Author’s response to reviews

Title: Central European Vaccination Advisory Group (CEVAG) guidance statement on recommendations for influenza vaccination in children

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First Author: Vytautas Usonis

Dear Ms Rajabi,

Thank you for reviewing our paper. We have revised the manuscript as requested.

In summary, we have defined the age group the recommendation targets, we have reviewed the data sources and included additional references to support the assertions in the text, and we have also included the additional information on vaccine safety as requested.

Below I have outlined how we have addressed the queries of each reviewer.

Reviewer #1

Major Compulsory Revisions:
None

Minor Essential Revisions:
1) The reviewer requested the definition of the upper age limit for the CEVAG
recommendation

We have updated the CEVAG recommendation throughout the manuscript to read:

‘CEVAG recommends the introduction of universal influenza vaccination for all children from the age of 6 months. Special attention is needed for children in the age up to 60 months as they are at greatest risk. Individual countries should decide on how best to implement this recommendation based on their circumstances.’

2) For Table 2 the reviewer requested to include the above and also make the requirement for annual immunisation more obvious. The reviewer also commented on the method of vaccine delivery being only limited to infants - what about delivery for older children?

We have updated Table 2 to make the annual requirements and vaccine information more clear.

3) The reviewer requested Line 3 in the background, pg 3 ‘rates’ should be deleted from ‘mortality rates’

This has been done.

4) The reviewer requested the ‘strategies for the future’ section to be updated to briefly reflect that a pandemic from the 2009 H1N1 strain has occurred.

We have updated the text to read (page 12, line 19):

‘The recent spread of 2009 Influenza A(H1N1) illustrates the speed with which new forms of the influenza virus spread around the globe and the threat from A/H5N1 remains high’

5) Referring to the sentence ‘In the EU no controlled Phase III immunogenicity trials …’, the reviewer requested ‘licensed split or subunit’ be replaced with ‘licensed trivalent split or subunit’

We have deleted this sentence.

6) Referring to the sentence ‘It has been shown that only 28% of children with laboratory-confirmed influenza are correctly diagnosed’, the reviewer requested clarification.

We have modified the text on page 5, line 16 to read:

‘It has been shown that for children with laboratory-confirmed influenza, only 28% of hospitalised children and 17% of children seen in the clinic are correctly diagnosed by their treating physicians’

7) The reviewer requested the last paragraph on pg 5. To be highlighted earlier, or put with section on existing recommendations.

We have added this paragraph to become the first paragraph of the ‘Existing recommendations’ section.
8) The reviewer stated that the expression ‘reverted back’ to be changed. Also the reviewer states that this paragraph repeats what is said in 2nd para on pg 10 and to consider re-working this part of manuscript

This sentence has been deleted as the 2nd paragraph was preferred and reworked

Discretionary Revisions:

1) The reviewer suggested stating commonly reported side effects from TIV, e.g. injection site reactions, systemic symptoms. i.e. what can reasonably be expected following immunisation

We have included this information into Table 2

2) The reviewer suggested stating difference between USA and Canadian recommendations for annual influenza vaccine for children

We have modified the sentence in the ‘Background’ to read (page 3, line 17):

‘…universal influenza vaccination in all children from the age of 6 months to 18 years is current practice in the USA and from 6 to 23 months in Canada’

3) The reviewer suggested that more serious complications of influenza are pneumonia, secondary bacterial infection, sepsis, (rather than example of OM)

We have included the serious complications as suggested and updated the reference

4) The reviewer stated that there have been a number of efficacy studies, and subsequent reviews with meta-analyses and a cochrane review on effetiveness of TIV in children (e.g. Manzoli et al., Smith et al., Negri et al.). In the RCTs the number of subjects aged < 24 months was limited, and some have concluded that efficacy in these youngest of children is less well demonstrated. The reviewer suggested this should be discussed, even briefly, even if it does not impact upon the final recommendations.

We have reworked this section of the manuscript to include more efficacy and effectiveness studies and arranged the paragraphs by age groups. We have included three meta-analysis studies (including those mentioned by the reviewer and a more recent version of the Cochrane review) and several case-control and randomised studies. We have included a paragraph on the efficacy/effectiveness of vaccines in children <23 months of age

5) The reviewer suggested the inclusion of the review by Jordan et al.,

The suggested reference is a review of the public health benefits of vaccinating healthy children. We have included the suggested reference in the section ‘Influenza vaccination of healthy children’

Reviewer #2

1) Referring to the sentence ‘… influenza-associated mortality rates were highest at 0.88 deaths/100,000…’, the reviewer stated ‘the 0.88/100,000 incidence is for
the under 6 months of age and not a global result’

We have changed the sentence on page 4, line 6 to:

‘Although overall influenza-associated mortality rates were highest at 0.88 in children were not high, a US study showed 63% of the 153 reported influenza-associated paediatric deaths/100,000 in the United States during the season 2003–2004 were less than 5 years of age’

2) Referring to the sentence ‘Children < 6 months of age … are most likely to develop serious complications’, the reviewer stated ‘usually, otitis media is rare in this infant age group’

This comment is no longer applicable as we have changed the sentence on page 4, line 12 to:

‘Children under 2 years of age are at highest risk of influenza and are most likely to develop serious complications such as pneumonia, secondary bacterial infection, and sepsis’

3) Referring to the paragraph beginning ‘Typical symptoms of early influenza’, the reviewer stated ‘Silvennoinen’s paper describes ambulatory children <13 yrs of age with 78% of them with rhinitis’

To acknowledge ambulatory children aged <13 years, in the sentence on page 5, line 4 we have replaced ‘infants’ with ‘children’, and added ‘many children treated for influenza in the outpatient setting have rhinitis during the early phase of the illness’

4) The reviewer stated ‘laboratory (culture, PCR) confirmation should be distinguished from rapid tests at bed side and their benefit for early and improved diagnosis in order to overcome the underdiagnosis which indeed exists’

We have added the following text to page 5, line 10:

‘Several rapid antigen detection tests are available and provide results in 10–30 min but with reduced sensitivity (70%–90% in children) compared with RT-PCR and with viral culture. Accuracy of these assays depends greatly on patient age, length of illness, sample type, and possibly viral type’

We have also added to page 5, line 25:

‘The use of rapid testing for influenza may enhance the precision of the influenza diagnosis but the reduced sensitivity of these tests means that negative test results should be confirmed with RT-PCR and/or viral culture’

5) The reviewer requested ‘number of registered cases’ to be replace by ‘notified cases’

We have replaced with ‘notified’ on page 4, line 18

6) The reviewer requested underreporting ambulatory care to be distinguished from hospitalisation; the former being more difficult

We have updated the text on page 4 to include a paragraph on hospitalised
cases followed by a paragraph on the outpatient setting.

7) The reviewer requested to distinguish by age group

We have included age groups when describing specific studies, for example: ‘Children between the ages of 6 and 23 months have the highest rates of visits to clinics and emergency departments attributable to influenza’.

8) Referring to the sentence ‘It has been shown that only 28% of children with lab confirmed ...’, the reviewer stated the sentence does not mean the same as in the reference

We have modified the text on page 5, line 16 to read:

‘It has been shown that for children with laboratory-confirmed influenza, only 28% of hospitalised children and 17% of children seen in the clinic are correctly diagnosed by their treating physicians’

9) Referring to the sentence ‘However, even among school age children, [clinical] diagnosis is well below 50%’, the reviewer quotes the exact wording in the study by Peltola et al.

We have replaced the sentence, page 5, line 21:

‘In this group a clinical diagnosis sensitivity of 21% and positive predictive value of 16% were observed’

10) Referring to the sentence ‘In young children, the clinical presentation of influenza related illness can consist of ... might not be attributed to influenza’, the reviewer requested the addition of ‘in absence of laboratory confirmation’

We have added the required text, page 5, line 10

11) The reviewer suggested presenting the vaccines (TIV) and what is known so far in children before considering the vaccination strategy

We have moved the section ‘Influenza vaccine’ to come before ‘Influenza vaccination of healthy children’

12) The reviewer suggested adding some scientific data by age groups on immunogenicity, and protective efficacy/effectiveness

We have reworked this section of the manuscript to include more efficacy and effectiveness studies and arranged the paragraphs by age groups. We have included three meta-analysis studies and several case-control and randomised studies.

13) The reviewer stated ‘the vagueness of ‘children’ contributes to a weakness of discussion especially when speaking of herd immunity /indirect benefit: demonstrated only when school aged children are (largely) vaccinated’

We have included the age range for the herd immunity study in day care children (aged 24–60 months) to highlight that this effect is not only in school children.

14) The reviewer stated ‘as only TIV are available all through Europe it should be pointed out that vaccines are the same for adults and children’
This comment is addressed in the following sentence on page 6, line 2:

‘The influenza vaccine currently approved for children and adults in Europe is the trivalent inactivated vaccine’

15) The reviewer stated ‘the discussion should start with what is known so far with TIV in children by age groups and the caveats (limitations, lacks ...)’

As well as discussing what is known so far with TIV in children we have included the following text (page 6, line 19):

‘Lower estimates for clinically diagnosed cases are possibly due to inclusion of misdiagnosed non-influenza cases and a proportion of cases that would not be prevented even with a totally efficacious vaccine’

Also (page 6, line 25):

‘The efficacy and effectiveness of influenza vaccinations depends on several factors, most importantly on the age and immunocompetence of the recipient, the similarity between the viruses in the vaccine and in circulation for a given influenza season, and the study design and outcome measured’

16) The reviewer requested that any data under 2 years of age should appear in this paper if known: otherwise this lack should be pointed out.

We have included three studies on children less than 2 years of age and also state:

‘Relatively few studies on influenza vaccine efficacy and effectiveness have been conducted in children aged between 6 and 23 months’

17) The reviewer requested that for TIV it should appear:

- recommended for children aged 6 months to 8 yrs (included)
- the (minimum 4 weeks) interval between the two doses in primary vaccination
- the half dose in children < 36 months of age
- the need for yearly booster

This information has been included in the ‘Influenza vaccine’ section and in Table 2.

18) The reviewer requested replacing ‘vaccine strain’ with ‘vaccine virus’

This has been done on page 7.

19) The reviewer stated ‘LAIV has been demonstrated to be efficient in the following 2nd season even with a drifted strain (Belshe)’

We have included the Belsh et al. reference in the following sentence (page 13, line 17):

‘Multiple studies have shown that LAIV provides sustained protection against influenza caused by antigenically similar strains through a second influenza season in children aged 6 months to 18 years without the need to revaccinate’
20) The reviewer stated that ‘both LAIV and MF59 adjuvanted vaccine would be of interest in the ability of an influenza vaccine to trigger an immune response against drifted viruses not in the vaccine formulation’ and requested this part of the discussion be reordered for clarification.

To better focus the manuscript we have included LAIV and MF59 adjuvanted vaccine in the ‘strategies for the future’ section. This leaves TIV as the main vaccine described in the ‘Influenza vaccine’ section as this is the only vaccine relevant to Europe.

21) The reviewer stated ‘for US recommendations: in 2003 there was an encouragement when feasible converted in a recommendation on year 2004 (but no ‘reverting back’).

This section has been deleted.

22) The reviewer stated ‘there is some confusion between vaccines and recommendations / strategies which are spoken on different occasions in this paper: a restructuration of this part would improve greatly the readability’.

We have deleted the last paragraph of the section entitled ‘Existing recommendations for vaccinating children against influenza’ as this is more related to strategy rather than recommendation.

23) Referring to the statement ‘The efficacy of influenza vaccines in children has been shown in several studies’, the reviewer stated that this ‘needs to be backed by strong references’.

This sentence has been deleted.

24) The reviewer stated ‘end of page 10: what is the significance of numbers in brackets?’

These numbers represented the number of countries recognising each high-risk condition. For simplicity the numbers have been deleted.

25) The reviewer requested to emphasise the fact there is no vaccine for children < 6 m.

The following sentence has been added (page 7, line 16):

‘There is currently no vaccine recommended for children less than 6 months of age’.

26) The reviewer stated that ‘this draft should focus on seasonal flu vaccination’.

We have deleted the paragraph on pandemic preparedness plans to keep the messages focused on seasonal influenza.

27) The reviewer stated ‘page 13: coverages rates should appear as a caveat and presumably are in high risk groups children many other European data (Spain, France) have been published on this topic’.

The study on vaccine uptake used for this paragraph also includes France and Spain. We simply mention the countries with the lowest and highest uptake and
focus on the CEVAG countries to highlight that increased awareness is required. We prefer not to go into too much detail with other European countries.

28) The reviewer requested ‘health workers’ to be replace with ‘health care professionals’
This has been done throughout the manuscript

29) The reviewer stated ‘there is a strong need to have some wording on how to trigger [the recommendation] and maintain it through the years’
We have modified the last paragraph to begin:
‘The introduction of universal influenza vaccination for all children is clearly desirable but continued education for health care professionals and the public on the benefits of immunisation and paediatric influenza is likely to increase acceptance of vaccination.’

30) The reviewer stated ‘the background of a routine recommendation should be summarized’
We have included the following text (page 8, line 20):
‘Amongst the evidence that is vital to consider before implementing any universal vaccination scheme as well as disease burden, other issues that need evaluation are the expectation of significant public health benefits, the safety of the vaccine to the recipient, the safety of the vaccine to the whole population and the demonstration of cost-effectiveness.’

31) The reviewer stated ‘tolerance: risk of Guillain Barre post vaccine should be related to the risk post flu disease’
We have modified the sentence to read (page 7, line 20):
‘The risk of developing Guillain-Barré syndrome following influenza vaccination is at most one in 1,000,000’

If you require any further information please do not hesitate to contact me.

Yours faithfully,

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