December 14, 2019

To the Editor of the Quaderni of the Italian Journal of Public Health (QIJPH)

Object: Reply to Sanofi Pasteur's letter. Letter to the Editor on the HTA Report of Flucelvax® Tetra cell culture-based influenza vaccine (Valutazione di Health Technology Assessment (HTA) del vaccino quadrivalente da coltura cellulare: Flucelvax Tetra), published in July 2019 on the *Quaderni of the Italian Journal of Public Health* (QIJPH 2019, vol. 8 N.5).

Dear Editor,

we thank you for the opportunity to respond scientifically to the Sanofi's letter which defines our data as "misleading" even if, as we will explain, perfectly consistent with the application of the HTA methodology developed by the European Network for Health Technology Assessment (EuNetHTA).
We will clarify below, on the basis of scientific evidence, the points of our HTA report, published in July 2019 on the Quaderni of the Italian Journal of Public Health (1), that were supposed "critical" by Sanofi Pasteur.

Our report evaluated, according to the HTA methodology, the cell culture-derived quadrivalent influenza vaccine (QIVc), Flucelvax® Tetra, in order to analyse its health, organizational, economic and ethical implications.
According to the HTA methodology, the elaboration of this Report was carried out by a multidisciplinary work group that identified, analysed and subsequently synthesized all the scientific information available on the topic. Therefore, systematic reviews of the existing scientific literature were done and the evidence was selected according to pre-established inclusion criteria following the HTA domains of the Core Model® of the European Network for Health Technology Assessment (EuNetHTA). According to the HTA approach, the drafting of this report was also submitted to an external multidisciplinary panel of experts for further discussion and refinement.
The HTA project was supported and funded by SEQIRUS. Nevertheless, the scientific contents reported in HTA report are those of the authors and were not conditioned by the Funder.

We bring to your attention the scientific evidence that confute the supposed critical points reported by Sanofi Pasteur.

Point 1. Chapter 4: Cell based influenza quadrivalent vaccine (Flucelvax)
"This chapter contains a review of data for the cell-manufactured vaccine (from SmPC forFlucelvax 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"

HTA report's Authors answer. The chapter 4 of our HTA report (1) contains a systematic review of literature regarding data of the cell-manufactured vaccine. The methodology of the review, clearly explained in the chapter, follows the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement (2) and all studies reported are referenced and available using the search criteria made explicit in the chapter. As regard the data of 36.2% of relative vaccine effectiveness, it refers to a study not published

yet but presented in a scientific conference that, according to the methods described, was not included in the results of the review. We decided to include the study into the report on the basis of the methodology indicated in the HTA Core Model Version 3.0 (3) and because it provided a first evidence on the effectiveness of the cell manufactured vaccine with respect to influenza-like illness (ILI). Nevertheless, it was clearly specified that the study was confidentially provided by the company and was not included it in the results of the review. Moreover, it was eventually stated (pag. 106 of HTA report) that "we await the publication of the study to confirm what has been presented in the confidential material of the Company". The approach used is perfectly consistent with the HTA methodology. Indeed, according to the methodology indicated in the HTA Core Model Version 3.0 (3), in the TEC Domain (Description and technical characteristics of technology), as well as in other domains, "the information concerning the technology may be obtained from its manufacturers" (pag 71 of HTA Core Model Version 3.0).
Moreover, as reported in the HTA Core Model Version 3.0 (pag. 72) "Review articles and textbooks can be helpful when searching for information about the history and characteristics of the technology. Published literature may be obtained by searching bibliographic databases such as MEDLINE..." but there are useful other sources and links like grey literature." As reported in the HTA Core Model Version 3.0 (pag. 72) in processing an HTA report "Grey literature (e.g., working papers from research groups or committees, white papers, or preprints), hand-searching of reference lists, as well as conference proceedings may be identified by searching the websites of HTA and related agencies, professional associations. Contacting manufacturers, clinicians, nurses, paramedics and patients and reading Internet discussion forums may also be valuable".
The analysis of the grey literature, which among others includes conference abstracts and ongoing research, is an essential part of the review approach since it may increase the comprehensiveness and timeliness of the review and foster a more balanced picture of available evidence (4). Moreover, the Cochrane Handbook for Systematic Reviews of Interventions reports that "Conference abstracts are a particularly important source of grey literature" (5).

With this respect, during the study selection process a Seqirus press-release dating back to 16th November 2018 on the relative effectiveness of QIVc versus egg-derived quadrivalent influenza vaccine (QIVe) (6) was identified. The press-release cited a study presented at the National Foundation for Infectious Diseases (NFID) Clinical Vaccinology Course 2018. It was then possible to locate the original abstract that is in public domain (7).
One of the challenges relative to the analysis of conference abstracts is intrinsic to its format, i.e. the relative shortness of available information. For this reason, the data owner (i.e. Seqirus) was asked for providing additional study details, as recommended by the Cochrane Handbook for Systematic Reviews of Interventions (8). Seqirus kindly provided a full report relative to the published poster (8) and the former was analysed in depth by the authors.

Furthermore, the HTA Core Model Version 3.0 (3) reports that "If the technology has obtained regulatory approval, the information that has been submitted as part of the approval process could be used as a source of data on the description and technical characteristics of the technology. This may be available from major EU or US regulatory bodies as well as from regulatory bodies in those countries where the technology has been approved for use. Further information (e.g., description of the technology, expected performances, and intended use) can be obtained from the manufacturer's website, or in the case of confidential information, by directly requesting it from the manufacturer".

Therefore, **on the basis of the above, the scientific validity of chapter 4 and the absence of misleading information are evident.**

Point 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".

HTA report's Authors answer. It is undoubtful that all pharmacoeconomic models deal with assumptions, especially when considering emergent technologies. We set the rVE of QIVc vs QIVe against A/H3N2 influenza strain in the age strata 9-74y to 36.2% (7) since this was, at the time of writing the chapter (HTA report closed in June 2019 and published online in July 2019), the only publicly available reference reporting rVE against ILI between the two vaccine types. Our assumption of considering only the relative advantage against A/H3N2 was based on two facts. First, the study by Boikos et al. (7) was conducted in 2017/18 influenza season in the United States that was clearly predominated by A/H3N2 (9). Moreover, we considered also results from Garten et al. (10) according to which "in contrast to the 93.4% of A(H3N2) viruses that were well inhibited by ferret antisera raised against cell-propagated A/Michigan/15/2014, only 48.2% of viruses tested were well inhibited by ferret antiserum raised against the egg-propagated A/Hong Kong/4801/2014 reference virus representing the A(H3N2) vaccine component" (9). Second, the 2017/18 Northern Hemisphere formulation of QIVc had only A/H3N2 subtype as cell-derived vaccine seed.

In Sanofi Pasteur letter to the Editor, it is also cited the paper by Izurieta et al. (10) that was published before our report. Results from that paper (10) were actually included in chapter 4 and showed that QIVc was significantly ($p<0.05$) more effective than QIVe by 10% (95% CI: 7-13%) [by 16.5% (95% CI: 10.3%-22.2%) in the interim analysis clearly predominated by A/H3N2- see Discussion therein] in preventing influenza-related

hospitalizations among the US elderly. However, that study considered only older adults aged 65 years or more and the study endpoint was based on a highly unspecific clinical outcome, which is hospitalization with ICD-10 codes relative to influenza. In our model most Italian elderly were not eligible for receiving QIVc. Moreover, the clinical outcome of ILI used by Boikos et al. (7) may be considered a more specific influenza-related proxy than registry-based hospitalization records used by Izurieta et al. (10). Another publicly available (by the time of our analysis) estimate by Klein et al. (11) reported a suggestive albeit non-significant superiority of the QIVc compared to QIVe ("…..relative VE against influenza A was 6.8% (95% CI:–11.2, 21.9; P=0.43) ……The adjusted absolute VE vs unvaccinated of ccIIV was 30.2% (95% CI: 17.1, 41.3; P<0.0001) and of ebIIV was 17.9% (95% CI: 12.1, 23.3; P<0.0001")) (11). However, results from Klein et al. (11) were available on the web only in abstract version, while estimates from Biokos et al. (7) were available in a larger poster version and included also a sensitivity analysis.

In order to be cautious, as indicated in the method section (page 121), since the rVE of QIVc vs QIVe reported in Boikos et al. (7) was against ILI, we also included the estimate provided from the sensitivity analysis in which the estimates of rVE were reduced for A/H3N2 to a value of 19.3%, using the propensity score method (7). Therefore, the present model considered both rVE estimates of QIVc vs QIVe (i.e., 36.2% in the base case and 19.3% in the sensitivity analysis; see for instance Tab. 16).

All these aspects were clarified in the methods section and we also stated in the discussion section that the main limitation of this study lies in the uncertainty regarding the assumed vaccine efficacy of QIVc relative to QIVe. Since QIVc is a new vaccine, meta-analyses on its rVE are not available. Following the publication of the report, at least four studies on the rVE of QIVc vs QIVe were released and were consistent with the estimates included in the model for the A/H3N2 viruses (12 - 15). Among these studies there were two mentioned in the Sanofi letter that were not available at the time of the closure of the report (June 2019).

Moreover, these studies reported new evidence of a greater rVE of QIVc vs QIVe, even though results were not significant. Only [DeMarcus 2019] (14) showed a higher rVE of QIVe vs QIVc against influenza A(H1N1)pdm09 subtype. We stress, however, that these estimates were not available at the time of closing the chapter, and therefore not included in the analysis. However, if new evidence and meta-analyses were available, an update of the economic evaluation section could be considered in the future.

Sanofi Pasteur's letter ends as follows: *"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".*

HTA report's Authors answer. In light of the evidence-based explanations provided and of the rigorous methodology applied, the disputes raised by Sanofi are, in our view, unsubstantiated and not impacting the validity of our work. Therefore, we reiterate the scientific validity of our HTA report.

Sincerely,

the Authors of the HTA report on Flucelvax Tetra (QIJPH 2019, vol. 8 N.5):

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