The objective is stated as piloting the governance structure (unclear of what: the study sites, the central analysis, the consortium?). The objective is now consistently formulated as follows: The overarching objective of this pilot study was to test the different operational aspects of the project including the IT infrastructure, the DRIVE governance for conducting IVE studies and streamlining key processes such as data collection, statistical analyses and dissemination of study results.

The information on sampling/swabbing remained also unclear to us. The study site visits were very helpful in this respect. Table 3 summarizes the information on catchment population and sampling strategies.

Changing the objectives seems hard as these are the objectives stated in the SAP. The discussion on brand anonymization and the reason pro and con are still ongoing. I suggest to wait for this.

Agree that the information on swabbing was still unclear, also for us. The study site visits were very helpful in this respect. See Table 3 for the explanations on catchment population and sampling strategies.

The study site visits were very helpful in this respect. See Table 3. Fig. 7 shows data for vaccine brand B, which was not used at the Rioja site. Information on La Rioja added in Table 3. Agree that the information on swabbing was still unclear, also for us. The study site visits were very helpful in this respect.

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5.3 Descriptive analyses

Table 13

3.7 Vaccinee definition

Scenario B: A child aged < 9 years who had not been fully vaccinated (see above) before the current season was considered as
1. vaccinated with the influenza vaccine of interest if >14 days have elapsed since the second record of injectable vaccination or the first record of LAIV vaccination during the current season
2. partially vaccinated
1. during the first 14 days after the second record of injectable vaccination or the first record of LAIV vaccination during the current season
2. after the first record of injectable vaccination until >14 days have elapsed since the second record of vaccination during the current season
3. unvaccinated until the first vaccination record during the season
4. unknown if information on influenza vaccination is missing.

Note 1: If no information on exposure in previous season was available in the dataset, the exposure definition 'scenario A' was used for all subjects.

I found this confusing, especially with respect to the partially protected definition in A and B. There seems to be some redundancy here - surely the same qualification in B that relates to a first dose in a child <9 could be incorporated in A?

The direction of the impact of the sensitivity analyses on the VE were added.

Does the second description of partially vaccinated not include the first one (e.g. could it be simplified to only the second one)? Re: note 1: was it considered to do a sensitivity analysis assuming if no information using scenario B.

Corrected.

3.7 Exposure (vaccination)

There is now a mismatch between the objectives as stated (correctly in my view) that the primary objectives is to pilot the DRIVE governance model (page 14) and those stated on page 19 section 2.1. Some distinction should be made between the objectives as stated in the SAP for the analytic aspects of the report and the over arching objective of piloting procedures for year 2.

Report has been reviewed for consistency.

5.3 Descriptive analyses

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Note 1: If no information on exposure in previous season was available in the dataset, the exposure definition 'scenario A' was used for all subjects.

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Note 1: If no information on exposure in previous season was available in the dataset, the exposure definition 'scenario A' was used for all subjects.

I found this confusing, especially with respect to the partially protected definition in A and B. There seems to be some redundancy here - surely the same qualification in B that relates to a first dose in a child <9 could be incorporated in A?

The direction of the impact of the sensitivity analyses on the VE were added.

Does the second description of partially vaccinated not include the first one (e.g. could it be simplified to only the second one)? Re: note 1: was it considered to do a sensitivity analysis assuming if no information using scenario B.

Corrected.

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Report has been reviewed for consistency.

5.3 Descriptive analyses

Table 13

I would like to understand how the information on vaccination status in the previous season was derived? Was this based on a field in the current year's record manually entered or was an extract of the entire patient record provided to allow this be derived by those conducting the analysis? This information may have been in Annex 9.7 or 9.8 which were not provided to the ISC.

I was also surprised that so few cases had received vaccine in the previous season - the %s being similar to that in the current season among cases and both larger than the proportion among controls in both years. does this imply some protection across seasons? Was this to be investigated in the analysis?

Oversight, added to Table 5.

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Oversight, added to Table 5.
43 **Vaccine types**

I am curious, given that this is not mentioned: are cell-cultured vaccines used at all in Europe? In a recent study (presented at the June 2018 ACIP), we found a small difference in VE between cell-cultured and egg-based vaccines. In any case, for future years, maybe cell-based vs. egg-cultured and tri- vs. quadrivalent vaccines can be analyzed.

Description of flu viruses in elderly hospitalized should be possible in future seasons since we will have additional sites conducting TND in hospital. If what you mean to is look at the proportion of elderly hospitalized that have flu, that may be more challenging but could still be considered.

44 **Figure 7**

*Figure 7. It is unclear to me how ‘random swabbing’ was implemented in Austria and Italy – was some kind of random number generator used to select patients to be tested? Also what is the difference between systematic and routine care?*

**Frozen.** Figure 7 would at least add a strata for people 65+. (providing data are available.)

Cell-culture vaccines are currently not used in Europe. When they become available this would be an interesting analysis to add.

44 **Fig 7**

It is unclear to me how ‘random swabbing’ was implemented in Austria and Italy – was some kind of random number generator used to select patients to be tested? Also what is the difference between systematic and routine care?

This figure shows IVE results for brand B. This analysis was not stratified by age (hence only showing >65 for all sites except Finland where the data is for 6m-2y and 65+y).

47 **Figure 11**

A comparison of [vaccine type redacted] vs. [vaccine type redacted] makes sense to me if it is stratified by age. Alternatively, it can be restricted to age groups for which data are available. But an overall comparison without clarifying which age groups are used seems misleading to me.

**Agree.** It has been previously decided to not redo the analysis for this year (as the objectives are piloting, and learning for next year), and rather spend time to prepare the data collection and analysis of next year. Worthing on careful interpretation has been added: Note that whilst [vaccine type redacted] is only indicated for children, the estimates were not stratified by age, nor restricted by age groups. This warrants caution when interpreting the results.

51 **Time since vaccination**

In methods, you state that cases occurring within 14 days post vaccination are defined as ‘partially vaccinated’, which is difficult to interpret, for a future season I would suggest instead excluding such cases completely. For a time to onset analysis, I would be sure to exclude any case occurring within 14 days post vaccination anyway. Since that is done, then an analysis could be performed. There are a number of reasons for finding such an unusual result as you did, but waning immunity does not explain the bimodal curve you found, with high VE the first month after vaccination, dropping afterwards before reaching higher levels again at 4 months after vaccination. So bias or chance are the best alternative explanations.

**Exposure definition: we will re-discuss this and maybe change the definition for next season. Unexpected results: I completely agree that the results for waning protection are unexpected. However, I think that changes in circulating influenza (and other) viruses over time might also explain the results, and this is something we can hopefully investigate in the future when having more data.**

55 **Confounder adjustment**

**Agree with the conclusion, for a future year, among the 5 covariates you chose, I would suggest to calculate confounder-adjusted IVE estimates that ALWAYS include age, sex, number of hospitalizations in previous 12 months. Influenza vaccination status in the previous season should be included only if available. I would not insist on +/- chronic conditions. Moreover, I would suggest trying to be as precise as possible regarding age groups. Thus, mispecification of these adjustments, so they areforced into any final model, should be strongly considered.**

Thanks for the advice.

61 5.7 Sensitivity analysis of primary objective

Excluding patients with swab date >4 days after ILI/SARI onset date changed the brand-specific IVE estimates and the IVE estimate for adjuvanted vaccine.

Excluding patients with swabbing >4 days after onset changed the VE: could you add how?

**Exclusion of patients with swab date >4 days after ILI/SARI onset date changed the brand-specific IVE estimates and the IVE estimate for adjuvanted vaccine.**

Moreover, I would suggest trying to be as precise as possible regarding age groups. Thus, mispecification of these adjustments, so they are forced into any final model, should be strongly considered.

62 **Discussion**

The focus of the 2017/18 influenza season for the DRIVE consortium was on piloting the DRIVE study platform.

The objective in the discussion on p62 it is cited as piloting the platform. Please use consistent wording throughout: primary objective was to pilot operational aspects.

Agreed. We tried to make the distinction between the objectives following the SAP and the ‘pilot objective’ more clear. Creative with words: the ‘primordial and overarching’ objective is to test the system, and the ‘primary’, ‘secondary’ and ‘exploratory’ objectives in accordance with the SAP. Hope this works for native English speakers as well.

Annexes are on SharePoint as separate documents. Adding them all into the report causes the Word document to crash. We will discuss this with the project leaders how to make sure you have access to all relevant documents: access to SharePoint or sending zipped folder with all documents - to be followed up.

Nicely put: the ‘primordial and overarching’ objective is to test the system, and the ‘primary’, ‘secondary’ and ‘exploratory’ objectives in accordance with the SAP. Hope this works for native English speakers as well.

62 **Discussion**

**Experiences and next steps: generic protocols**

**Adherence to minimum data requirements**

Adherence to the minimum data requirements and the pre-defined data formats is important to have complete information, to avoid misinterpretation of the shared data and to allow for common statistical analysis, using standardized analysis scripts. In 2017/19, a substantial amount of time was spent on data cleaning.

The definition originated from the protocols. We agree it was confusing and now reformulated. See Section 3.9.1. (Definition and alignment with generic protocols/SAPs to be checked carefully.)

62 **Discussion**

The revised year one report is now considerably better and addresses all the major comments made by the ISC and those made by EFPIA that were endorsed by the ISC. It is regrettable that none of the Annexes were provided with the report - in particular 9.1, 9.7 and 9.8 which appear to be new would have been useful to see as they would have informed the ISC review of the final report.

Pre-existing protocols/data collection were used for this pilot year, therefore the ethics approval obtained for this was assumed to apply to DRIVE.

General comment

Harmonized the terminology in Table 4.

**Please consider consistent use of either past or present tense.**

General comment

Although I am not going to mention this in every page, I would welcome, if possible, that results tables are reported following my first comment for objectives. The authors can decide to use either one-stage or two-stage pooling, as appropriate, or, as suggested, present both. For this pilot year, I would present a two stage pooling as primary, though, as I think was done here.

General comment

Vaccination status in the previous season was a field in the current year's record (yes/no/missing); those conducting the analysis did not have access to the full patient record. This is indeed described in Section 3.9.1. [Definition and alignment with generic protocols/SAPs to be checked carefully.]

General comment

Annexes are on SharePoint as separate documents. Adding them all into the report causes the Word document to crash. We will discuss this with the project leaders how to make sure you have access to all relevant documents: access to SharePoint or sending zipped folder with all documents - to be followed up.

Note: 2017/2018 should be 2017/2018.

The definition originated from the protocols. We agree it was confusing and now reformulated. See Section 3.9.1. (Definition and alignment with generic protocols/SAPs to be checked carefully.)

General comment

Please consider consistent use of either past or present tense.

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The definition originated from the protocols. We agree it was confusing and now reformulated. See Section 3.9.1. (Definition and alignment with generic protocols/SAPs to be checked carefully.)

General comment

Please consider consistent use of either past or present tense.
Since the ISC was not provided with the Annexes it may be that the information I would have liked to see was in Annex 9.8 (additional Tables). Anyway it would have been of interest to see how the percentage swabbed varied by week/month of study and also by study site, especially given the odd results for VE from time since vaccination. Which individual/sites vaccine contributed to the anomalous > 4 month result as this is clearly the outlier.

This remained unclear to us as well until we were able to visit the study sites. See Table 3 for clarification. [The Appendices were made available on SharePoint and also sent to ISC by email.]

<table>
<thead>
<tr>
<th>Question posed to ISC in P95 responses</th>
<th>Reviewer 1 comment 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>I feel it would be more consistent to apply the exclusion criteria centrally as this would ensure uniformity and would allow ad hoc analyses in the event of queries about findings. If the GDPR (not sure what that acronym refers to) specifies the minimum data set why would this exclude capturing the fields needed to apply the exclusion criteria as these are as necessary and any other field.</td>
<td></td>
</tr>
</tbody>
</table>

In the Annex there are site-level plots showing the nr of subjects (nr of cases, nr of controls) enrolled every week. Information on the % swabbed among all ILI subjects at the site was not collected. [The Appendices were made available on SharePoint and also sent to ISC by email.]

<table>
<thead>
<tr>
<th>Question posed to ISC in P95 responses</th>
<th>Reviewer 1 comment 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>I feel that a set of common confounders should be applied across all sites as pooling data surely assumes a common effect across sites?</td>
<td></td>
</tr>
</tbody>
</table>

GDPR: general data protection regulation (new EU privacy legislation, in place since spring 2018, requiring that we do not collect more data than needed). Agree, so we just argue why we need a bit more data than we will probably end up using.

<table>
<thead>
<tr>
<th>Suggestion for next season</th>
<th>Objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>If power is sufficient to analyze vaccine brands, and if the information is available, then it would be appropriate to identify vaccines by Brand (as opposed to A, B, C, etc). There is no public health reason not to disclose this information in a well-powered study.</td>
<td></td>
</tr>
</tbody>
</table>

From a statistical point of view, it doesn't matter as the VE estimates remain unchanged if you include/exclude a non-significant confounder. From a statistical point of view, it actually makes more sense to exclude non-significant confounders as you gain power. However, I felt it was more difficult to explain: (We have considered all potential confounders for all sites, however, the confounders eventually accounted for in the final regression model were different for the different study sites), and clearly caused a lot of confusion. What makes sense to the statistician doesn't make necessarily sense to the epidemiologist, but happy to change this as the epidemiologist is the end user of the statistical results (as the results are not really affected by this anyways).