DRIVE
Development of Robust and Innovative Vaccine Effectiveness

# WP7 deliverables' review
# D7.4"First seasonal final report of conducted studies"

| Page | Section | Original text | ISC Comment | WP7 reply |
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| 14 | Executive summary | Objectives<br>The primary objective was to pilot the DRIVE governance model for IVE studies as well as the DRIVE infrastructure, tools and procedures developed during the first year of the DRIVE project. | The objective is stated as piloting the governance structure (unclear of what: the study sites, the central analysis, the consortium?). | The objective is now consistenly formulated as follows: "The overaching 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." |
| 17 | Milestones | Table 2 | Only in the discussion the different notation of sampling by FISABIO becomes clear; this was rather confusing when reading it the first time. Suggest to either explain here, or just report start and end data for this study. | 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. |
| 18 | Background | For the DRIVE consortium, the influenza season 2017/18 was considered a pilot season. The main 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 objective of the study is cited a bit different throughout. The phrasing in the background (p18) seems most logical and correct. | The objective is now consistently formulated. See also reply to the first comments. |
| 18 | Background | Influenza is a major public health problem and vaccines are the cornerstone for preventing influenza. Vaccine effectiveness (VE) can vary every season due to differences in circulating strains and level of match between these circulating strains and the vaccine strains | VE can vary indeed, but there are more potential reasons for this than just the two options mentioned, please reformulate more open. | We reformulated as follows: Vaccine effectiveness (VE) can vary every season due to differences in e.g. circulating strains, and level of match between these circulating strains and the vaccine strains, the influenza vaccination coverage in the population and prior exposure to the antigen. |
| 19 | Objectives | Objectives… | Putting together such dissimilar results from a diversity of sites is a challenge. Thus, for this and future years, I would propose the following objectives: Overall VE, by outpatient and hospitalizations/ER visits, by age, and by brand (if possible). In regard to tables and figures, I would suggest: vaccine effectiveness (VE): (A) OVERALL: 1. Overall VE against outpatient visits 2. Overall VE for inpatients/hospitalizations/Emergency | The objective is now consistently formulated. See also reply to the first comments. |
| 19 | 2.1 Primary objectives | To pilot the DRIVE governance model for IVE studies as well as the DRIVE infrastructure, tools and procedures developed during the pilot year. | The objective is stated as piloting the governance structure (unclear of what: the study sites, the central analysis, the consortium?). | 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. |
| 19 | 2.1 Primary objectives | To estimate seasonal IVE against any medically attended (primary care/hospital) laboratory-confirmed influenza case,<br>• by vaccine brand<br>• by influenza vaccine type<br>• by any influenza vaccine | Should IVE by vaccine brand, vaccine type and any vaccine not be moved to the secondary objectives also? In particular if you use 'brand A', etc. Otherwise not very consistent to state that these results cannot be used, if it remains a primary objective. Furthermore, if some IVE results from the pilot season are presented such as in the executive summary, should there not be at least a short technical explanation why they should not be used (not just a formal argument that they were not generated to be used)? E.g. lack of standardization, risk of bias, limited sample size, heterogeneity, etc. could explain why such results cannot be considered valid estimates. | 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. |
| 20 | Time since vaccination | 2.3.2 Time since vaccination<br>To explore waning of the vaccine effect by estimating seasonal overall IVE by any influenza vaccine by time since vaccination using the combined TND data. | For this pilot study, althoug it is fine to go through the exercise to determine effectiveness by time since vaccination, I would prefer not to present the data, given sparsity of data, and the many heterogeneities, this might be ok for future years, depending on the data available. | 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. |
| 21 | 1.1 Overview study site characteristics | Apart from study design, the studies differed with respect to healthcare setting, catchment area, swabbing strategy of influenza-like illness (ILI) cases, ILI case definitions, age groups, and laboratory tests performed. An overview of the most important study site characteristics is given in Figure 1. | The information on the swabbing is still not fully clear. Where it is stated that swabbing is random: how is this random selection done? n/N? Same for systematic: how? According to fig. 3.1 La Rioja had both systematic and swabbing of all, what does this combination of methods mean? According to fig. 3.1, Valencia swabbed all, but according to fig. 7 (p44) Valencia did systematic swabbing, which one is correct? What is meant by swabbing method 'routine care'; all? | Check numbers: influenza all = A + B + unspecified. Co-infections are only counted to obtain the number of 'all' influenza cases. Footnote added. Case/control ratio: corrected |
| 22 | Catchment population | | For each site, please indicate if virological confirmation is available; it is not specified for La Rioja, for instance | Done. |
| 22 | 3.2 Catchment population | The catchment population of the included sites are described in more detail below and summarized in Table 3. | Furthermore, on p22, it is not clear how many sampling physicians there were, how and when selected, what % of all, etc. In fig. 7 La Rioja is not mentioned/included as a sampling site? | The definition originated from the protocols. We agree it was confusing and now reformulated. See Section 3.9.1. This will also be further discussed and reviewed within WP7 to align definition also for the protocols and SAP |
| 24 | Case definition | | For FISABIO, the case definition describes only ILI, but they also perform RT-PCR, so laboratory confirmation should also be used (particularly when we want to determine VE by strain), I assume this is just an oversight (or a misunderstanding by me). | Corrected. |
| 24 | Table 4 | | What is the difference between "Primary data collection" and "interview and medical records"? | The attrition diagrams now give the number of excluded subjects by 'mutually exclusive reasons for exclusion', subjects are only counted when not excluded before. See Figure 5. The attrition diagrams in Appendix 9.8 were modified as well. |

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| 28 | 3.7.1 Vaccinee definition | | 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. |
| 28 | 3.7 Exposure (vaccination) | **3.7.1 Vaccinee definition**<br>Scenario B: A child aged < 9 years who had not been fully vaccinated (see above) before the current season was considered as<br><br>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<br>2. **partially vaccinated**<br>1. during the first 14 days after the second record of injectable vaccination or the first record of LAIV vaccination during the current season<br>2. after the first record of injectable vaccination until >14 days have elapsed since the second record of vaccination during the current season<br>3. **unvaccinated** until the first vaccination record during the season<br>4. **unknown** if information on influenza vaccination is missing.<br><br>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. | 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. |
| 29 | Objectives | | 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. |
| 31 | Chronic conditions | | Compared to the classifications I presented above, the interpretation of VE for persons with vs. without chronic conditions in a study such as this is limited. Therefore, for future years, I would not make this classification a condition for study participation, but it is fine if the data are available. Some specific chronic conditions are, of course, of particular interest, but that is the subject of another discussion altogether.. | We feel it is inappropriate to change the objectives for this year after the analysis has been done. The analyses follow the approved generic protocols and SAPs (and as such, the DRIVE governance model). The primary objective of this season was to set-up and pilot the DRIVE system (see also replies [to the related comments]). We agree that the objectives should be re-discussed for next year. Although this discussion is not finalized yet, we agree that pooling across healthcare settings and age groups is problematic (but done nonetheless; otherwise there was not much to pilot this year). |
| 34 | 1.1 Statistical methods | 3.11.5 Sensitivity analyses<br><br>Exclusion of ILI/sever acute respiratory infection (SARI) patients if the respiratory specimen was taken ≥ 4 days after ILI onset | Typo page 34: sever should be severe. | This is an ongoing discussion. Happy to see you have a strong opinion about this. |
| 35 | 4 Ethics approval/informed consent | ISS Italy | It says "The ethics committee approval was only required to collect the minimum data set needed to fulful the I-MOVE protocol requests". Does this mean that the I-MOVE ethics approval was assumed to apply to DRIVE without additional approval as the recipient of the data is different to I-MOVE and for DRIVE may requre a different data extract. | See our previous reply. We will take this on board for next year. |
| 38 | Influenza epidemiology | | For future years, it would be interesting to use this system to determine, as a secondary objective, the predominace of flu viruses among the hospitalized elderly, if data were available.. | We agree that the sparsity of data is problematic. On the other hand, transparency is key and important to maintain trust to all stakeholders. I find this a dilemma, scientific rigour vs. transparency. For this pilot season (with main objectives of piloting the system, learning and discussing what to do next), we opt to analyse data and present results even if the data were limited. |
| 40 | 5.3 Descriptive analyses | Table 13 | Please clarify/check numbers. E.g. line 1: influenza all 1085, but 432 infl A+654 infl B=1086 infl all? Also unclear on what data ratio all cases/controls is calculated, cannot be reconstructed from table? | Yes, it is available for all sites, please see Table 6. |
| 40 | 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 to 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.<br>I was also suprised 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. |
| 42 | 5.3 Descriptive analyses | Figure 5 | Presumably, an excluded person can be excluded for more than one reason? E.g. second box: 372 excluded for missing vaccination data, 73 excluded for being partially vaccinated, which is more than the total number excluded already (while these categories seems to be mutually exclusive?). | How to deal with chronic conditions is indeed a topic for further exploration. A working group has been established, led by Ritva from THL. |

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| 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 is to look at the proportion of elderly hospitalized that have flu, that may be more challenging but could still be considered. |
| 44 | Figure 7 | | Nice figure, I would at least add a strata for people 65+ (provided 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 generated 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 >6m 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. Wording 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 | Tilme 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. Once 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, droping afterwards before reaching higher levels again at 4 months after vaccination. So bias or chance are the best alternative explanations.. | Exposure defintion: we will re-discuss this and maybe change the defintion 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, prespecification of these adjustments, so they are forced 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? | Annexes are on SharePoint as seperate 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. |
| 62 | 6. 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. |
| 62 | 6 Discussion | **Experiences and next steps: generic protocols**<br><br><u>Adherence to minimum data requirements</u><br><br>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 | Typo: 2017/2019 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 | General comment | | Please consider consistent use of either past or present tense. | Harmonized the terminology in Table 4. |
| 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 a 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. | 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 Appendix 9.1. Our apologies for not providing access to the Appendices. [The Appendices were made available on SharePoint and also sent to ISC by email.] |
| General comment | | | 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 regretable 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. |

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| Missing | | | 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 individuals/sites vaccine contributed to the anomalous > 4 month result as this is clearly the outlier. | This remained unclear to us as well untill 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.] |
| Question posed to ISC in P95 responses | Reviewer 1 comment 4 | | 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 excluison criteria as these are as necessary and any other field. | In the Annex there are site-level plots showing the nr of subjects (nr of cases, nr of controls) enrolled everyweek. 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.] |
| Question posed to ISC in P95 responses | Reviewer 1 comment 5 | | I feel that a set of common confounders should be applied across all sites as pooling data surely assumes a common effect across sites? | 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. |
| Suggestion for next season | Objectives | | If power is sufficient to analyze vaccine brands, and if the information is available, then it woud 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. | From a statistical point of view, it doesn't matter as the VE estimates remain +- unchanged if you include/exclude a non-signifcant 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). |