged  $\geq$  60 years. *Human vaccines & immunotherapeutics*, 18(6), [e2106749]. <https://doi.org/10.1080/21645515.2022.2106749>

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To cite this article: J. Kevin Yin, Stephanie Pepin, Robertus van Aalst, Matthew M. Loiacono & Sandrine I. Samson (2022): Reply to letter to editor by Hadigal et al. regarding the immunogenicity and safety trial of high-dose influenza vaccine in adults aged  $\geq 60$  years, Human Vaccines & Immunotherapeutics, DOI: [10.1080/21645515.2022.2106749](https://doi.org/10.1080/21645515.2022.2106749)

To link to this article: <https://doi.org/10.1080/21645515.2022.2106749>



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Published online: 01 Aug 2022.



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## Reply to letter to editor by Hadigal et al. regarding the immunogenicity and safety trial of high-dose influenza vaccine in adults aged $\geq 60$ years

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### ABSTRACT

Hadigal et al. argued the recommendation of high-dose influenza vaccine over standard-dose formulation is not supported by comparisons of numbers-needed-to-vaccinate (NNV) nor aligned with the WHO mandate of improving vaccine coverage. However, the authors' NNV calculation was inaccurate. A preferential recommendation for vaccines preventing influenza/complications can increase coverage. Furthermore, the impact of vaccination is a function of efficacy/effectiveness and the vaccine-preventable fraction of disease burden; therefore Hadigal et al. should interpret the absolute risk reduction by vaccination within the context of overall disease burden. To address the threat of COVID-19 pandemic, authorities should implement concomitant influenza/COVID-19 vaccination to reduce the burden of cocirculation of influenza and SARS-CoV-2 viruses and increase the coverage of proven influenza vaccines as per WHO mandate.

Dear Editor,

Adults aged  $\geq 65$  years bear disproportional burden of influenza. In this age group, high-dose influenza vaccine has been shown to afford superior efficacy against lab-confirmed influenza and associated with less complications/hospitalizations in randomized controlled/real-world settings, when compared with standard-dose formulation.<sup>1</sup> We recently published an immunobridging trial demonstrating superior immunogenicity and similar reactogenicity of high dose quadrivalent influenza vaccine (IIV4-HD) vs. standard dose quadrivalent vaccine (IIV4-SD) in adults aged  $\geq 60$  years.<sup>2</sup> Hadigal et al. from Viatrix Inc. commented on IIV4-HD following our publication,<sup>3</sup> and here we would like to address their viewpoints.

First, we believe the numbers-needed-to-vaccinate (NNVs) reported by Hadigal et al. for trivalent IIV3-HD vs. IIV3-SD (19 vs. 18; inferred for IIV4-HD/IIV4-SD) are inaccurate and underestimate the incremental value of IIV3-HD, due to the use of 7.2% as the background attack rate of laboratory-confirmed influenza in their calculation. This attack rate was pooled from three heterogeneous studies, which were conducted in different seasons/countries compared with the pivotal trial of IIV3-HD in older adults<sup>4</sup> (USA; 2011/12 and 2012/13). In fact, the 7.2% translates to an absolute vaccine effectiveness (VE) of 74% ( $1 - 0.01882 / 7.2\%$ ) for IIV3-SD in the IIV3-HD trial; this is unrealistic for individuals of any age, and even more so for older adults, in whom the VE of IIV-SD3/4 is further reduced due to immunosenescence and other factors.<sup>5</sup>

For comparison, the U.S. CDC reported an overall vaccine effectiveness of 43% in 2011/12 and 26% in 2012/13 in this age group.<sup>6,7</sup> With IIV3-SD being the standard of care in both years, we can use the CDC reported VEs as proxies for VE of IIV3-SD. The correct background attack rates for the study years of IIV3-HD trial can now be calculated using the CDC reported VEs and the attack rate amongst the IIV3-SD recipients in the IIV-HD trial for the corresponding seasons (Table 1). Using the season-specific background attack rates in the USA, we show that IIV3-HD has a much lower NNV compared with IIV3-SD, with a delta of 86 for 2011/12 and 36 for 2012/13, respectively (Table 1). The benefits of IIV3-HD over IIV3-SD as expressed in the NNV comparisons are supported by the randomized controlled trials and real-world evidence of >34 million older adults over ten consecutive seasons<sup>1</sup>

Second, the authors' assertion that preferential recommendations of IIV4-HD over other formulations are "misaligned with the WHO mandate to improve vaccine coverage" is unfounded. In its latest position paper, the WHO states that, should IIV4-HD /other newer influenza vaccines "be available and affordable to countries, they should be recommended as long as their use does not jeopardize the ability to provide influenza vaccination to other target groups."<sup>8</sup> Rather, the introduction of influenza vaccines with proven superior protection could potentially improve the vaccine coverage. Colleagues from the U.S. CDC reported that perceived effectiveness of influenza vaccine is positively associated with the vaccine uptake in older adults.<sup>9</sup> A preferential recommendation for a vaccine proven to outperform the

**Table 1.** Number needed to vaccinate in high-dose trivalent influenza vaccine (IIV3-HD) vs standard-dose trivalent vaccine (IIV3-SD), using season-specific attack rate in the USA.

Season	Vaccination status	Attack rate in participants*	Background attack rate†	Absolute risk reduction (ARR)	Number needed to vaccinate (NNV)	Delta of NNV: (IIV3-SD – IIV3-HD)
2011/12	Vaccinated with IIV3-HD	0.00317 (23/7253)	–	0.00700 (1.02%/0.00317)	143 (1/0.00700)	86 (229–143)
	Vaccinated with IIV3-SD	0.00580 (42/7244)	–	0.00437 (1.02%/0.00580)	229 (1/0.00437)	
	Unvaccinated	–	1.02% (0.00580/(1–43% <sup>6</sup> ))	–	–	–
2012/13	Vaccinated with IIV3-HD	0.02346 (205/8737)	–	0.01654 (4.00%/0.02346)	60 (1/0.01654)	36 (96–60)
	Vaccinated with IIV3-SD	0.02960 (259/8749)	–	0.01040 (4.00%/0.02960)	96 (1/0.01040)	
	Unvaccinated	–	4.00% (0.02960/(1–26% <sup>7</sup> ))	–	–	–

\* Derived from Supplementary Appendix, Table S9 of IIV3-HD trial.<sup>4</sup>

† Calculation: attack rate in participants receiving IIV3-SD/(1 – vaccine effectiveness reported by CDC for the corresponding season); as a result, the effectiveness of IIV3-SD in the IIV3-HD trial equals the CDC reported estimates.<sup>6,7</sup>

standard-dose formulation in randomized trials can strengthen the public's perception about influenza vaccine effectiveness, which in turn improves the vaccine coverage. In Germany, IIV4-HD has been preferentially recommended over other influenza vaccines to all the 24.1 million adults aged  $\geq 60$  years; this policy was successfully implemented in the first season (2021/22), with sufficient doses of IIV4-HD delivered ahead of market utilization.

Third, the authors seem to have interpreted the absolute risk reduction (ARR) without taking into account overall disease burden. The impact of vaccination is a function of vaccine efficacy/effectiveness and the vaccine-preventable fraction of the disease burden. The author cited ARRs of 0.84% to 1.3% from COVID-19 vaccines, implying the benefits of such vaccines are not as impressive as the vaccine efficacy estimates (67% to 97%) suggested. However, given the persistence and resurgence of COVID-19 pandemic, even vaccines with ARRs of 0.84% to 1.3% can result in considerable reduction of COVID-19 cases, hospitalization, and deaths. The same principles apply for newer influenza vaccines, such as IIV4-HD.

Finally, we support the call of Hadigal et al. for continuing vaccinating against influenza during the COVID-19 pandemic. Influenza has resurged in Australia this year following the lift of border restrictions for COVID-19 pandemic, with the number of influenza notifications to date well exceeding the historical record.<sup>10</sup> Fortunately, several influenza vaccines such as IIV4-HD can be co-administered without comprising the immunogenicity and safety.<sup>11,12</sup> To minimize the impact of potential COVID-influenza 'twindemic' and to maintain/improve influenza vaccine coverage as per WHO mandate, we suggest that authorities should provide clear recommendation and necessary policy measures to reinforce the importance of influenza vaccination and the implement concomitant influenza and COVID-19 vaccination programs.

## Disclosure statement

All authors are full-time employees of Sanofi, a manufacturer of influenza vaccines, and may hold shares and/or stock options in the company.

## Funding

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

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