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Italian Journal of Public Health QJPH 2019, vol. 8 N.5 RATING OF HEALTH TECHNOLOGY ASSESSMENT (HTA) of Flucelvax® Tetra cell culture-based influenza vaccine (Valutazione di Health technology assessment (HTA) del vaccino quadrivalente da coltura cellulare Flucelvax Tetra)

Dear Editor,

I am writing to you regarding your publication of an HTA assessment – including an economic model of Flucelvax Tetra performance- developed with an unrestricted grant from Seqirus, which can be found in the Italian Journal of Public Health QJPH 2019, vol. 8 N.5. (1) This complaint is specifically in connection with the authors' use of misleading scientific data to drive the publication to a "conclusion" of superiority and cost-effectiveness of cell culture manufactured vaccine (Flucelvax Tetra) over egg-manufactured vaccines.

Specifically, the topics covered in Chapter 4, vaccine data regarding Flucelvax Tetra and Chapter 5, the economic evaluation of the introduction of the new cell-based vaccine in Italy which contains the description and discussion of a dynamic model, are of significant concern.

We bring to your attention the following critical points found in the HTA document:

1. Chapter 4: Cell based influenza quadrivalent vaccine (Flucelvax)
 - This chapter contains a review of data for the cell-manufactured vaccine (from SmPC for Flucelvax QIV and cTIV, immunogenicity data). In the first paragraph of pg. 105, the authors state that the cell-manufactured vaccine showed a 36,2% relative vaccine effectiveness vs egg manufactured vaccines, based only on information given by the manufacturer, and no publication reference. This data was therefore not included in the meta-analysis for Flucelvax Tetra
2. Chapter 5: Economic evaluation of the introduction of a new influenza quadrivalent cell based (Flucelvax Tetra) vaccine in an Italian context.
 - a. In this chapter, the authors develop an economic model of cost effectiveness and the analysis outputs are based on a base case scenario of relative vaccine effectiveness (rVE) against A/H3N2 of 36,2% of Flucelvax Tetra vs egg-manufactured quadrivalent vaccine (see page 121 and Table 5 of chapter 5 ,page 120). It is only here, in chapter 5 that the authors introduce the reference for this estimate as Boikos et al. (ref.21, chapter 5), which is a poster. This poster was presented at the National Foundation of Infectious Diseases meeting in November 2018 (2), and the study has not been published in any peer-reviewed journal.

- b. Furthermore the authors state that the assumption of the 36.2% rVE represents a “conservative” approach to the analysis against A/H3N2, while assuming 0% rVE for A/H1N1 and B strains which means egg-manufactured and cell-manufactured vaccine effectiveness are the same. The basis for this assumption is not referenced. From data presented in the Boikos et al. poster, it is not possible to assume that the rVE estimate for Flucelvax QIV is referring only to A/H3N2 influenza strains. Moreover, published evidence suggests possible better performance of egg based vs cell based for H1N1.

We are contesting the validity of the scientific data used by the authors as the basis for this extensive economic model that has resulted in a model with multiple biases and flaws. We believe the use of the rVE point estimate of 36.2% of Flucelvax vs egg-based quadrivalent vaccine for the base case scenario to evaluate vaccine effectiveness in the HTA publication is misleading because it is stated without explanation. Indeed, at least four other studies on effectiveness of cell-manufactured vs. egg-manufactured vaccines have been completed, and three of these have been published in peer-reviewed journals (3) (4) (5) (6). These studies evaluated rVE for a variety of endpoints/outcomes and demonstrate no consistent trend in results favoring cell-manufactured over egg-manufactured vaccines. If these data, also available to the authors to inform their analysis, had been considered then the outcome of the analysis is likely to have been notably different.

In conclusion, we consider that the poster presented by Boikos et al is not a suitable reference for the statements regarding the supposed superiority and cost effectiveness of cell-manufactured vaccines over egg-manufactured vaccines, and such statements that can be considered misleading and not scientifically correct. Indeed the publications of this economic model based on limited evidence from a poster might drive wrong assumptions as the basis for public health decision-making, and undermine existing influenza vaccination programs.

We request the immediate withdrawal of this HTA publication from the public domain until a new economic evaluation based on scientifically sound data is used to describe relative vaccine effectiveness for cell-manufactured influenza vaccine.



Sincerely,
Ros Hollingsworth
Sanofi Pasteur

REFERENCES:

- (1) Italian Journal of Public Health QJPH 2019, vol. 8 N.5. (Italian language)
<https://www.ijph.it/pdf/2019-v8-n5.pdf>
- (2) Boikos T. (2018). Effectiveness of the Cell Culture- and Egg-Derived, Seasonal Influenza Vaccine during the 2017-2018 Northern Hemisphere Influenza Season. Presented at NFID Clinical Vaccinology Course, November 2018
- (3) Demarcus L, et al. Comparing influenza vaccine effectiveness between cell-derived and egg-derived vaccines, 2017-2018 influenza season. *Vaccine*. 2019 Jun 11 [ePub ahead of print]
<https://doi.org/10.1016/j.vaccine.2019.06.004>
- (4) Izurieta, H. et al. Relative effectiveness of cell-cultured and egg-based influenza vaccines among the U.S. elderly, 2017-18. *JID*, Dec 2018
<https://academic.oup.com/jid/advance-article-abstract/doi/10.1093/infdis/jiy716/5250955>
- (5) N. Klein et al, presented at the Infectious Disease (ID) Week Congress in San Francisco in October 2018, "*Vaccine Effectiveness of Flucelvax Relative to Inactivated Influenza Vaccine During the 2017-18 Influenza Season in Northern California*"
<https://idsa.confex.com/idsa/2018/webprogram/Paper74111.html>
- (6) Bruxvoort KJ, et al Comparison of Vaccine Effectiveness against influenza hospitalization of cell-based and egg-based influenza vaccines, 2017-2018, *Vaccine*. 2019 Sep 16;37(39):5807-5811