results of the pilot season 2017/18’

The report, including the executive summary have been substantially revised. No pooled VE estimates are presented in the executive summary.

We decided to change the title into ‘Setting up brand-specific IVE in EU - results of the pilot season 2017/18’

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Agree - there was also the short in the SBP to do a pooling on un-aggregated data from each study site which is at present missing

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No head to head comparisons were done of [vaccine type redacted] vs [vaccine type redacted].

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Please report the finding from the US

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Please add that this concerns the 2017/2018 influenza season.

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Please add the estimate + CI

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Background

The epidemic period in the North America’s was different than in Europe due to H3N2 being the predominant strain and with [vaccine type redacted] being the primary vaccine used. Hence it is not expected that the VE is similar (nor does it provide validation for the estimates found for Europe from previous years).

Results

General comment on section

The overall pooled VE was 17% (95%CI 1-30). In order to provide a comment about overall VE, we suggested to translate it into another language more comprehensive for lay public; e.g. 1 person vaccinated over 5 did not develop the disease despite flu exposure thanks to the vaccine.

Background

Influenza in a major public health problem. Vaccines are the cornerstone of preventing influenza, however, there’s a controversy about the impact of influenza vaccination programs.

Background related to the paragraph

According to ECOH and Flu News Europe, influenza viruses circulated at high levels between weeks 52/2017 and 2018. The majority of the detected influenza viruses strain were of type B.

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According to ECDC and Flu News Europe, influenza viruses circulated at high levels between weeks 52/2017 and 2018. The majority of the detected influenza viruses strain were of type B.
In the paragraph:

“...in Spain, a total of ...”

It seems huge; could you please explain and clarify.

Suggest to aim complete the table with the input from the local study teams.
22 In 7.2 Target group for vaccination:

Table 8: Availability of influenza vaccine types and brand for each study site in 2017/18 season. (Please also see DRIVE D1.3, Annex 4.2.2 and Table 6: Vaccine availability and recommendations by specific type of vaccine are summarized.)

<table>
<thead>
<tr>
<th>Study site</th>
<th>Vaccine type/brand available</th>
<th>Vaccine type/brand recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This was an error in data entry. This has been removed from the analysis.

22 In 7.2 Target group for vaccination:

Comment related to the Table 8

Vaccine type/brand should be presented by age group, targeted populations and countries. There is a list of unknown brands in Austria, it should be highlighted and discussed for improvements next season.

22 In 7.2 Target group for vaccination:

Comment related to the Table 8

Information on the licensed age indicator for the individual brands should be added as well as a description of specific recommendations to use certain vaccine type/brand for certain populations.

Vaccine type recommendations have been added in Table 5.

22 In 6.4 Vaccination in the previous season:

Influence vaccination in the previous season was categorized as yes/no. This does not account for potential previous flu infections.

The SAP was followed for this analysis. This will need to be addressed for next season’s SAP. Also, this may be extremely difficult to account for.

24 In 6.9 Data quality:

Comment related to the paragraph

Is there any data management report available for the pilot season? Adequate, no important given that the first year is a pilot and no information was provided on the quality and completeness of the information needed.

A data management plan has been added on an addendum.

24 In 6.10 Sample size description:

General comment on section

Based on the parameters that determine sample size and when an analysis is undertaken or not.

Is the brand-specific estimation, and estimates for the brand that received 'reasonable' estimates: f1 (for the dose brands) and f2 (for the reference brands), f2 cannot be calculated (infectious or estimated) only where it was estimated from the extensive sample size calculations? It was concluded that setting a priori thresholds for calculating the sample size is a technical possibility as it is demonstrated that the sample size requirements is independent on the prior-setting.

24 In 6.1.1 Measure of effect:

Comment related to the paragraph

Describe should be added for the vaccine recipients of the different vaccine types/brands and non-vaccinated (by cases and controls), as well as for the stratified analyses to be able to understand the results.

Adequate, there was no information on how this was done.

The explanation is correct. The effect measures used to pool together are the site-specific (and adjusted) IVE estimates. This has been added more clearly in the methods.

24 In 6.1.2 Measure of effect:

General comment on section

For the primary and secondary objectives, the effect measures for 2 stage pooling were used.

The data used for this analysis are the same as in the previous season's meta-analysis. There is no need to redefine these objectives, but it is important to clarify the assumptions made in the previous season, including the assumptions made about how the data were pooled. It is also important to show the results from the previous season's meta-analysis, as well as the current season's meta-analysis, to allow for comparison of the results and to provide context for the current season's findings.

Agree, the data used for this analysis are the same as in the previous season's meta-analysis. There is no need to redefine these objectives, but it is important to clarify the assumptions made in the previous season, including the assumptions made about how the data were pooled. It is also important to show the results from the previous season's meta-analysis, as well as the current season's meta-analysis, to allow for comparison of the results and to provide context for the current season's findings.

24 In 6.1.3 Meta-analysis:

For the primary objective, a stratified meta-analysis was performed, following the same methodology described in section 6.1.3.

The SAP was followed for the analysis.

24 In 6.1.4.3 Analysis method:

For every secondary objective, a stratified meta-analysis was performed, following the same methodology described in section 6.1.4.3.

The data used for this analysis are the same as in the previous season’s meta-analysis. Therefore, it is not necessary to redefine these objectives, but it is important to clarify the assumptions made in the previous season, including the assumptions made about how the data were pooled. It is also important to show the results from the previous season’s meta-analysis, as well as the current season’s meta-analysis, to allow for comparison of the results and to provide context for the current season’s findings.

24 In 6.1.5 Subgroup analysis:

To explore sources of the vaccine effect, IVE was modelled as a smooth function of vaccine type and age. Vaccines were categorized into a few discrete categories, as shown in the figure.

No attractions to report here but the certain analyses were done where they didn’t appear in the report.

No analysis had been performed and has been added to the report.

24 In 6.1.6.4 Reporting analysis results

Reported analysis results

The results should be presented.

The data used for this analysis are the same as in the previous season’s meta-analysis. Therefore, it is not necessary to redefine these objectives, but it is important to clarify the assumptions made in the previous season, including the assumptions made about how the data were pooled. It is also important to show the results from the previous season’s meta-analysis, as well as the current season’s meta-analysis, to allow for comparison of the results and to provide context for the current season’s findings.

24 In 6.1.7 Reporting analysis results

Comment related to the Table 12

The values of the parameter that determine the min sample size to detect age 0-9 and presentation the minimally detectable vaccine effectiveness for each analysis, including the stratified analyses, are missing from the results. Sample sizes available for each analysis should be included in the report.

24 In 6.1.8 Reporting analysis results

Comment updated by the company following the review comment: The revised comment has been reviewed by the DRC. The values of the parameter that determine the min sample size to detect age 0-9 and presentation the minimally detectable vaccine effectiveness for each analysis, including the stratified analyses, are missing from the results. Sample sizes available for each analysis should be included in the report. Similarly, for example it is not clear why in the ‘flu region there was no brand specific VE possible, when in effect there was only 1 vaccine used.

The suggestion to retrospectively calculate ‘min det. VE’ (see also comment 16.1) is a good one and will be considered for the SAP for next year. For this year, we will not add additional analyses as our focus is on the data collection and preparations for next season.

24 In 6.1 Results

General comment on section

It was understood that VE estimates with very wide confidence intervals (> +20%) would not be presented, yet they are here.

Adequate, no comment given that there is not very wide confidence intervals would not be reported, however, no threshold was defined. Also, no time. It is very helpful to present and discuss results, discuss limitations and see how we can improve the studies for next season.
12. Discussion

In this study, we did not allow for any stratification by virus type or age group within each brand.

Table 3

<table>
<thead>
<tr>
<th>Vaccine Type/Brand</th>
<th>VE (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/Amoy/1A/2006</td>
<td>55.2 (0.99 - 88.4)</td>
</tr>
<tr>
<td>A/Amoy/4/2006</td>
<td>34.3 (0.47 - 72.4)</td>
</tr>
<tr>
<td>A/Brisbane/10/2007</td>
<td>53.1 (0.99 - 87.1)</td>
</tr>
<tr>
<td>A/Hong Kong/156/2007</td>
<td>45.8 (0.97 - 86.3)</td>
</tr>
<tr>
<td>A/California/4/2009</td>
<td>11.2 (0.57 - 41.0)</td>
</tr>
<tr>
<td>All vaccines combined</td>
<td>37.3 (6.71 - 68.0)</td>
</tr>
</tbody>
</table>

Information on vaccine coverage was not collected as part of this study.

The SAP was followed for the analyses.

See earlier comment.
12. Discussion

Study-specific estimates were higher in primary care settings (28%, 95%CI 3–47%) than in hospital settings (6%, 95%CI 3–15%). These are earlier estimates above. It is not clear why certain analyses were performed and others were not possible to conduct. Specifically for [vaccine type redacted] and [vaccine type redacted 2] it would have been able to be to by brand and by age.

The SAP was followed for the analyses. No more interpretation of the results in the report.

In Spain-Valencia, and the restriction in the onset to swab period resulted in although remaining non-significant. [vaccine brand redacted] was mostly used redacted, increasing from 1% (95%CI -29–24) to 13% (95%CI -22–37), on onset had an important effect on the IVE estimate for [vaccine type redacted]. When excluding the Finnish data from the analysis, the difference between IVE for [vaccine type redacted] and [vaccine type redacted 2] disappeared (16%, 95%CI -48–22 vs. 18%, 95%CI -15–41).

The SAP was followed for the analyses. No more interpretation of the results in the report.

It is said to pool estimates from these two completely different populations?

The SAP was followed for the analyses. No more interpretation of the results in the report.

This is a prerequisite to get credible results in the conclusion, the order of priority for the presentation of the results should be:

1. Setting (presenting one hospitalisation can not be compared with preventing one QD visit)
2. Age (corrected to strain and immune response)

stratification by both brand and age, or brand and setting was not possible

Agree, this comment well reflects the problem with the report

Please see comments on executive summary as well.

The SAP was followed for the analyses. Next year there will be more sample size, and it will be important to clarify for next year. MVP analysis are necessary to obtain meaningful results.

The report indicates some of the fundamental problems with vaccine effectiveness studies for the purposes as mentioned in the introduction comparison of VE for various influenza vaccine types and for transparency of results is a timely manner.

Although the report acknowledges these "weaknessess", they apparently bear no consequences on the reported outcome and the interpretation of the study outcomes. However, the VE outcome estimates are dependent on the actual circumstances of the monitored factors during the study period and the study sites.

no consequences on the reported outcome and the interpretation of the study outcomes. Although the report acknowledge these "weaknessess", they apparently bear no consequences on the reported outcome and the interpretation of the study outcomes. However, the VE outcome estimates are dependent on the actual circumstances of the monitored factors during the study period and the study sites.

The SAP was followed for the analyses. No more interpretation of the results in the report.

The SAP was followed for the analyses. No more interpretation of the results in the report.

No more interpretation of the results in the report.
Comment related to the paragraph "Results in relation to other studies"

Please add the related comparable figures from US and I-MOVE.

No more interpretation of the results in the report.

Comment related to the paragraph "Future research"

The discussion has been substantially revised.

Discussion has been substantially revised.

Comment related to the paragraph "Future research"

The discussion has been substantially revised.

We successfully estimated pooled IVE across 5 different sites, obtaining comparable results to other studies conducted in Europe and the US. As per previous comment, the comparison to the US is expected to be different due to different strain epi and vaccine use. This should be commented on.

The discussion has been substantiably revised.

Comment related to the paragraph "Future research"

The discussion has been substantially revised.

Meaning of the study

The aspect of age is not taken into consideration.

The discussion has been substantially revised.

Conclusion

Model-specific estimates of the were obtained for four brands: pooled estimates for two brands for which there was enough sample size.

The conclusion has been substantially revised.

Results in relation to other studies

Compared to the US FLU VE network, who recently presented their preliminary IVE results during season 2017/18, and the European interim 2017/18 IVE results published by the I-MOVE/I-MOVE+ network, our point estimates were somewhat lower but the IVE estimates were similar (best protection against A(H3N2), relatively higher IVE among children).

The discussion has been substantially revised and contains the sites for next year and how the lessons learnt will shape the next season.

The results and discussion sections have been substantially revised and no longer provide any interpretation of pooled IVE estimates.

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