DRIVE D7.6 Brand-specific influenza vaccine effectiveness in Europe season 2018/19
ISC comments – reply grid
04/07/2019

No	ISC Comment	WP7 reply
1	In the future, as possible, I would favor larger studies performed in regions with universal vaccination recommendations for the age groups of interest (including the elderly) , and obtaining data on multiple risk factors for influenza so proper adjustments can be made. I can send lists of covariates I have used, of which a few very important ones can be selected, if it is of interest.	In Europe, universal vaccination in non-elderly age groups is only in place for children in certain age groups in Finland and the UK (and Austria but vaccine coverage is very low, around 8%). There is no universal vaccination in adults 18-64y. We would be glad to receive your list of covariates.
2	For studies in the elderly, I would favor a preference for considering hospitalized outcomes, less exposed to health seeking behavior bias.	Thanks for this suggestion, we will discuss this within WP7.
3	I hope we can perform comparative effectiveness in areas that provide more than one vaccine type, including new vaccines, as possible	Perhaps once we have sufficient sample size, though we will have to take confounding by indication by vaccine TYPE into account, as risk of influenza complications sometimes plays in role in deciding which vaccine type is recommended.
4	I believe the teams have performed an excellent work!	Thank you!
5	**Table 3: Confirmation of vaccination status:** In the table on page 28, it is indicated that the confirmation of vaccination status for the BIVE (Italy) test negative project is (only?) the physician interview: If true, I hope the validity of this vaccination confirmation strategy can be tested in a random sample of participants, to inform future research..In any	GPs were contacted to obtain information on vaccination status of hospitalized patients who reported being vaccinated (or being unsure of vaccination status). The GP then provided information on vaccine adminsitration and vaccine brand from medical records.

	case, I would not favor studies without verification by vaccination registry or similar documentation	Added additional information in the table: Primary care physician interview "for patients who reported being vaccinated (or unsure), the physician consulted medical records"
6	**Case definition:** In general, I consider that not testing some suspected cases is not a serious concern in a test negative study, and an improved selection of suspected cases saves resources and simplifies the design. Thus, regarding SARI Case confirmation (page 34): I wonder if the positive predictive value of simpler (and cost saving) algorithms could be tested for future consideration: One example could be to use hospitalized cases with cough + fever (regardless of any other symptoms), with onset <7 days prior to hospitalization… Something similar could be used to refine the long list of "eligibility diagnosis, symptoms and signs" used by FISABIO; maybe the PPV of a simpler list (cough + fever (with symptoms starting within <7 days)) could be higher. Of course, at the end it would be ideal if all studies use one unique case definition, but given differences in the health systems, etc, that will make the studies different anyway, this would not be an imperative.	Thanks for this suggestion, we will discuss this within WP7.
7	**Discussion** The discussion seems reasonable. However, I would be less conclusive in blaming the bad "match" between vaccine and circulating strain for the low effectiveness for H3 viruses . H3 viruses are more mutagenic than H1 viruses, thus, VE for H3 viruses is usually lower; also, the methods to define a "god match" are not very	Rephrased, now stating "this may be partially explained by…".

	transferable into effectiveness (there re many seasons in which the “match is great and VE pitiful).	
8	**Discussion** Regarding your comments on the results of the healthcare worker cohort (page 114): The explanation given in the discussion (regarding potential bias) is reasonable, and underscores the difficulties that such study design brings. Thus, I agree that those results are not really useful. My suggestion is to modify the procedure for case capture for this study for the next season if the site wants to participate again . Getting bad data on HCWs is worst than obtaining no data, I think.	The site has proposed to proactively follow up reporting of ILI, rather than assuming that no reporting=no ILI. Final decision on participation of this site next year is pending.
9	**Discussion - Limitations:** Agree with the observation that “The covariate at least one chronic condition” was not sufficiently granular: I would drop this covariate for future studies and use more specific covariates (e.g. chronic respiratory disease in the year prior, and also other specific risk factors for flu complications). I believe to have made this observation previously. I would also drop the prior year influenza vaccination covariate for future studies, it is difficult to obtain and of limited use unless you analyze multiple prior years of vaccination and of flu infections to find something useful).	We will take this into account for next year’s studies.
10	**Discussion - Limitations:** Agree with the difficulties in obtaining brand specific estimates. Sample size is going to be a problem, we may want to push for larger studies. Also, unhappily, I don’t think we had any site using High dose	In the 2018/19 season, in Europe High dose Fluzone was only licensed in the UK, however, this vaccine was not listed in the UK’s influenza vaccine recommendations (only QIV, LAIV and aTIV were).

	Fluzone (Sanofi) , cell-cultured (not yet licensed in Europe) or recombinant (not license either?) flu vaccines. Maybe this can change next season.	Sanofi's recombinant vaccine Flublok were indeed not licensed in Europe. Seqirus' cell-culture vaccine Flucelvax Tetra only obtained marketing authorization in the EU in December 2018.
11	**Discussion - Confounding by indication** (page 115): Agree this is an important concern. One simplistic solution would be to only include studies in which the vaccinated and unvaccinated subjects of a given age group are comparable (e.g., prioritize the selection of jurisdictions with universal vaccination for that age group). We can discuss other alternatives such as matching, inverse probability of treatment weighting, etc, but for that we would need to have more extensive info on risk factors for each individual, and even then we can't be sure we got it right (unmeasured confounders will always hunt us).. this is worth a discussion prior to the next season). In any case, I can send a list of potential confounders we have used.	Please see reply to comment #1.
12	**Discussion - Challenges:** Page 116: I believe the study was completed in very reasonable time despite the limitations: Congratulations to the teams involved!	Thank you
1	**Executive summary:** I strongly suggest to bring the summaries forward, start with a brief (1 page) table of contents, then these summaries (the lists of contributors, tables, abbreviations, detailed content if desired can come (much) later; start with what it is about not the administrative part. Now it takes a long time to get to any	Revised, the new order is: • Table of contents (shortened, showing only 2 levels) • Executive Summary • Lay summary • List of figures, tables, abbreviations, • Background • … (as before)

	content, which may be not very energising for the reader/stakeholder. **Reference documents**: I would move this to the back also. **Study team:** I would move this to the end of the document; is a bit like acknowledgements?.	• References • Other information • Study team • Reference documents • Annexes
2	**Primary objective, brand-specific IVE only:** any laboratory-confirmed influenza subtype/lineage included in the vaccine: regardless of match I assume.	Yes, regardless of match.
3	**Secondary objective:** Above only for brand-specific IVE; here only for trivalent? Or should this have been deleted here?	This was indeed only calculated for the trivalent vaccines, this has now been specified in the text.
4	**Table 1:** I think it is worth a reflection to what extent Drive should focus on including studies which are only conducted at a single site. What added value?	For the register-based cohort study: The problem with THL is that it provides data for mixed HC setting, hence not considered poolable with the data from the TND studies. However, it covers (almost the) entire population in Finland, and THL can generate robust brand-specific IVE estimates while the pooled TNDs cannot. Therefore the THL dataset is important to keep, and we are seeing whether it is possible that THL can differentiate PC from HOSP cases. For the clinical cohort studies: We agree that studies in specific population and conducted only at a single site are of limited additional value for DRIVE, and concentrating resources on sites that can contribute to the primary objectives would be preferred. Final decision on inclusion of clinical cohort studies next year is pending.
5	**Figure 1:** Re the legend on lab tests: RT-PCR & antigen detection is confusing: does this mean both are done always? Or sometimes, or only either one? If that is the	Corrected, and now reads and/or.

	case, please replace & by and/or. Maybe add a note to page x where is explained when what testing (pcr, ab, pcr&ab) is performed (and why).	We have contacted the THL virologist and are awaiting a reply. However, it is possible that it is not known why/when which test is performed.
6	**Table 2, study period:** Why the difference in inclusion for analysis period? Why not harmonise and stop all at week 14 and start in week 48? Not a clear relation with swabbing period (in particular, 10 April will not include week 16)	This depends on the time when influenza was circulating locally. Please refer to the definition in the section Study Period. "For the TND studies, the study period for the analysis started when the influenza virus circulation began (first week of two consecutive weeks when influenza viruses are detected at the study site level, based on the data as provided to DRIVE) in the country/region and finished after the influenza season (defined as the end of the week prior to the first of two consecutive weeks when no influenza viruses are detected at the study site level, based on the data as provided to DRIVE) or 30 April 2019, whichever occurred first."
7	**Table 2, CIRI-IT/laboraotyr testing influenza 'RT-PCR or rapid diagnostic test":** See comment previous page: not '&' but 'or'?	Checked with the site, finally only RT-PCR was used.
8	**Table 3, study period:** Same comment as for same row in GP table	Please see reply to comment #6.
9	**Table 3, lab test influenza HUVH:** On p24: only pcr in figure?	Corrected the figure
10	**Table 3, vaccination status:** Would be good to know how ofter data were dependent on interview rather than registration.	We have contacted the sites that indicated patient/relatives interview was an option. HUVH and NIID confirmed that for none of the subjects vaccination status was ascertained this way. Therefore, this was removed from Table 3 from theses sites. MUV indicated that in " In the very most cases the physician who performs the swab is also the physician who has also vaccinated the patient as the physician

		is the family doctor of the patient. Only in some cases e.g. if the patient does not visit the family doctor for seeing him with the respiratory infection (e.g. the physician is on holiday or the patient is a vacationer) and no vaccine documentation was available the patient was asked if he/she was vaccinated. From our data - which we are receiving - we cannot discriminate between the patients where the patients record or vaccine documents were available and those who were only asked if they are vaccinated. I estimate, that each dataset which has also the date of vaccination included, these data must be from medical records as I am pretty sure, that no patient will remember the date of the vaccination. If he remembers his date of vaccination then I assume that he is surley vaccinated. To my knowledge, those Patients where only the month of the vaccination was reported were excluded from the dataset for analyses."
11	**Table 5, first swab date Greece (11.1.2019):** Any reason for such a late start?	In Greece, the epidemic period was from week 52/2018 to week 16/2019, and the intensity was 'low' during in weeks 52-2, medium as of week 3, and high after week 4. The start of the reported epidemic period was a few weeks later than in most other places. However, in general there are some concerns with this site.

12	**Study period THL 17-20 weeks:** How does this relate to the study periods mentioned in the tables? All shorter, all different.	Correct, this should also read week 40 to 17 like in the table, no data was received beyond week 17. Also specified that this is specifically for THL.
13	**Swab sampling strategy**: insertion of 'been shown to have' after self-collected swabs	OK
14	**Table 9, verification of ILI symptoms:** For the sites where this is not indicated: is it not known how many were missing? For sites where verification was possible: was this done by Drive team (if so: how good a match?)	If not indicated, this means data on symptoms was not collected. This is now specified in the table. Verification was done by the DRIVE teams. The match was very good, and is described in more detail in the data quality report. The data quality has substantially improved compared to last year. I think the interim upload with data quality checks using the ESSA was very helpful in that respect.
15	**Adherence to the recommended ILI/SARI exclusion criteria:** To exclude less severe patients, or for logistics?	This definition was chosen as it is used in an ongoing study at the site.
16	**Exclusion Pregnancy cohort "received influenza vaccine < 6 months prior to study":** Is this correct? You could only be included if vaccinated >6 months before study entry (so even longer before potential influenza infection)? Much protection from vaccination may have waned by then.	At the time when the pregnant women are offered vaccination, they are also asked to enrol into the study. Subjects who were recently vaccinated before that (<6months ago) were excluded. Added that this refers to "vaccines received recently but prior to the 2018/19 northern hemisphere campaigns"
17	**Exposure definition, Note 2: If no information on exposure in previous season was available in the dataset, the exposure definition 'scenario A' was used for all subjects:** Why was it not considered to do at least a sensitivity analysis, and if no information for the children, to sue scenario B? Also, it would be good to have information how many children were it this unclear situation (similar as you later give information on the people in note 1). If very small numbers/% of total children<9, it will not be very relevant.	There were very few children with a double vaccination. We will discuss this within WP7. Pending: how many children <9 received 1 dose and no vaccine last year or no info?

18	**Covariates:** It is a bit unconventional to introduce table 12 before table 10. Moved sentence on Table 12 to end of paragraph	Moved this table to the section where it is first mentioned and referred to it later.
19	**Covariates:** Maybe include a sentence to summarise that 1/4 of the GP sites and 4/5 hospital sites had information on each of the 12 conditions included, and that 1/4 GP and 1/5 hosp respectively had information on none of these.	Added.
20	**DRIVE ESSA:** This implies they could also decide not to do this; or is that only theoretical? Would they not submit for specific reasons (quality, communication, ..?)	Rephrased. "The tool is designed so that data can be uploaded for monitoring only (so less complete, more dirty data would be acceptable) or final data could be submitted for analysis." The idea is that the tool can also be used as a Data Capture Monitoring Tool, but that possibility wasn't used yet.
21	**Sample size considerations, "As data from different sites was pooled and as capacity building is an ongoing activity within DRIVE, smaller sample sizes per site were allowed.":** Any sample size?	No minimum sample size was defined.
22	**Site-specific: Sensitivity analysis on partially/recently vaccinated subjects :** See before: not considered for children<9 with incomplete information on previous season?	No, this was not considered. However this would only be applicable for very few cases, if any (judging by the very low number of children <9 with incomplete vaccination).
23	**Meta-analysis, "For every meta-analysis performed, the potential impact of outliers and influential estimates on the pooled estimate was evaluated.":** How defined? Cut-off?	Added the following text from the SAP: "Studentized deleted residuals r will be used to identify outliers in the metaanalysis. Site-specific IVE estimates will be considered outlying from meta-analysis when $\|r\| > 2.5$, where $\| r \|$ indicates the absolute value of the residual."

24	Should the reference to Table 12 in the section target groups be a reference to Table 13 instead?	Corrected
25	**Influenza epidemiology in Europe, lack of influenza B circulation:** So this should imply no real VE difference between TV and QV.	Correct
26	**Influenza epidemiology in Finland:** I found it confusing to mix information from these two different populations, why not separate out as for Italy and Spain? Eg, THL has no information on typing, kan HUS typing be extrapoloated to all of Finland? **Influenza epidemiology in Finland, "About 4,000 influenza A and 20 influenza B cases were observed in the elderly.":** Elderly : in HUS **Influenza epidemiology in Finland, "The most influenza related cases were diagnosed in the northern and eastern part of Finland.":** in THL:?	Split into two subsections. There is information on influenza type but not subtype/lineage in the THL register-based cohort data we have received and that covers (almost) the entire population. THL also runs the national sentinel surveillance, subtypes are available from there and are used to describe epidemiology in Finland but not used to assess IVE.
27	**TND primary care setting, "For the combined data of the primary care TND studies, the majority of patients were adults (46%) and male (51.8%).":** 46% is not a majority; also, this needs to be assessed compared to the denominator, and I assume far more than 50% of the population in the study countries are adults. So beter rephrase that the majority were children (54%), whereas they formed approx. x% of the general population (if known).	Rephrased. "For the combined data of the primary care TND studies, the majority of patients were children and adults 18-64y (45% and 46%) and male (51.8%)."
28	**TND primary care setting, "Both ISS (Italy) and MUW (Austria) have a case-control ratio close to 1:1 whereas for RCGP RSC (UK) and CIRI-IT (Italy) the case-control ratio was**	As long as the swabbing is not driven by vaccination status this should not be a problem at all.

	much higher.": Suggesting selective swabbing? See prior comment, it might be worth a discussion to what extent that is or is not a good idea or a problem re validity or efficiency. Also, it is likely that the ratio differs in the peak of the season, compared to the start and end; so might be biased by duration of inclusion. Maybe include information on range of c-c ratio? See figure 5: during the mid season, differences between sites seem limited; but more active (negative) swabbing (surveillance) prior to start?	
29	**Table 17, at least one chronic condition (yes/ yes specific conditions known/no):** Can you include a line with 'yes, unknown"? I'm confused by the % given for the conditions known, what is the 100% they relate to?	For Table 17 and 18, the information on specific chronic conditions has been moved to a separate table in the exploratory objectives. The 100% they relate to it the number of subjects with information on that chronic conditions. This explanation has been added to the table.
30	**Table 17, influenza vaccination:** I do not understand what is meant with this categories of influence vaccination? It differs ++ from the category just below; confusing!	Corrected, the first one now reads "influenza vaccination status in previous season".
31	**TND studies, For the combined data of the majority of patients were elderly (44.9%) and male (52.8%): hospital setting:** See before, 44.9% is not a majority	Rephrased: "For the combined data of the hospital based TND studies, the largest age group was elderly (44.9%) and the majority of patients were male (52.8%)."
32	**TND studies, information on Influvac was mainly collected in hospital based studies:** But also restricted geographically? Might be relevant also, apart from setting	Added.
33	**Table 18, at least one chronic condition (yes/ yes specific conditions known/no)::** Same comment as in table GP	Please see reply to comment #29.
34	**Table 18, influenza vaccination:** Same confusion as in table TG	Please see reply to comment #30.

35	**Table 19, study population characteristics THL:** Would be more informative to stratify by age; and to add % to n	The table is now stratified by age. Given the format of the data (only aggregate data was shared) and the fact that the cohort compromises an open population it is not possible to calculate the %.
36	**Table 22, summary of VE estimates:** Maybe also add information on how many subjects?	Number of subjects has been added to Table 22 and 23.
37	**Table 27, nr of sites with data for pooled estimates by setting and age:** All GP sites included the whole population, so why not '4' in every colomn for any vaccine?	The number of studies listed is the number of studies for which valid VE estimates were obtained.
38	**Figure 18:** It is remarkable that the VE is so much higher in the 65+ compared to the 18-64 yrs olds; contrary to general trends with reduced VE in the elderly. Also, it seemed not similar to the trend in the unpooled summary estimates in 9.4.1 (but I'm not sure how to related the summary to the pooled estimates)	For Figure 18/Influvac (where this comment is): there are wide CIs but the mean estimates indicate IVE is higher in 18-64 compared to 65+. Figure 19/Fluarix Tetra (next figure): here indeed it is striking IVE for 65+ is higher than for 18-64, especially for the hospital studies where the point estimate is more than double.
39	**Discussion: Estimation of IVE for any vaccine:** I agree, plenty of data to show mismatch between VE and vaccine match; can be nice for communication, but it is more complicated.(previous (other) vaccinations, other infections, other (immunological) conditions, antigenic sin, genetics, ..)	Please see reply to comment #7.
40	**Discussion: Estimation of IVE for any vaccine:** How is robust different from precise? It was defined by the width of the CI before.	Rephrased. "The width of the 95% confidence intervals for estimates in other strata was >40% and were therefore not considered sufficiently robust."
41	**Discussion: Estimation of IVE for any vaccine:** Remarkable that the VE is lower in the 'healthy' children population than in the 'medial indication' group?	Yes – bias by healthcare seeking behaviour might play a bigger role in the general population compared to the 'at risk population', and in the primary care studies compared to the hospital studies, and

		in the healthcare worker cohorts compared to the pregnancy cohorts, and in cohort studies (such as Finland) than in TND studies…
42	**Discussion: Estimation of IVE for any vaccine:** So publish quickly	
43	**Discussion, Healthcare worker cohort, "there was underreporting of ILI symptoms, especially in the unvaccinated subjects":** Why this assumption? Maybe the vaccinated group felt protected, so more underreporting? Was a survey done?	Added: "There was likely more underreporting in the unvaccinated subjects, as the % of subjects with a laboratory-confirmed influenza negative swabs among all enrolled subjects was much higher (8.9%) for in the vaccinated group than in the unvaccinated group (3.9%)."
44	**Discussion, Healthcare worker cohort, negative IVE estimates**: Chance is another option, rather low case numbers (although the cohort met the inclusion criterium of 1000, unlike the pregnant women). More data and more than 1 sites&country might be essential for valid estimates of any special cohort..	Please see reply to comment #43. Agree that > 1 site for special cohorts will be important to obtain meaningful results.
45	**Discussion, limitations related to the data, covariate 'at least 1 chronic condition':** As previously mentioned, the ISC has been arguing from the start that this was not a sensible covariate to include. Information on type of condition and the number of conditions is needed for any interpretation, and quality of such data is likely to be limited if not electronically available from registers. Long discussions in Valencia with Topi and Javier!	We will discuss how to improve collection of chronic disease data and think about the usefulness of propensity scores for next season.
46	**Discussion: limitations related to the data, "A careful trade-off between inclusion of possible confounder**	Added

	information and the risk of losing records": And the potential to have sufficient quality of data	
47	**Discussion: limitations related to the data, "However, obtaining sufficient sample for brand-specific IVE estimates is expected to be challenging also in more intense seasons and this year, even for the primary objective estimating IVE for any vaccine, sample size was insufficient for most strata.":** So better focus on increasing sample size for the main outcomes, than adding 'special' cohorts?	Agree, to be discussed within DRIVE.
48	**Discussion: Limitations due to confounding by indication, small sample size:** So be careful not to do to much datadredging	Rephrased, added "However, sample size was too small to draw robust conclusions." rather than the details
49	**Discussion: recommendations, "The primary objectives were not met in the 2018/19 season and increase in recruitment and/or further expansion of the DRIVE network is needed,":** But with focus on meeting the primary objectives	Agree, to be discussed within DRIVE.
1	**Background, register-based cohort:** am not sure I understand what a register based cohort means – elsewhere this is referred to as a National Infectious Disease Register – how is this a cohort?	This study is a cohort that includes the entire population of Finland (in 2 age groups). Different registers are linked to obtain the required information. The following information has been added above Table 4: "The cohort THL register-based cohort includes all children aged 6months to 6 years and adults 65+y registered in the Finnish Population Information System. This system is then linked to the National Vaccination Register to obtained vaccination status for all subjects in the cohort and the National Infectious Disease Register to identify influenza cases."

		The following information has been added in Table 4: Data source for subjects define the cohort: Population Information System.
2	**Table 19/text above it:** Table 13 says target groups in Finland for vaccination are up to 35 months.	Table 13 corrected, to 6m-6y.
3	**THL, IVE results, FLuenz Tetra:** Very low compared with UK estimates for 2918/19 for national TND data	Added: "It is noted that the above estimate for LAIV above, from the UK, is higher than the estimates from the THL register-based cohort study in Finland."
4	**Discussion, comparison to I-MOVE results:** Any comment on this – end of year estimates for LAIV in UK similar to mid year ones. Also data from Cabad also available	Please see reply to comment #3.
5	**Discussion, EMA guidance "EMA guidance encourages the assessment of IVE in specific risk groups [1]. Therefore, a clinical pregnancy cohort and a clinical healthcare cohort were followed during the 2018/2019 season." :** Don't think this justifies their inclusion given the small size. A lot of work for no useful data. Also data on VE in those with co morbid conditions is available from others	Agree, to be discussed within DRIVE.
6	**Discussion, robust IVE estimates:** What is meant by this?	Robust is defined as confidence intervals with a width <40%.
	ISC, Pag 16.: delete MD	Done
	Pag 24 Table 8.2 with study sites, add country to names? Like table 9	Does this refer to Figure 1? Added country to Figure 1.
	Secondary objectives, Pag 21, "the following vaccine types will be considered": vaccine are to be considered	Rephrased.

	Table 7, Pag 33, catchment population for studies in the general population: size of catchment population	Edited the column title to include 'size of'.
	Table 9, Pag 37 verification of ILI/SARI case definition based on clinical symptoms: providing number of records as denominator would be helpful	Denominator added for the sites where nr of missing records is provided.
	Exclusion criteria HCW, Pag.39 8.6.4, "was unwilling to participate or unable to communicate and give consent": unable to communicate? What does it mean? This should be health staff	Corrected, unable to communicate has been removed.
	Epidemiology, Pag 61: difficult to compare incidence across the countries	We did not collect information on incidence, it could be collected next year if available to the sites. To facilitate comparison of subtypes across the countries, an additional figure has been created showing the dominant subtype in different countries over time.
	Table 16, number of records received by site: very low figures for RCGP, UK	Correct, RCGP started data collection very late, the first swab was taken in February.
	Table 16, number of records received and records retained by site. Pag 64. 88% of records retained from TNT primary care compared to only 68% of hospital TNT. Fisabio even lower proportion. Pregnant women cohort also have a high proportion of discarded records. Why? Is this a marker of overall quality? Any indication for the forthcoming season?	This in part has to do with whether the exclusion criteria were already applied locally or whether they had to be applied after the data was uploaded. For example, at FISABIO samples taken >8days after symptom onset were included in the dataset (3.9%), and vaccination status was unknown for 8% of subjects. In addition, obtaining confirmation of vaccination status is likely more challenging in hospital-based studies than in primary care studies. For more details see the attrition diagrams in Annex 5.

	Table 17 Pag 66, study characteristics: is very complex and difficult to follow. Influenza vaccination unknown in more than 60%? Is that referred to history of vaccination? Split in subtables?	The first influenza vaccination has been corrected to 'influenza vaccination in previous season' in Tables 17 and 18. The sections on specific chronic conditions from Tables 17 and 18 have been moved to the exploratory objectives to simplify the table.
	Figure 5 Pag 69, Distribution of Influenza-like-illness cases over time: is that referred to confirmed cases only or to all the ILI cases?	This concerns all ILI cases, showing whether it was confirmed influenza (and the type/subtype of influenza) or influenza-negative.
	Figure 6 Pag. 70, Cumulative number of vaccinations over time: Does it refers to each GP vaccination coverage?	It refers to the vaccination coverage of the enrolled subjects.
	Figure 7 Pag. 71, Distribution of vaccine brands: does it refers only to cases?	It refers to brands in all vaccinated subjects, both cases and controls.
	Figure 7 and 11, Pag. 78, distribution of vaccine brands: Beyond the geographic location, is there any reason for the different distribution of vaccine brands in GP cases and Hospital cases?	No, geographic location is the only factor as vaccines available vary widely between countries or within regions.
	Table 22 Pag 87., summary of VE estimates by site: The column N. of sites unclear	N sites means refers to the number of sites for each an estimate is available. E.g. there are 2 sites with estimates for Vaxigrip Tetra in children 6m-17y in primary care setting. This was renamed to N estimates instead.
	"The main objective of the 2018/19 season was to estimate brand-specific seasonal IVE in Europe by health care setting and age group. The DRIVE platform is still expanding, and not all vaccine brands used in Europe are covered during the 2018/19 season. **This Study Report describes the characteristics of the participating study sites, the methods used, and the IVE estimates obtained for the 2018/19 influenza season, as**	Thank you. We will add some text on this in the background section after "the DRIVE platform is still expanding" to indicate not only that not all brands are covered but also that sample size is still limited.

	well as the challenges and proposed recommendations for next season." From the report page 14, above, the main issue for the first year was to explore the feasibility of recruitment, collection of data and operational parameters from the partners. This was done and should be applauded. I feel that the actual results are less relevant at this point relative to the processes that have been instituted as well as the capabilities to review these processes for each of the sites/studies and overall. This is a large complex project with multiple dimensions and countries and the investigators and authors of this report should be commended for what they have achieved in a relatively short time in a challenging political (scientific/academic) environment within the EU. There is an impressively large catchment for Italy, England, Austria, Finland and Spain.	
	There needs to be an index in the document where the brand names are linked to the type of vaccine. I could not find this.	This has been added, see Table 15 of the report sent to EFPIA.
	Given the many disparate results that we are finding at this stage, there needs to be pre-emptive central commentary about many of the current limitations of this study and how the overall study is also as much about process development to implement systems for post-licensure monitoring of vaccine effectiveness. There are so many caveats when it comes to the measure of VE for influenza vaccines, that the uninitiated reader needs to at least understand why VE is "all over the map" figuratively and literally. A brief	We will add this to the background section in the next version.

	explanation of this is warranted early on and why the overall process of evaluation over the long term is required.	
	Specific issues: I agree that the objectives and executive summary should appear much earlier in the report	Please see reply to comment #1.
	Pag 16. Although I am still a guest researcher at the NIH, better to use my title as independent consultant	We will update this in the next version.
	Pag 60. How do you define European region? EU? Geography? What baseline? Based on entire region? North South variations?	European Region is defined as the 50 Member States (MS) with routine influenza surveillance systems in the WHO European Region. Source: https://flunewseurope.org/System Baseline in individual countries across the region. Source: https://flunewseurope.org/Archives week 17
	Pag 61 figure 4 Could use a definition of "intensity" for the graph	We will add this in the next version. The definitions of the different levels of intensity are listed below: **"**Intensity is a measure of influenza activity within individual MS. • Baseline or below epidemic threshold: ILI or ARI rates that are very low and at levels usually seen throughout the inter-epidemic period. • Low: ILI or ARI rates that are relatively low compared to rates from historical data but higher than the baseline. Influenza virus detections have been reported.

		• Medium: ILI or ARI rates that are similar to rates usually observed, based on historical data. Influenza virus detections have been reported. • High: ILI or ARI rates that are higher than rates usually observed, based on historical data. Influenza virus detections have been reported. • Very high: ILI/ARI rates that are much higher than rates usually observed, based on historical data. Influenza virus detections have been reported." Source: https://flunewseurope.org/System
	Pag 64 table 16 Why so few records from the UK?	Data collection in the UK started very late, in February, due to delays in obtaining ethics approval.
	Quantitative adjectives should be avoided wherever they can. " High", "low" and ,"very" should be avoided in epidemiology papers.	