DRIVE
Development of Robust and Innovative Vaccine Effectiveness

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

Page	Section	Original text	EFPIA Comment	ISC feedback	WP7 response
1	Title	First seasonal final report of conducted studies – pooled analysis	In the title you should explicitly state 2017/2018 influenza season. it is not important that this is the first… but the season is. Also please either indicate the list of participating countries or alternatively indicate: Multicountry study to assess the brand specific seasonal vaccine effectives in Europe.	Disagree with removing first as this initial season has been run as a pilot rather than producing definitive results. It is OK to as 17/18 but first or pilot year should be indicated in the title	The original title was as described in the 'Description of Action'. We decided to deviate from this (and to inform IMI about this change) to stress the pilot nature of this study.
1	Title	First seasonal final report of conducted studies – pooled analysis	Please add that this concerns the 2017/2018 influenza season. The term "conducted studies" is not reflecting that the analysis relied on "existing" data. Is "final" referring to end of season VE? As there was no interim report suggest to remove. Suggested title: *Multicountry aggregated meta-analysis to assess the 2017/2018 seasonal influenza vaccine effectiveness in Europe by vaccine, seasonal and study design characteristics.*	Disagree - the title should indicate that this is a first analysis of the DRIVE project	We decided to change the title into 'Setting up brand-specific IVE in EU - results of the pilot season 2017/18'
8	3. responsible parties	N/A	It would be preferable to have a table to present the other contributors as well	Ignore - table of countries contributing data is given early on in the report.	See ISC response.
10	4. Executive summary		If available, I'd optimally present the proportion of A vs B and then indicate that the season was essentially a B-Yamagata lineage + H3N2 season …		The report, including the executive summary have been substantially revised and now focus on the pilot nature of the past year.
10	Results	The overall pooled IVE was 17% (95%CI 1-30). The best protection was observed against A(H1N1)pdm09 (51%, 95%CI 30-65), whereas no protection was found against A(H3N2). Sample size from TND studies allowed for pooled brand-specific estimates for two brands	Please add the estimate + CI		The report, including the executive summary have been substantially revised. No pooled IVE estimates are presented in the executive summary.
10	Results	[vaccine type redacted] had a higher adjusted pooled IVE (30%, 95%CI 11-44) than [vaccine type redacted] (17%, 95%CI -2-32); however, this difference is probably not significant and appeared to be driven mainly by the [vaccine type redacted]	From the CI it is unlikely that the difference are significant indeed. I'd prase it diffently. Based on the estiate + CI we cannot say that the [vaccine type redacted] perform better than the [vaccine type redacted] I'd phrase it down. Or even say that that no difference was observed. As mentioned the findings on [vaccine type redacted] vs [vaccine type redacted] are somehow interfered by the [vaccine type redacted] and thus I'd also present here the [vaccine type redacted] findings vs [vaccine type redacted] findings.		The report, including the executive summary have been substantially revised. No pooled IVE estimates are presented in the executive summary.
10	Results	Overall, Adjusted pooled estimates tended to decreased with age, from 27% (95%CI -9-51%) in children to 14% (95%CI -2-28) in those aged 65 years and older.	You cannot say objectively that the VE decreased, as the difference is not meaningful.	Agree - in fact neither VE estimate is statistically significant	The report, including the executive summary have been substantially revised. No pooled IVE estimates are presented in the executive summary.
10	Results	IVE was higher for people without chronic conditions and those vaccinated in the previous season, relative to those with one or more chronic conditions and those not vaccinated in the previous season, respectively	This sentence is not clear. Please rephrase. And slit it in two if needed.	It is perfectly clear to me -ignore	The report, including the executive summary have been substantially revised. No pooled IVE estimates are presented in the executive summary.
10	Conclusion	The observed low overall IVE may be partially due to the mismatch of the B and A(H3N2) components of the predominantly used [vaccine type redacted] vaccines.	In the document you would have to be more specific about the antigenic characteristics of H3N2 viruses.		The report, including the executive summary have been substantially revised and no longer provides interpretation of the pooled IVE estimates.
10	Conclusion	The results are in line with previously published IVE estimates from North America and Europe during the 2017/18 season although the point estimates in the DRIVE meta-analysis are somewhat lower.	Please report the finding from the US		The report, including the executive summary have been substantially revised and no longer provides interpretation of the pooled IVE estimates.
10	Results	*Comment related to the paragraph*	The results section should start with information on studies sample size; could you please add the total number of persons (cases controls) and % of flu + and proportions per age groups ; would be good to add also the proportion of vaccinees per vaccine type/brands (with % unknown brands)	I see no reason to change the format of the current descriptive analyses of the results to conform with what may be Sanofi Pasteur house style	The report, including the executive summary have been substantially revised. No pooled IVE estimates are presented in the executive summary.
10	Results	The overall pooled IVE was 17% (95%CI 1-30).	The vaccine effectiveness should be provided at least by setting and age groups with distinction between [vaccine type redacted] vaccines and [vaccine type redacted] vaccines (when heterogeneity is so large, it is meaningful to provide an overall estimate)	The results should follow the statistical analysis plan? This is a pilot study and detailed analyses by setting etc. were not part of the primary objectives of the pilot	The report, including the executive summary have been substantially revised. No pooled IVE estimates are presented in the executive summary.
10	4. Executive summary	*General comment on section*	Below comments on the Executive summary refer primarily to the elements and phrasing of what is contained the executive summary. Later comments on the full report may still affect what is presented in the executive summary.		NA
10	4. Executive summary - Background	The 2017/18 influenza season in Europe was characterized by co-circulation of influenza viruses of the B/Yamagata lineage and A(H3N2) subtype and, to a lesser degree, A(H1N1)pdm09 and B/Victoria.	Suggest to move the seasonal characteristics to the results section (this is not background) and more clearly describe there the mismatch for H3N2 and that B-Yam was predominated but not included in the [vaccine type redacted].		The report, including the executive summary have been substantially revised. Seasonal characteristics moved to results section. It has been reported which viruses were included in [vaccine type redacted] vs [vaccine type redacted] and the epidemiology in the different across has been described.
10	4. Executive summary - Background	The DRIVE consortium (Development of Robust and Innovative Vaccine Effectiveness) has been established to answer the updated European regulatory requirements which include annual brand-specific influenza vaccine effectiveness (IVE) estimates. This report presents the IVE estimates in the 2017/18 season as a result of the first pilot studies of the DRIVE consortium.	The executive summary is missing a clarification of the purpose of the "pilot". Suggest to describe in the background of piloting the pooled aggregated meta-analysis approach to estimate brand specific VE.	Agree - there was also the intent in the SAP to do a pooling on non-aggregated data from each study site which is at present missing	The report, including the executive summary have been substantially revised. No pooled IVE estimates are presented in the executive summary.
10	Methods	*General comment on section*	Please clarify that the analysis was based on existing data and that the local data collections were not aligned.		The report, including the executive summary have been substantially revised.
10	Results	The overall pooled IVE was 17% (95%CI 1-30). The best protection was observed against A(H1N1)pdm09 (51%, 95%CI 30-65), whereas no protection was found against A(H3N2).	Please add at least for overall VE that this is compared to no vaccination to remind the audience of how to interpret the VE estimate. Please add the estimate + CI for H3N2.		The report no longer contains interpretations of IVE estimates.
10	Results	[vaccine type redacted] vaccines had a higher adjusted pooled IVE (30%, 95%CI 11-44) than [vaccine type redacted] vaccines (17%, 95%CI -2-32); however, this difference is probably not significant	No head to head comparisons were done of [vaccine type redacted] vs [vaccine type redacted] - and "speculating" on potential difference (or absence thereof) is not appropriate.	Agree	The report, including the executive summary have been substantially revised. No pooled IVE estimates are presented in the executive summary.

10	Results	Overall, Adjusted pooled estimates tended to decreased with age, from 27% (95%CI -9-51%) in children to 14% (95%CI -2-28) in those aged 65 years and older.	You cannot say that the VE "decreased" as no trend analysis was performed (or direct comparison). It can only state that the point estimate was lower for one or the other.	Agree	The report, including the executive summary have been substantially revised. No pooled IVE estimates are presented in the executive summary.
10	Conclusion	The observed low overall IVE may be partially due to the mismatch of the B and A(H3N2) components of the predominantly used [vaccine type redacted] vaccines.	The low VE is *unlikely not* due to the strain epidemiogy and mismatch to the composition of the [vaccine type redacted] vaccines. Suggest to state: *is likely due to*	Don't understand this comment	The report, including the executive summary have been substantially revised. No pooled IVE estimates are presented in the executive summary.
10	Conclusion	The results are in line with previously published IVE estimates from North America and Europe during the 2017/18 season although the point estimates in the DRIVE meta-analysis are somewhat lower.	The strain epidemiology in the North America's was different than in Europe with H3N2 being the predominant strain and with [vaccine type redacted] vaccine 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 these 4 countries).		The report, including the executive summary have been substantially revised. No pooled IVE estimates are presented in the executive summary.
10	Results	*General comment on section*	Include presentation of: -the total number of persons (cases controls for TND, overall and cases for cohort, by age group) and proportion positive tests. - Add key descriptives and vaccine exposure by type/brand. - To present sample sizes and case numbers with the presented VE estimates.		The report, including the executive summary have been substantially revised. No pooled IVE estimates are presented in the executive summary.
10	Results	*General comment on section*	As per the general comment on the overall report - context should be provided as to what the vaccine effectiveness estimates represent: at least by age groups, setting and context of the circulating strain patterns.		The report, including the executive summary have been substantially revised. No pooled IVE estimates are presented in the executive summary.
11	5 Lay Summary	The overall effectiveness of all flu vaccines was 17% which can be considered lowsuboptimal. Possible reasons include that the circulating viruses were partially different than those included in the vaccines. The effectiveness against certain influenza subtypes was as high as 51%. The effectiveness also appeared higher in children and generally healthy people as opposed to older adults and those with chronic illnesses.	What is missing here is the pattern of virus circulation also that varied across countries. I'd add a paragraph on this; I'd add a table of the circulating strains compared to the one included in the commercialised vaccines or cross refer to the section 7XX later on. .		The report, including the lay summary have been substantially revised.
11	5 Lay Summary	The effectiveness against certain influenza subtypes was as high as 51%. The effectiveness also appeared higher in children and generally healthy people as opposed to older adults and those with chronic illnesses.	Be specific here. Against H1N1?		The report, including the lay summary have been substantially revised.
11	5 Lay Summary	The effectiveness also appeared higher in children and generally healthy people as opposed to older adults and those with chronic illnesses.	I am not 100% sure we can say this as the difference although ot formally tested is unlikely to be significant.		The report, including the lay summary have been substantially revised.
11	Lay summary	*Comment related to the paragraph*	Could you explicitely state who is the targeted audience: health care professionals? Or lay public?		The report, including the lay summary have been substantially revised.
11	Lay summary	Because the viruses that cause flu are continuously changing, vaccines against them need to be reformulated each year	Should we not briefly explain how it is managed (WHO recommendations on strains given to vaccine manufacturers)		The report, including the lay summary have been substantially revised.
11	Lay summary	Nowadays, there are several different flu vaccines ,	Suggestion to add: targeted different populations and with different components and manufacturing processes		The report, including the lay summary have been substantially revised.
11	Lay summary	Since this was only the first year of DRIVE, more emphasis was placed on laying the groundwork for the studies than trying to provide an effectiveness estimate for every single flu vaccine.	Suggestion to present it in a more positive way: e.g. The season 2017-2018 was considered as a pilot testing the feasibility to estimate brand-specific IVE using in a multi-country/setting platform. It is expected to increase the sample size and countries representation of the platform in the coming seasons to provide robust influenza vaccine effectiveness for all vaccine brands used in Europe.		The report, including the lay summary have been substantially revised.
11	Lay summary	The overall pooled IVE was 17% (95%CI 1-30).	In addition to previous comment about overall VE; Suggestion to translate VE 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		The report, including the lay summary have been substantially revised.
11	Lay summary	[vaccine type redacted] were 30% effective, but because of statistical limitations, it cannot be said for certain if some vaccine types or brands were better than others .	Suggestion to delete for lay public		The report, including the lay summary have been substantially revised.
11	Milestones	*Comment related to the table*	Suggestion to add calendar dates (e.g. October 2nd for Week 41)		Start and end of flu seasons are commonly reported in weeks
11	5 Lay Summary	Possible reasons include that the circulating viruses were partially different than those included in the vaccines.	Change the sentence: *Possible reasons include that the circulating viruses were partially different than those included in the vaccine or were not included in the vaccine.*		The report, including the lay summary have been substantially revised.
11	5 Lay Summary	The effectiveness against certain influenza subtypes was as high as 51%.	If we mention the highest VE observed we should also include the VE for the strain for which strain the lowest VE was observed.		The report, including the lay summary have been substantially revised.
11	Lay summary	Since this was only the first year of DRIVE, more emphasis was placed on laying the groundwork for the studies than trying to provide an effectiveness estimate for every single flu vaccine.	This is not clear - the lay public won't understand or appreciate what we mean with "groundwork for the studies". Suggest to rephrase along the lines: *In this 2017-2018 pilot analysis, the aim was primarily to test an approach in which vaccine effectiveness as determined in different EU countries are pooled to generate brand specific VE.*	Original was much clearer!	The report, including the lay summary have been substantially revised.
11	Lay summary	[vaccine type redacted] were 30% effective, but because of statistical limitations, it cannot be said for certain if some vaccine types or brands were better than others .	This ignores that the 30% was primarily driven by the VE in the [vaccine type redacted]. In addition, as per above the objective and the analysis were not designed for direct comparisons and to conclude which vaccine is better.		The report, including the lay summary have been substantially revised.
12	7 Background	Influenza is a major public health problem. Vaccines are the cornerstone of preventing influenza; however, there is some controversy about the impact of influenza vaccination programs.	I'd explain a little bit more, on the fact that the virus is evolving quite rapidly, that the forecast does not allow always to have a perfect match between the vaccines strains and the circulating strains…		Revised.
12	7.2 Influenza epidemiology in Europe, season 2017/18	According to ECDC and Flu News Europe , influenza viruses circulated at high levels between weeks 52/2017 and 12/2018. The majority of the detected influenza viruses were of type B,	Please provide %/Proportion here.		
12	Background	*Comment related to the paragraph*	May be good to develop further the background section with information about influenza and vaccination programms in the EU context (for EMA submission)	I don't think I was made aware that this "final" report when it is finalised will be the vehicle whereby manufacturers submit their annual reports to EMA. Is this correct?	Not for this year. I don't know about the next years and I suppose this needs further discussion
12	Background	This information is also of public health importance, and since many European public health institutions have extensive experience of IVE studies	Suggestion to say: This information is also of public health importance since monitoring vaccination programms are under PHIs mandates		This has been reported by region, if provided by the sites.
12	Background	Consequently, the possibility to study the IVE of full range of influenza vaccine brands used across Europe was limited.	As proposed in the lay summary, suggestion to present that in a more positive way.		Removed.
12	7 Background	however, there is some controversy about the impact of influenza vaccination programs.	Rather than stating that there is controversy around VE overall, suggest to state that generally there is stilll limited knowledge on VE by vaccine type and brand, seasonal and population characteristics.		Revised.
12	7 Background	Consequently, the possibility to study the IVE of full range of influenza vaccine brands used across Europe was limited.	The fact that we did not have the opportunity to measure VE accross all brands is not a "consequence" of our main objective for this pilot. It is related to the fact that we relied on existing data collection and the available sample size.	Agreed.	Removed.
12	7 Background	General comment on section	Please specify proportions for the circulating strains where available.		This has been reported by region, if provided by the sites.
13	7.2.2 Spain	In the Valencia region, the epidemic period was from week 45/2017 to week 20/2018, reaching its peak in the week 04/2018 with a total of 75 cases. The season was characterized by co-circulation of influenza A(H1N1)pdm09, A(H3N2) and B/Yamagata-lineage;	Any idea on the proportions? I'd put the last sentence just after this one. And also specify whether the remaining 5% where unknown of H1N1.		No additional information available to us.

13	7.2.2 Spain	Among all influenza A, 59.6% were A(H3), 14.7% A(H3N2), 10.8% A(H1N1)pdm09 and 15% A not subtyped.	H3N??? Typo?		Corrected.
13	7.2 Influenza epidemiology in EU, season 2017-18	*Comment related to the paragraph*	Could you please add references to the figures provided per countries. May be good to have a table summaring key national information using similar data accross countries; e.g. - % of flu cases per age groups/settings and circulated strains - vaccination coverage for targeted populations ...		References? One lesson learned described in the discussion is to be more specific on the information sites need to provide, so that texts can be standardized.
13	7.2.2 Spain	73% of patients developed pneumonia and 1,258 cases were admitted to the ICU	Seems huge; could you please explain and clarify		it is stated '73% patients with severe infection developed pneumonia'.
13	7.2.3 Italy	In Italy, during the 2017-18 season, the national sentinel surveillance system (InfluNet) reported a very high ILI incidence rate ,	Could you please add the figure and its reference		No additional information available to us.
13	7.2.2 Spain	In Spain, a total of … (etc).	Please clarify if this section applies to the whole of Spain or if specific to the study settings Rioja or Valencia.		Specified.
13	7.2.2 Spain	Of the 4,497 patients belonging to target groups for vaccination, 53% had not received the seasonal influenza vaccine.	On which data is this based?		Removed.
13	7.2.2 Spain	(22% of whom information was available)	What defined if information is available?		Removed.
14	8. Study objectives	*Comment related to the paragraph*	As mentionned previously, VE should be presented by setting and age groups as a first intention		The SAP was followed for the analyses. This will need to be addressed in next season's SAP.
14	8.2 Secondary Objectives	age group	There is a strong correlation between age groups and virus types/strains suggesting univariate analysis may be misleading		The SAP was followed for the analyses. This will need to be addressed in next season's SAP.
14	8.2 Secondary Objectives	age group (6 months – 14 years, 15 – 64 years and 65+ years)	Please add all along the report that "Children " is for 6 months -14 years (not so obvious especially in the executive and lay summaries)		Age of children specified everywhere.
14	8.2 Secondary Objectives	presence of any chronic condition	It is mainly relevant for 50-64 years		The SAP was followed for the analyses. This will need to be addressed in next season's SAP.
14	8.2 Secondary Objectives	To estimate seasonal IVE by any influenza vaccine, stratified by type of outcome :	Suggestion to say: by virus type		The description in the report is following the terminology in the protocol and SAP. This might be revisited next year
14	8.2 Secondary Objectives	To estimate seasonal overall IVE by any influenza vaccine, stratified by study characteristics :	Suggestion to say: by health care setting (methods should be added: TND/cohort)		The SAP was followed for the analyses. This will need to be addressed in next season's SAP.
14	8.2 Secondary Objectives	• presence of any chronic condition (yes vs. no, see also Section 5.3.3)	Section 5.3.3. does not exist		Revised.
14	8.2 Secondary Objectives	To estimate seasonal IVE by any influenza vaccine, stratified by type of outcome:	As mentioned previously this is better stated as "*by virus type*". Type of outcome would usually suggest analysis for example by lab confirmed ILI or symptomatic ILI.		see comment 68
14	8.2 Secondary Objectives	To estimate seasonal overall IVE by any influenza vaccine, stratified by study characteristics :	What about the different designs: TND and cohort?		The SAP was followed for the analyses. This will need to be addressed in next season's SAP.
15	9.1 Study design	For the exploratory objectives, only TND data was used.	I understand for the first part but why for the second sub-objective?		Because only the TND studies provided individual-level data, only aggregate data was received from the cohort site.
15	9.2 Study setting and study period	*Comment related to the paragraph*	The ratio LCI/ILI should be added per countries		Added to Table 13
15	8.3 Exploratory analysis	For this exploratory objective, we estimated seasonal overall IVE by any influenza vaccine.	If the purpose of this pilot is to see whether any differences are observed between pooled aggregated and individual level data to estimate brand specific VE, why is the exploratory analysis only performed for overall VE?	What does the SAP say?	The SAP was followed for the exploratory analyses.
15	8.3 Exploratory analysis	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.	Why was only the TND data used for this analysis?		Because only the TND studies provided individual-level data, only aggregate data was received from the cohort site.
15	9.1 Study design	*General comment on section*	For the report to be read independently there should somewhere be a brief description of the TND/cohort approach - in the body text or the appendix.		The suggestion is unclear to us, sorry.
15	9.2 Study setting and study period	*General comment on section*	It is not explicitly clear from most of these descriptions whether it concerned sampling per protocol or at the health care professional descretion. Which selection of subjects were applicable?		This has been detailed in Table 3.
16	9.2.1 Austria	Within this sentinel network, nasopharyngeal swabs are collected from selected patients	please explain		The information on the catchment population and swabbing is given in Section 3.2
16	9.2.3 Italy	For virological surveillance, nasopharyngeal swab are collected from a sample of ILI cases	please explain		The information on the catchment population and swabbing is given in Section 3.2
16	9.2.4 Spain Rioja	The cycEVA study is the Spanish component of I-MOVE.	Not sure if relevant to the current report and whether this would be clear to any reader what I-MOVE is without further explanation.		The report is meant for DRIVE internal use and EMA. We think no additional explanation is needed for our intended audience.
16	9.2.4 Spain Valencia	For the 2017-2018 influenza season FISABIO enlarged the time window of the VAHNSI study from 1st of September to 30th of June (4 months longer than currently) to capture, in the period 1st September to 30th June (10 consecutive months) admissions with laboratory confirmed (RT-PCR), respiratory syncytial virus and their seasonality with confidence.	The current analysis is for the 2016-17 season. Is this relevant? Or is this an error of the year? If the latter how does this match with the period in table 2?		The period of data collection is different from the period of data used for analysis (see Fig. 2).
17	9.2.2. Finland	*General comment on section*	It is not clear for Finland what is the policy for swabbing. Please add the description.		Added to Table 3.
18	9.5.2 Laboratory confirmation	Table (last column)	What are you referring to when you mention strain?		Availability of information on strain. Clarified.
18	9.5 Outcome	The only exception was the Finnish database study where the outcome of interest was laboratory-confirmed influenza irrespective of the clinical presentation.	Sentence repeated twice ; to be deleted		Removed.
19	9.6.1 Inclusion and exclusion criteria in individual TND studies	Inclusion and exclusion criteria from the core TND protocol (D7.1) are listed here.	The core protocols were not applied in the current season. Suggest to rephrase/clarify.	Agree that it wasn't always clear what was intended when the core protocols are implmented in year 2 and what was actually applied in this first year.	A paragraph explaining this has been added to 9.1 study design
19	9.6.2. Inclusion and exclusion criteria in individual cohort studies	-: No information provided in protocol and/or dataset.	Suggest to aim complete the table with the input from the local study teams.		
20	9.7.1 Vaccinee definition	Note 2: The partially vaccinated subjects were excluded from the primary analyses; their significance was assessed through sensitivity analyses (Section 8.2.4).	This analysis was not performed. Paragraph 8.2.4 is an incorrect reference?	Table 16 does include an analysis with partially vaccinated either considered vaccinated or unvaccinated so don't understand this comment.	This analysis has now been performed and added to the report and annex.
21	9.7.2 Target group fro vaccination	*Comment related to the Table 7*	May be good to present that in the other way: Targeted populations -> Austria >Finland>….. Children Adults Elderly Prenancy Health care professionnal ...		There is overlap between the groups (e.g. different definitions of elderly), so kept as it was.

22	9.7.2 Target group for vaccination	Table 8. Availability of influenza vaccine types and brand for each study site, 2017/18 season. (Please also see DRIVE D3.3, Chapters 4.2.2–4.2.4 where vaccine availability and recommendations by specific type of vaccine are summarized.)	[vaccine brand redacted] (1.7%)? (Italy) That's a surprising finding as we do not have any [vaccine type redacted] commercialised anymore? Are you sure about this finding?		This was an error in data entry. This has been removed from the analysis.
22	9.7.2 Target group fro vaccination	*Comment related to the Table 8*	Vaccine types/brands should be presented by age groups, targeted populations and countries. There is a lot of unknown brands in Austria, it should be highlighted and discussed for improvements next season		Vaccine type recommendations have been added in Table 9. The brands have been anonymized, the more information that we provide, the easier re-identification will be.
22	9.7.2 Target group for vaccination	*Comment related to the Table 8*	Information on the licensed age indication for the individual brands should be added as well as a description of specific recommendations to use certain vaccine types/brands for certain populations.		Vaccine type recommendations have been added in Table 9.
24	9.8.4 Vaccination in the previous season	Influenza vaccination in the previous season was categorized as yes/no.	It does not account for potential previous flu infections.		The SAP was followed for the analyses. This will need to be addressed in next season's SAP. Also, this may be extremely difficult to account for.
24	9.9 Data quality	*Comment related to the paragraph*	Is there any data management report available for the pilot season?	Agree, this is important given that the first year is a pilot and no information was provded on the quality and completeness of the information received.	A data management plan has been added as an annex.
24	9.10 Sample size description	*General comment on section*	Expand on the parameters that determine sample size and when an analysis is undertaken or not.		For the brand-specific estimates, we only provided the estimates for brands that yielded 'reasonable confidence intervals'. For the other brands, the estimates could simply not be calculated (infinite estimates) or extremely wide CIs were obtained. From the extensive sample size calculations we performed, it was concluded that setting a-priori thresholds for calculating IVE based on sample size is (although technically possible as demonstrated) is not meaningful from an epidemiological point of view as the between-study variance (which strongly dominates the sample size requirements) is impossible to know a-priori.
25	9.11.2 Measure of effect	*Comment related to the paragraph*	Please give details on the full adjusted model (coding of variables and coefficients) per site	Agree, there was no information on how this was done.	More details on the covariate adjustment is given in section 5.4.1; 'differences in covariate adjustment'
25	9.11.1 Descriptive analyses	*General comment on section*	Descriptives 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 analysis to be able to better understand the results.		We agree that having a good notion of who is using which brand is important. Therefore, we are setting up a survey to investigate whether certain vaccine brands are preferentially used (or recommeded for use) with specific subpopulations.
25	9.11.2 Measure of effect	*For the primary and secondary objectives, the effect measures for 2-stage pooling were:* • *Study site-specific crude IVE estimates and their 95% confidence intervals (CIs).* • *Study site-specific confounder adjusted IVE estimates and their 95% CIs.*	Is this correct: "study site specifc"? For the primary and secondary analysis of the current report it is not the "pooled" crude and confounder adjusted IVE which is relevant for the primary and secondary analysis?		The explanation is correct. The effect measures used to pool together are the site-specific crude (and adjusted) IVE estimates. This has been stated more clearly in the methods.
25	9.11.2 Measure of effect	*General comment on section*	Why were hospital and GP setting combined in the meta analysis?		The SAP was followed for the analyses.
26	9.11.3 Meta-analysis	An indication for the heterogeneity among estimates from different study sites was obtained by calculating I2.	I2 does not tell us how much the effect size varies. I2 tells us about the extent of inconsistency of findings across studies in the meta-analysis, and reflects the extent to which confidence intervals from the different studies overlap with each other. Suggest to present also the 95% CI of the I2.		This is a very good suggestion. We decided to not perform additional analysis using the pilot data and rather focus on the preparation of the data collection for next year. We will take this on board for the SAP for next season. Thanks!
26	9.11.4 Stratified analysis and Multivariate analysis	*General comment on section*	It seems inappropriate to perform any analysis in the full population age group, when the vaccine indication/use is restricted to specific age groups (i.e. [vaccine type redacted] and [vaccine type redacted]) and the exposed cases/controls are of a different age than the unexposed group. This would give a different baseline risk of flu in the unexposed and exposed. Why not restrict the analysis to the appropriate age group aligned with the age indication as per the label? Please see also comments on available sample size for the by brand and age analysis.	Agree, but I assume this was more a test of the processes rather than an attempt to get definitive results. The first year report seems to focus on the latter rather than emphasizing evaluaton of the processes that will hopefully result in definitive results in the second year.	The SAP was followed for the analyses. This will need to be addressed in next season's SAP.
26	9.11.4 Stratified analysis and Multivariate analysis	For every secondary objective, a stratified meta-analysis was performed, following the same methodology described in section 10.14.3.	10.14.3 does not exist.		Revised.
26	9.11.4 Stratified analysis and Multivariate analysis	Analysis was adjusted for the following set of confounders:	Is analysis in this sentence the meta-analysis? Please clarify that the meta-analysis has been adjusted for this set of confounders combined and that only the site specific estimates are adjusted for the (more limited) set of confounders presented in table 14 (on a different note - why is table 14 not part of the methods?)		In Step 1, site-specific analyses. This is presented (now as Figure 8) as part fo the results because it is driven by the data.
26	9.11.5 Exploratory analyses	To explore waning of the vaccine effect, IVE was modelled as a smooth function of time since vaccination, avoiding the need to create time categories.	Is this analysis still pending?	Agree, confusing as report says final and that certain analyses were done whereas they didn't appear in the report.	The analysis has now been performed and has been added to the report.
26	9.11.6 Sensitivity analysis	No sensitivity analysis for outlying and influential estimates was conducted, since none were identified.	The results should be presented.		Results of sensitivity analyses have been added to the report and annex.
28	11.1 Descriptive analyses	*Comment related to the Table 12*	It shows that there is a strong interaction between age and virus type ; as mentioned above, this should be accounted for in the analysis. May be good to add the vaccination coverage rates in the cases and controls, and the rate of flu+.		The SAP was followed for the analyses.
28	11 Results	General comment on section	The values of the parameter that determine the min sample size to detect sign VE>0 and presentation the minimally detectable vaccine effectiveness for each analysis, including the stratified analysis, are missing from the results presentation. Sample sizes available for each analysis should be embedded in the report. NOTE 16NOV2018 (Margarita Riera, P95): *Comment updated by the company as follows. The revised comment has not been reviewed by the ISC.* The values of the parameter that determine the min sample size to detect sign VE>0 and presentation the minimally detectable vaccine effectiveness for each analysis, including the stratified analysis, are missing from the results presentation. Sample sizes available for each analysis should be embedded in the report. Similarly, for example it is not clear why in the Rioja 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 156) is a good one and will be considered for the SAP for next year. For this year, we will not do additional analyses as our focus is on the data collection and preparations for next season.
28	11 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.	Agree, no conclusions can be drawn about such differences from this underpowered pilot analysis.	It was indeed stated that CIs with very wide confidence intervals would not be reported. However, no threshold was defined. Also, we think it is very helpful to present and discuss results, discuss limitations and see how we can improve the studies for next season.

28	11.1 Descriptive analyses	Tables 13	As per earlier comments: add descriptives for the vaccine recipients of the different vaccine types/brands and non-vaccinated (by cases and controls), as well as for the stratified analysis		See earlier comment.
28	11.1 Descriptive analyses	*General comment on section*	Overall vaccine coverage and by vaccine types is missing.		Information on vaccine coverage was not collected as part of the study.
30	11.2 Results of primary objective	*Comment related to the paragraph*	VE is more affected by age/strains than vaccine type; this is not well reflected in the analysis; the analysis should at least present data per each age subcategory		The SAP was followed for the analyses.
30	11.2 Results of primary objective	*Comment related to the Table 14*	As mentionned previously, details on final models for adjustment should be provided per site		This information is added in section 5.4.1
30	11.2 Results of primary objective	*Comment related to the paragraph*	As per earlier comments: VE is more affected by age/strains than vaccine type ; this is not well reflected in the analysis. The primary objective is brand specific VE, but it was previously commented that this should be additional stratified by age as the VE is highly dependent on age.		See earlier comment.
30	11.2 Results of primary objective	*Comment related to the paragraph*	Though confidence intervals are wide - the estimate for the [vaccine type redacted] were not as expected. Was there confounding by indication which may have affected the analysis? i.e. more frail elderly received [vaccine brand redacted]? NOTE 16NOV2018 (Margarita Riera, P95): Comment updated by company. This revised version of the comment has not been reviewed by the ISC. *The estimate for the [vaccine type redacted] are low - though interpretation is hampered by wide CIs and appears strongly affected by the estimate in the hospital setting of the Valencia region where overall VE was even negative. Presenting baseline descriptives by brand would help to understand if confounding by indication which may have affected the analysis. (i.e. more frail elderly received [vaccine brand redacted]).*		No more interpretation of the results in the report.
31	11.2 Results of primary objective	*Comment related to all forest plots*	Please include sample size for each estimate When heterogeneity is large (e.g. more than 50%), it is meaningful to provide an overall estimate? The scale is odd; why is it not symetrical around 0?		It is not symmetrical because whilst VE cannot exceed 100%, it can take on any negative value. It is symmetrical at the log-scale, which was used to do the analyses, and then transformed to the VE scale
31	11.2.1 IVE by any vaccine and by vaccine brand	The forest plot and pooled adjusted estimates	Given that estimates are not very different after adjustment, what is the added value of adjusting (looking at the appendix)		The SAP was followed for the analyses.
31	11.2.1 IVE by any vaccine and by vaccine brand	*Figure 2*	The hospitals and GP settings should not be combined.		The SAP was followed for the analyses.
31	11.2.1 IVE by any vaccine and by vaccine brand	*Figure 2*	Please add the sample size numbers		It is unclear what is meant with 'sample size numbers' as we clearly illustrated that sample size calculations for pooled analysis are difficult as they depend on the between-study variance (which is difficult to know a-priori). The suggestion to retrospectivley calculate 'min det. VE' (see comment 156) is a good one and will be considered for the SAP for next year. For this year, we will not do additional analyses as our focus is on the data collection and preparations for next season.
31	11.2.1 IVE by any vaccine and by vaccine brand	Due to small numbers, brand-specific pooled analyses were only performed for [vaccine brand redacted] and [vaccine brand redacted], the remaining brands were combined as 'other'. In addition, we could estimate IVE for [vaccine brand redacted] and [vaccine brand redacted] in the Finnish cohort study. [vaccine brand redacted] had an adjusted IVE against any influenza of 32% (95% CI, 13 – 48), while for [vaccine brand redacted] it was 9% (-7 – 24).	These needs to be clarification on why certain analysis were performed and others where not based on sample size. Also for the age by brand analysis - it is not clear. For example one would expect that this should be possible for [vaccine type redacted] and [vaccine brand redacted] since the study population should essentially be the same in the overall and the specific age groups because these vaccines are only used or indicated for specific age groups. (unless there is substantial off label use which seems unlikely).		We followed the SAP for the analysis. Regarding brand-specific VE, we calcualated the VE for several brands. However, for many brands the VE could not be estimated due to the very small sample size or the CI's were extremely wide (> 100%). The discussion on sample size and when to report results is a good one, and we suggest to discuss this again and ask the opinion of the ISC.
32	11.2.2 IVE by vaccine antigen ([vaccine type redacted])	*Figure 3*	[vaccine type redacted] results represent results for only a children population of 6m to <3 years. The 2 results are correlated.		No more interpretation of the results in the report.
35	11.2.5 IVE by vaccine type	*Comment related to the Figure 6*	There is probably a prescription bias: [vaccine type redacted] are more prescribed for older people (e.g.70+ in Valencia) which are more affected by H3N2		No more interpretation of the results in the report.
35	11.2.5 IVE by vaccine type ([vaccine type redacted])	*Figure 6*	The [vaccine type redacted] VE estimates are the same as obtained for [vaccine brand redacted] as there is only 1 [vaccine type redacted] leading to overlap.		No more interpretation of the results in the report.
36	11.3.1 IVE by age group	*Comment related to the Figure 7*	The low heterogeneity between the sites estimates here confirms the previous comment: estimates should always be provided per age groups		The SAP was followed for the analyses.
36	11.3.1 IVE by age group	*Comment related to the Figure 7*	It is unclear how the heterogeneity can be 0 for some of the presented analysis. Heterogeneity is purely statistical and might lead to the wrong impression that the studies are comparable when in effect some studies are very different in terms of populaion and circulating strains.		Agree that the I2-statistic is a statistical measure of heterogeneity, that should be complemented with a epidemiological discussion on differences between studies.
39	11.3.4 IVE by influenza type and subtype	*Comment related to the Figure 10*	Suggestion to remove Influenza A analysis (not appropriate to group H1N1 and H3N2 due to huge heterogeneity). May be good to add here the circulated strains & sample size per strains		The analysis was specified in the SAP and the results are reported. We agree that presenting the results by type is less informative in case of substantial strain heterogeneity
39	11.3.4 IVE by influenza type and subtype	*Figure 10*	For the B-yamagata strain, were all vaccines included in the analysis? Or only [vaccine type redacted]?		All vaccines, as per SAP.
40	11.4 Exploratory objectives	*Comment related to the paragraph*	Is it appropriate for this pilot season?		The SAP was followed for the analyses.
40	11.4 Exploratory objectives	*Comment related to the paragraph*	Is it appropriate for this pilot season?		The SAP was followed for the analyses.
42	12 Discussion	Additionally, IVE estimate was available for [vaccine brand redacted] (32%, 95%CI, 13–48), notably only used in children aged 2 years in Finland. The low sample size did not allow for any stratification by virus type or age groups within each brand.	Could it be possible to do the analysis by Virus type + Vaccine Antigen ([vaccine types redacted]), vaccine antigen ([vaccine types redacted]) and by Valency ([vaccine types redacted])		The SAP was followed for the analyses.
42	12. Discussion	[vaccine type redacted] had a higher pooled IVE (30%, 95%CI 11-44) than [vaccine type redacted] (17%, 95%CI -2-32). However, this difference is probably not statistically significant, and seemed to be driven by the [vaccine type redacted], which also provided the biggest contribution to the sample size for [vaccine type redacted]. When excluding the Finnish data from the analysis, the difference between IVE for [vaccine type redacted] and [vaccine type redacted] disappeared (16%, 95%CI -48–52 vs. 18%, 95%CI -15–41).	This statement is also valid for other analysis where you analysed per vaccine without accounting for age.		No more interpretation of the results in the report.
42	12. Discussion	The low sample size did not allow for any stratification by virus type or age groups within each brand	This is a MUST and it affects the credibility of the results (mainly for age)		The SAP was followed for the analyses.

42	12. Discussion	Finally, pooled estimates were higher in primary care settings (28%, 95%CI 3–47%) than in hospital settings (-6%, 95%CI –33–15).	This is very important and these estimates should not be pooled.		The SAP was followed for the analyses.
42	12 Discussion		Please see comments on executive summary as well.		
42	12 Discussion	The low sample size did not allow for any stratification by virus type or age groups within each brand.	Please see earlier comment above. It is not clear why certain analysis were performed and others were not possible to conduct. Specifically for [vaccine brand redacted] and [vaccine type redacted] it would be expected to be able to do by brand and by age.		The SAP was followed for the analyses. This was written when we knew sample size would be low so these analyses were not foreseen.
42	12. Discussion	[vaccine type redacted] had a higher pooled IVE (30%, 95%CI 11-44) than [vaccine type redacted] (17%, 95%CI -2-32). However, this difference is probably not statistically significant, and seemed to be driven by the [vaccine type redacted], which also provided the biggest contribution to the sample size for [vaccine type redacted]. When excluding the Finnish data from the analysis, the difference between IVE for [vaccine type redacted] and [vaccine type redacted] disappeared (16%, 95%CI -48–52 vs. 18%, 95%CI -15–41).	Excluding Finland is essentially excluding a large child population. The fact that the difference appears to go away could also be due to the exclusion of children who show to have a higher VE. This relates also the general comment on the corrolation between estimates.		No more interpretation of the results in the report.
42	12. Discussion	Finally, pooled estimates were higher in primary care settings (28%, 95%CI 3–47%) than in hospital settings (-6%, 95%CI –33–15).	Is it valid to pool estimates from these two completely different populations?		The SAP was followed for the analyses.
42	12. Discussion	Finally, pooled estimates were higher in primary care settings (28%, 95%CI 3–47%) than in hospital settings (-6%, 95%CI –33–15).	What explains that the estimates observed for the hospital based VE are so much lower. Is this generally the case and why? Please add some brief commentary on this.		No more interpretation of the results in the report.
43	12 Discussion	However, the exclusion of subjects swabbed more than 4 days after symptom onset had an important effect on the IVE estimate for [vaccine brand redacted], increasing from 1% (95%CI -29–24) to 13% (95%CI -22–37), although remaining non-significant. [vaccine brand redacted] was mostly used in Spain-Valencia, and the restriction in the onset to swab period resulted in the exclusion of an important number of subjects, particularly among vaccinated controls.	Tend to slightly increase the IVE estimate. What is suggests is you might have case misclassification (false negative), and the results is even less conclusion.		No more interpretation of the results in the report.
43	Strengths and weaknesses of the study	In Austria, those who received antiviral treatment prior to swabbing were excluded	This could have induce a significant selection bias. In the future this should be avoided and antiviral use should be considered instead.		Harmonized protocols will be used in the next season.
43	12. Discussion	stratification by both brand and age, or brand and setting was not possible	This is a prerequisite to get credible results: As a conclusion, the order of priority for the presentation of the results should be: 1. setting (preventing one hospitalisation can not be compared with preventing one GO visit) 2. age (correlated to strains and immune response) 3. vaccine type/brand Here below a proposed presentation for VE results For each Vaccine type/brand (stratified by site) Setting 1 VE Setting 2 VE all setting VE (if low heterogeneity accross setting) Age 1 VE Age 2 VE Age 3 VE all age VE (if low heterogeneity accross age) most of the vaccines target only one or two age groups	Is this flexibility allowed given the analysis was supposed to be conducted according to the agreed SAP?	The SAP was followed for the analyses. Next year there will be more sample size, and it will be important to clarify for next years' SAP which analyses are necessary to obtain meaningful results
43	Strength and Weaknesses	As with all influenza vaccine studies, some differences in effectiveness estimates between sites may not be due to methodology but due to differences in influenza epidemiology, evolution of the circulating strains during the epidemic, mismatch due to egg adaptation, and differences in the target populations and healthcare infrastructure, as well as access to and practices in health care to obtain samples.	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 in a timely manner. 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-estimate outcomes are dependent on the actual circumstances of the mentioned factors during the study period and the study sites. Comparing VE-values of different vaccine types in different study centres with different circumstances cannot well discriminate between outcomes differences due to specific study circumstances or to different vaccine-type performances. Since VE values do not correspond 1:1 to vaccine characteristics, but are also depedent on the actual epidemiological circumstances, relevant scientific nuances are required for a proper interpretation of VE study outcomes. However, such nuances are difficult to address in public communications about the study results in a transparent way. Reported low VE estimates may suggest to the public that the vaccines are so poor performing, that it is not "worth the bother" to vaccinate. However, because of the annual average large numbers of people affected by influenza infections on population level, vaccination with vaccines with relatively low VE	Agree, this comment well reflects the problem with the report purporting to provide interpretable results which are then commented on when in fact the paucity of data and its heterogeneity precluded this.	The discussion has been substantially revised and no longer provides any interpretation of pooled IVE estimates.
43	12 Discussion	However, the exclusion of subjects swabbed more than 4 days after symptom onset had an important effect on the IVE estimate for [vaccine brand redacted], increasing from 1% (95%CI -29–24) to 13% (95%CI -22–37), although remaining non-significant. [vaccine brand redacted] was mostly used in Spain-Valencia, and the restriction in the onset to swab period resulted in the exclusion of an important number of subjects, particularly among vaccinated controls.	For Italy, the period to allow swabbing is not provided in the protocol. Is there a fixed period? Could this have to do with the findings?		No more interpretation of the results in the report.
43	12. Discussion	stratification by both brand and age, or brand and setting was not possible	As per previous comments - results are highly correlated. VE should be presented by age group, setting and strain pattern as a first intention to avoid misinterpretation of what the VE estimates represent.		The SAP was followed for the analyses.
44	Meaning of the study	The overall pooled IVE for the 2017/18 season was low. This is probably related to the mismatch for A(H3N2) and B/Victoria components (for which almost half of the isolates identified this season in Europe were from a different clade than those included in the vaccines), as well as the predominance of B/Yamagata	Please be explicit about the clades		No more interpretation of the results in the report.

44	Unanswered questions and future research	We successfully estimated pooled IVE across 5 different sites, obtaining comparable results to other studies conducted in Europe and the US. Despite limited harmonization in the applied protocols, we could explore the effect of several confounders and produce adjusted IVE estimates. However, the	This is contradictory with the above where you mention that the estimate found were systematically lower for DRIVE than US and ECDC, but of similar trned than the UK		No more interpretation of the results in the report.
44	12. Discussion	*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.
44	12. Discussion	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(H1N1)pdm09 and lowest for A(H3N2), relatively higher IVE among children). The UK have also recently published their preliminary results for this season, with similar estimates to the ones we report, with overall IVE of 15% (95% CI -6.3–32) in primary care settings	Please add the 2 references (5 and 6) in the related section (14)		No more interpretation of the results in the report.
44	12. Discussion	*Comment related to the paragraph "future research"*	Suggestion to provide information regarding the selected sites through the tender and thus provide expectations regarding vaccine brands covered for the next season ; should be of importance for EMA. Should be added also what is planned to be developped as study tools (from other WP)	Agree - this report didn't give an indication of what could be expected for the second year.	The discussion has been substantially revised and contains the sites for next year and how the lessons learnt will shape the next season.
44	Unanswered questions and future research	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 substantially revised.
44	Unanswered questions and future research	Despite limited harmonization in the applied protocols, we could explore the effect of several confounders and produce adjusted IVE estimates. However, the precision of the IVE estimates was not optimal due to limited sample size.	There was no real exploration of confounding factors.		The discussion has been substantially revised.
44	Unanswered questions and future research	*Meaning of the study*	The aspect of age is not taken into consideration.		The discussion has been substantially revised.
45	Conclusion	Brand-specific estimates of IVE were obtained for four brands: pooled estimates for two brands for which there was enough sample size,	What defined enough sample size?		The conclusion has been substantially revised.
43/44	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(H1N1)pdm09 and lowest for A(H3N2), relatively higher IVE among children).	I'd report the estimate per se.		The discussion has been substantially revised.
NA	General key comment		Throughout the report the presented VE estimates should be better contextualized. There is a lot of correlation between the calculated VE estimates. Presenting stratified analysis by country, type of vaccine or brand when effectively they only represent a certain age group, a certain valency or strain distribution or setting can lead to mis- or overinterpretation or duplication (for example – estimates for Valencia are essentially repeated in the stratified analysis and hospital setting). Presenting brand-specific VE independent of their age indication/or use is not appropriate - VE simply differs by age groups.	Agree.	The results and discussion sections have been substantially revised and no longer provide any interpretation of pooled IVE estimates.
NA	General key comment		The weaknesses and how they affect the observations are underlighted.		No more interpretation of the results in the report.
NA	General key comment		Throughout the report there is phrasing that suggests that head to head comparisons where made, for example "relative to", "compared to", "vs" etc.. Please rephrase to reflect that these are stratified analysis, each against no vaccination.		No more interpretation of the results in the report.
NA	General key comment		The parameter values that determine the min sample size to detect sign VE>0 and presentation the minimally detectable vaccine effectiveness for each analysis, including the stratified analysis, should be presented. There also needs to be clarification on why certain analysis were performed and others where not based on sample size.		It is an interesting idea to perform sample size calculations retrospectively. However, this was not part of the SAP and would require an amendment to the SAP. Due to the pilot nature of this analysis, we decided to not do additional analysis for this year. We will take this suggestion into consideration when developing the SAP for next season.
Na	General key comment		Descriptives should be added on the vaccine recipients - by vaccine type and brand for cases and controls.		See earlier comment.