DRIVE D7.6 Brand-specific influenza vaccine effectiveness in Europe season 2018/19

EFPIA comments, 1st round (26/07/2019) – reply grid

Nr	EFPIA Comment	ISC Reply	WP7 Reply
	1. Key Comments for improvements to the 2018-19 season report.		
#1	- <u>Executive Summary & Context</u> *An executive summary (3-5 pages) is critical. The summary should guide the reader through the results and giving sufficient information for most readers, without the need to study the whole report. The summary should go beyond a straight analysis output and move more toward a publication type narrative. Results need to be explained to the reader. There are somewhat exceptional circumstances this season, and the reader should understand the impact – else he/she will be easily lost.* Important topics to be covered in the summary: o Circulating strains (no B), match (H1N1) and mismatch (H3N2) o Estimates of % H1N1 versus % H3N2 o Mild season o Limited amount of data captured per vaccine brand, distributed over appropriate-yet multiple strata (age, strain, setting) resulted in non-robust	Agree with their comments on the need for a strong executive summary with highlights of what this year was supposed to achieve as opposed to the actual results of VE at the different study sites (on executive summary being critical) Similar to our advice. (on results need to be explained to the reader) Rather paternalistic statement; context is ok, but avoid giving the impression that because the results are not as expected drive tries to discredit them. Scientifically, unexpected results can be the most interesting.	The executive summary has been added.

	IVE estimates with wide to very wide confidence intervals ○ Conclusions - Limited data does not allow conclusions on most brand specific IVE for the seasons 2018-19. Capturing sufficient brand-specific data proves to be challenging. Efforts are needed to increase the amount of brand-specific data	(on exceptional circumstances this season): Not sure, every influenza season has somewhat exceptional circumstances, nothing really major last year. Careful not to frame scientific uncertainties, intrinsic to rapid estimates, in particular re influenza VE with suboptimal designs compared to RCTs, s excuses to discredit unexpected results. If estimates had been more as expected/hoped, with similar wide CI, would the same caveats have been stressed as much? (on readers being easily lost): Don't underestimate readers! Many of them will have ample experience with the challenges of estimating influenza VE	
#2	For the purpose of the submission to EMA, a clear disclaimer should be added to indicate that the report is draft and concerns preliminary data.	Not sure why this is needed, what more is expected? Soon new data will be coming in. I would suggest these data should be submitted asap for publication to ES, if Drive wants to build on showing added value compared to current	Draft report has not been submitted to EMA to our knowledge. Final report will be ready August 23rd and submitted to IMI by end of August. If there is a need to still submit as a draft to EMA rather than wait for the final report, we can add a disclaimer.

		situation, not sit on the data, but encourage reflection and debate.	
#3	- <u>Lessons learned and limitations.</u> *Lessons learnt on the impacts of the study design and characteristics should be described to increase the informativeness of the report to support the further evolution of the future protocols and SAPs. We showed the progress in having some brand data but still need to be cautious regarding precision and way to interpret them. Limitations should be better described in terms of sample size, confounder adjustment and heterogeneity. The presentation of the demographics and all case numbers for vaccinated/unvaccinated and/or cases and controls is essential. Results should be placed on context of the sample sizes. Specific comments to this respect are:*	(on being cautious regarding precision and way to interpret them): always.. (on heterogeneity): See above, avoid giving the impression to hide behind science to ignore undesired results.	
#4	• Sample size/precision is the most important and it is only covered by 4 lines (p45).	No need to repeat SAP	Pre-defining the minimum required sample size is theoretical possible, but practically of limited value as it depends on many factors that are difficult to know a-priori (attack rate, case to control ratio, vaccination coverage, between-study heterogeneity). Also, sample size requirements will be less for sites where only a single or few vaccine brands are used (like Finland) compared to sites where many vaccine brands are used (like Italy, Austria), making it difficult to have 'one-fits-all' sample size requirements. Also, site-specific estimates will be pooled through meta-

			analysis, which additionally calls into question the need to have strict sample size requirements by site. In addition, capacity building and network expansion (start with smaller studies and scale-up sample size when the studies are promising) were considered important arguments during the EFPIA brainstorming meeting last year to not strictly require a minimal sample size per site. However, it was also recognized that small studies are of limited value and that resources should not be spread too thinly. Therefore, sample size recommendations were made, but these are recommendations and not strict requirements (Section 7.12 of DRIVE 18-19 report). During the EFPIA brainstorming meeting it was also agreed to not focus on sample size, but on precision instead as there is no simple 1-to-1 relationship between 'sample size' and 'precision' in the context of IVE studies and precision is what matters at the end. Throughout the study report, we make a clear distinction between robust (having 95% CI width < 40%) and not-robust estimates, and only discuss the robust estimates.
#5	• The SAP contained elements regarding the sample size/precision and there is no concrete link made with the a-priori		It is impossible to make a concrete 1-to-1 link between 'sample size' and 'precision' as explained

	assumptions about acceptable level of uncertainty surrounding the VE (wild confidence interval). Min. sample size as advised upfront was not met for the UK, ISS, HUS. Other sites just met the 200 (HUVH, Fisabio)		above. Also the influenza season was mild, making it more difficult to obtain large number of cases. The number of cases in ISS was > 1000. The number of cases for the UK (RCGP RSC) was low as a result of late ethical approval. It is indeed a good question whether we should try to enlarge the sample size of the 'promising' study sites, and what should be understood by 'promising' sites (information on subtypes/lineages, information on certain covariates, sufficient coverage, …?)
#6	Confounding issues and ability to account for them should be described in more detail. • Descriptives should be provided for the exposed and unexposed by cases and controls at the brand and type level to help understand presence of confounding.		These tables were initially generated, but we decided to not report them as the information was too scarce to allow a proper interpretation of the distribution of confounders by brand. The tables have now been added as annex.
#7	Which confounders were "influential" (i..e strong confounders) and for which analysis?		It's indeed a good point to look at the importance of the individual confounders, especially as records might get discarded from the analysis because of incomplete information on the confounders. Therefore, it is important to only adjust for 'important' confounders (see below). An additional post-hoc analysis was done (and presented at the WP4 meeting in Helsinki) to get some insight in the covariates that did substantially alter the IVE estimates. See "Post hoc analysis confounders" presentation

#8	• The analysis was a complete case analysis, dropping records with missing information for the outcome, exposure of interest or any of the covariates. However, for sites for which some confounders were entirely missing, the IVE estimates were confounder-adjusted to the extent possible. This is an "unequal treatment" between sites and a concern because excluding data reduces the statistical power and may introduce bias. Why this different approach – not in the SAP? Modern statistical methods to handle missing covariate data should be considered. A lot of data was lost due to missing data.	Clarify how many data were actually lost?	The approach was mentioned in the SAP: SAP, section 15.1.3, p51: "The analysis will be a complete case analysis, dropping records with missing information for the outcome, exposure of interest or any of the covariates. …For sites for which some confounders are entirely missing, the IVE estimates will be confounder-adjusted to the extent possible…. When a covariate contains a large percentage of missing data (>= 10%), no adjustment will be made for that covariate to avoid losing too many records, unless the covariate adjustment is considered more important than the information loss" This approach was chosen as not all sites allow for the same level of covariate adjustment (why applying missing data methodology for some sites while for other sites the same covariates are entirely missing?). A complete case analysis will not result in biased estimates if the missingness mechanism is Missing Completely at Random, which is often the case in observational studies (unlike clinical trials). The amount of records that was discarded across all sites because of missing covariate information was limited (see Annex Attrition diagrams, discarded from analysis/missing covariate information). Only for

			Austria and ISS, a substantial amount of records were discarded because of missing covariate information; (AUSTRIA, 101/1127, 8% of the data, and ISS :116/2573, 4% of the data). For all other TND sites, very few records (< 5 records) were discarded because of missing covariate information. For Austria, records were discarded because of missing covariate information on chronic conditions (33), pregnancy (53) and influenza vaccination in the previous season (15). For ISS, records were discarded because of missing covariate information on 'number of GP visits' (116). We agree that covariate adjustment is an important point that merits further discussion: - Are all covariates sufficiently important to risk losing records? E.g, we might argue that 'influenza vaccination in the previous season' is not sufficient to capture previous exposure (as it also depends on having had influenza before), so it might be better to not adjust for this variable - We currently strive for a minimum set of common confounders to facilitate the interpretation of the results. However, some sites are able to adjust for more covariates then the minimum set of common confounders. Should we stick to the approach of the minimal set of confounders

			(least common denominator) or should we try to have the best confounder adjustment possible per site (and lose the common denominator)?
#9	• Adjustment for calendar time to be better explained.		Calendar time was included as covariate (symptom onset time since start of the study, in days). To account for changes in the risk of infection over the season, it was modelled as a potentially non-linear smooth function. (e.g. cubic splines with restricted maximum likelihood for smoothness selection). This means that we allow for a flexible but smooth relationship between the calendar time and the influenza rate/risk. The smoothness selection guarantees that the function is flexible enough to capture the required time trends, but does not use more degrees of freedom than strictly required. In the absence of a time trend, the smooth function will be equal to a linear function. This explanation has been added to the report
#10	Statistical • Results should be presented in the context of their sample size.		See above (explanation on sample size and precision) Multi-panel and forest plots were adapted to display more information.
#11	Statistical • Heterogeneity is not enough considered as a quality/relevance indicator for pooling, whereas for some of the analysis this was		Clinical differences are a reason for not pooling estimates. Therefore, it has been decided (and approved during the EFPIA brainstorming meeting of

	present and substantial even. Is there a threshold for heterogeneity or significant differences between the characteristics of the groups?		last year) to not pool across age groups, healthcare settings and populations. Statistical differences are <u>not</u> a reason for not pooling. In this case, the pooled estimate is just to be considered a descriptive measure with poor predictive value for individual studies. In this case, it is important to also give the range of estimates observed (Table 22 of the DRIVE 18/19 report). When the number of studies allows, it would indeed be interesting to gain a better understanding of the sources of heterogeneity. However, given that DRIVE is only having a few studies per setting, this is currently not really possible
	1. Presentation of the data *There is opportunity to simplify the presentation by removing redundant data elements, shortening the report by moving tables the annexes and improving the descriptions of the underlying populations and data.*	(on moving table to annexes): I agree, good idea, increases readability.	
#13	- As above, the number of case and control for each analysis, across vaccine brands should be displayed together with estimates.		Multi-panel and forest plots were adapted to display more information.
#14	- Tables should be adapted to provide nb of cases/controls, one point estimate per VE with 95% CI - Forest plots should provide more detailed information on number of cases, site/country		As above
#15	- The grey vs black distinction in the presence of so many non-robust estimates is not visible.		We made the black/grey distinction more visible. We also add a cautionary footnote to every multi-panel

	Consider to move non-robust estimates to the annex		plot in the main report to draw attention to the color difference.
#16	- While it was agreed to present all data irrespective of the 95%CI, with confidence ranging well over 100, we question if it does make sense to disclose such estimates at all.		We indeed follow the SAP to present the results as a-priori agreed. Not presenting estimates with wide confidence intervals (> above a certain threshold) will bias towards the reporting of IVE estimates with low/high VE.
#17	Decluttering: - The report is too long (should be 50p max). Many part should be put in an appendix (e.g. Parts 7.10-7.11-7.14-8.2-8.6 – 11 -12 -13, Tables 10-11-13-14-17-18-19, Figures 7-11). Some information need to be summarized.		We fully agree that the report is long and contains lots of information. We indeed need to agree upon what level of detail that is required, and as a next step for improvement towards next year, a mock-up report seems indeed appropriate. The current version of the report is indeed a lot of repetition of the SAP, which can be avoided. Many of the suggested sections have been moved to the Annex.
#18	- Remove the min/max (particularly at the overall strain level. it increases the volume of data and 2. it is confusing and not really discussed and it is not always clear what is selected for the min max – at the site or pooled level ? Else the tables 22-25 should move an appendix.		See earlier statement on the importance of providing ranges of estimates in case of heterogeneity. The section header is 8.4.1. Site-specific estimates (see page 85, DRIVE 18/19 report) We now also made this clear in the caption of the table.
#19	- If no cases for B, then it does not make sense to calculate overall and just for strains		It was a proposal from EFPIA to also produce IVE estimates for the combined strains included in the

	included in the vaccine. This also avoids to present twice “any influenza” which is confusing.		vaccine. We found it a very valid suggestion, and would like to stimulate the discussion/thinking by presenting the results. In the absence of B-circulation, it is indeed not very telling. However, we decided to keep this for the current version of the report to stimulate discussion during the annual forum. There is also an added value of having exactly the same way of reporting over the years.
	The qualitative ‘poor, moderate, high’ VE should be explicitly explained/defined and used only if VE is robust. A use of the deliverable on VE interpretation should be probably used if such statement are retained.	Don’t understand this last sentence?	Updated to indicate terminology from D4.6 was used.
	1. Clarifications analysis		
#20		Is the pooled analysis based on the individual level data or the meta-analysis of IVE estimates? Were the site specific analysis conducted by the site or by P95?	The entire analysis is conducted centrally by P95, including data quality checks, applying study in/exclusion criteria, estimation of the site-specific IVE estimates and the meta-analysis. See section 7.11 on ‘Data management’ of the DRIVE SAP (previously also in the report but suggestion in comment #17 to move to annex). See also the data quality reports describing in detail the data that were uploaded by every site to the central server. We now made this more explicit (“Site-specific and pooled analyses were conducted centrally on the DRIVE Research Server. For each site, an attrition

			diagram was created, descriptive analyses were performed and site-specific IVE estimates were calculated. Pooled IVE estimates were obtained by meta-analysis of site-specific IVE estimates.")
#21	ISS - the majority of severe infections (67%) were due to influenza virus A/H1N1 – how is severe infections defined?		Since 2009-2010 there is surveillance of serious laboratory-confirmed influenza cases in Italy. Serious cases have to be notified to the Istituto Superiore di Sanità through the web site https://www.iss.it/Site/FLUFF100/login.aspx ISS defines severe infections as follows: - Severe acute respiratory infection (SARI) cases with hospitalization in Intensive Care Unit and/or Extra Corporeal Membrane Oxygenation therapy; - Acute respiratory distress syndrome (ARDS) cases with hospitalization in Intensive Care Unit and/or Extra Corporeal Membrane Oxygenation therapy.
#23	Fisabio - why only half or records retained? Plus the ILI/SARI case definition could not be verified for 619 (17.1%) of the cases. This will be taken into account when interpreting the results		FISABIO uploaded more data than strictly required. See data quality report FISABIO (p2): 'The data sets used for central data quality checks were uploaded for 'analysis' using the DRIVE Electronic Study Support Application on 16/05/2019. The uploaded dataset contained records on 7019 patients, of which 3615 are ILI/SARI patients, comprising of 2743 patients reported to be ILI/SARI, 619 patients < 5 years from whom a swab was taken and 253 patients that fulfilled the DRIVE ILI/SARI case definition but had symptom onset > 7 days before swabbing.'

2.	**3. Minor comments**		
#24	Three types of spelling: 2018/19, 2018-19 and 2018-2019. To be harmonized.		Harmonized, 2018/19
#25	"777363 – DRIVE – WP7 – SAP 2018/19" Incorrect?		Corrected.
#26	Three different types of spelling: A(H1N1), A/H1N1 and AH1N1. To be harmonized. Same comment for A(H3N2).		Harmonized: A/H1N1, A/H3N2.
#27	8.1.3 Add which strains are new		Done.
#28	Subtype A/H1N1 indicated both as A/H1N1 and A/H1N1pdm09, which is confusing.		All changed to A/H1N1
#29	In some figures “IVE against any” and “IVE against any strain”, see e.g. Fig. 19. Results are sometimes not consistent		In Figure 19 VE against ‘any’ is 49[-50,85] and against ‘any vaccine strain’ is 50 [-45,85]. There was little B circulation, therefore there were insufficient data for valid IVE estimates against ‘B’. However the data on B cases was included in the ‘any vaccinate strain’ analysis. This explains the difference in the IVE estimates.
#30	CIRI-IT/Austria MUV/BIVE were not adjusted for number of hospitalizations in the last 12 months or number of primary care consultations in the last 12 months (as applicable) because this was not available. However, it should be recognized that this was not consistent with the SAP		This was recognized in the SAP, see #8
#31	Adjustment for smooth function of symptom onset date is not listed among the covariate adjustment.		Added and better explained (see comment #9)

#32	Inconsistency for Fluarix for nr of sites as origin of the data: 2 sites per table 27 and 1 site per table 24		Corrected Table 27.
#33	Exposure definition - Scenario B is different from the SAP and it is not clear how this is now defined. 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. Previous vaccination is not used in the definition and fully vaccinated is not defined.		In the SAP "partially vaccinated" contained 1) subjects recently vaccinated (<14d) and 2) also the time between vaccinations 1 and 2 for subjects on a 2-dose schedule. In the report these have been named separately, "recently vaccinated" and "partially vaccinated". See first sentence in Scenario A: "An individual aged >9 years, or a child aged <9 who has been fully vaccinated (at least two injectable doses or one LAIV dose) during the previous influenza season was considered as… ".
#34	Where the site specific analysis conducted by the sites, or by P95?		P95, see #20
#35	Strain circulation data appears to be based on the data which is collected – not the external circulation reported – this could be skewed by the population included in the study and status of vaccination. Should it only consider the distribution in the unvaccinated?		Information on strain circulation based on surveillance data is reported irrespective of surveillance status. Similarly, the study population was not selected based on vaccination status. Therefore kept as it is.
For brainstorming, discussion for next year			
#36	Major issues for the next season are • How to increase the amount of data captured • Handling of confounding • Mock report	(on amount of data captured): Not just amount in general, but in particular amount and quality to achieve primary objective	Fully agreed

	• How to limit the amount of information presented		
#37	This season's results are disappointing due to the limited amount of data per brand. This is something to discuss within the consortium DRIVE, because DRIVE was proposed in the hope that collaboration would help to collect sufficient data. Some (I-Move?) will consider this as a failure of DRIVE.	Agree that the actual calculation of vaccine effectiveness for each individual brand is unrealistic given the statistical requirements and data collection necessary for appropriate stratification and is probably unlikely for every year. There needs to be a set up for a strong emphasis of realistic expectations, so it does not appear as a failure of the study. (on limited amount of data per brand): But also: many more compared to nothing before! So what is realistic? What is needed for whom to strengthen public health (including should EMA reconsider what it needs/wants)? This is also discussion topic for GA I believe. (on failure of DRIVE): Why? Brand specific data are now emerging, improvements are needed, including more quality data and rapid disclosure, as well as further analysis/development of methods	Agree, and the question is whether the right sites were selected last year? New sites season 18/19 RCGP-RSC: very small sample size due to late ethical approval and pilot study with 5 GPs only HUS: small sample size LNS: joined late, could not provide all data required for inclusion in the pooled estimates NIID: large sample size, but very low vaccination coverage UoA: pregnancy cohort, population cannot be pooled IT-BIVE; fine CIRI-IT: the HCW cohort study subject to bias CIRI-IT TND: fine VHUH: fine So 6 out of the 9 sites did not contribute much information at the end. 3 sites could potentially contribute information next year if larger sample sizes would be achieved/information would be complete. Spain La Rioja did not collaborate this year, whereas they did in the previous season. In addition, it was a very mild influenza season this year. Also we agreed to present IVE by age group x

		on opportunities to improve robustness/precision, generalisability, timeliness, etc. But not being perfect should not be an up front uexcuse not to take (some of) the available limited data serious.	setting x population, implying that the data from THL could not be pooled with the data from the other sites. So despite high expectations, the 'disappointing results' are not unexpected.
#38	From the experience this year and sites to be included what realistically we feel we could generate next year. Is there any need to consider including in the report some words about the feasibility of generating brand specific data every year for each single vaccine?		Added a sentence prior to the recommendation of using secondary data "Generating robust age- and setting stratified brand-specific IVE data for all brands in Europe based solely on TND studies is unlikely to be feasible."
#39	The mock report is critical next year to ensure alignment of the data presentation and to be able to meet the timelines. For the data generated, it should be clarified what should go in intext and what should be out text (annexes) to facilitate the review.		Agree this is the next step forward. We might agree to rewrite the 18/19 report (not for the EMA deadline for this year), but as a way to facilitate the discussion and to pave the way of the mock report.
#40	The heterogeneity between sites should be investigated and also the reason behind the quite important portion of missing data Should the subjects be excluded, a missing category added, or imputation methods used…		Not sure the amount of missing data is that large (see #8)
#41	Approach for confounders/stratifications should be transparent and also be in line with the minimum data set requested.		Being strict on the minimal set of confounders would imply losing some sites. We think the approach of

			covariate adjustment was transparent, but might have to be revisited
#42	Better characterize the characteristic of the population to allow exploring sub-groups or at least be able to describe extensively the populations incl. the specificities		Exploring subgroups while we do not meet the primary objective? We think the exploratory objective on estimating IVE within some chronic conditions is sufficiently telling.
#43	The demographics should be presented for vaccinated/unvaccinated and/or cases and controls (see example below)		The demographics were graphically represented in Figures “Distribution of covariates”, and Tables “Study population characteristics”. The demographics per age, setting and brand are now provided in the Annex (see comment #6).
#44	Impact of confounder-adjustment to be studied. There are many covariates adjusted for relative to the number of cases available. We have applied a fixed and a variable set of covariates per site – but this does not recognize specific confounding indications at the brand or type level due to preferential recommendations– where should we land?		Agree that covariate adjustment is an important topic. Only for Austria and ISS, some records were discarded because of missing covariate information. A working group on covariates will be set up.
#45	A considerable portion of the data could not be used due to missing confounder data. This is a concern because excluding data reduces the statistical power and may introduce bias. Efforts are needed to reduce the amount of missing confounder data. Modern statistical methods to handle missing covariate data should be considered.	(on considerable portion): XX%	
#46	The impact of excluding swab samples that were collected too late is to be investigated.	?	A sensitivity analysis on time between date at symptom onset and swab date was performed.

#47	Where does further standardization make sense? What is “fixable” and what is not?	(on “fixable”): better: what has added value and what does not?	More concrete suggestions?
#48	What are further considerations towards whether data should be pooled and when?		More concrete suggestions?
#49	What are the limitations in the confounder adjustments and how could we further improve? a fixed set for all, or a tailored set for some and by age group? Particularly wrt to comorbidity adjustment and the adjustment for health care visits. Are health care visits (GP/visits) actually a proxy of poorer health conditions? Should we adjust in some way for factors related to preferential recommendations for certain types of vaccines? There is no adjustment for week of the influenza season – why and should we consider? How does previous vaccination affect the analysis? Specifically over 65y are the unexposed perhaps people who generally do not get vaccinated at all? Is there a need for age specific adjustments – rather than a one size fits all. We are not learning if we don’t look into this more closely…..	(on healthcare visits as proxy of poorer health conditions): Similar across EU, so poolable?	Covariate adjustment is indeed an important topic for discussion. We agree to do a post-hoc analysis to better understand the impact of the covariates adjusted for. However, note that we did adjust for week of the influenza season.
#50	The VE for TND studies should be ideally presented unadjusted and adjusted in the same table (see example below)	I agree	Done
			We should have a consolidated list of topics to discuss during the next brainstorming meeting.

EFPIA Review:

The 2018-19 report is more balanced with emphasis appropriately on establishing the system (achieving a number of sites to work in a coordinated fashion), improving standardization and quality of the data and clearly acknowledging the limitations. The non-robust data are not over-interpreted which is considered appropriate given the lack of robustness in the data.

General ISC reply to EFPIA comments (1st round):

ISC1: Agree that this year's study was more about procedural issues and the process and operations necessary to collect timely data for a coordinated and timely analysis across the European region

ISC2: I have little to add to previous ISC comments. I did not see any substantive methodological points raised by EFPIA whose comments largely related to format and issues arising from the lack of power for brand-specific analyses and compliance with the data requirements for DRIVE participants. Also many of the EFPIA comments were in the form of a series of questions eg. *"What are the limitations in the confounder adjustments and how could we further improve? a fixed set for all, or a tailored set for some and by age group? Particularly wrt to comorbidity adjustment and the adjustment for health care visits. Are health care visits (GP/visits) actually a proxy of poorer health conditions? Should we adjust in some way for factors related to preferential recommendations for certain types of vaccines? There is no adjustment for week of the influenza season – why and should we consider? How does previous vaccination affect the analysis? Specifically over 65y are the unexposed perhaps people who generally do not get vaccinated at all? Is there a need for age specific adjustments – rather than a one size fits all. We are not learning if we don't look into this more closely…. ".*
It is unclear to me what EFPIA expects by way of a response here. There was a protocol and stats analysis plan which EFPIA had an opportunity to comment on and these unstructured post-hoc suggestions for potential additional analyses are to me unhelpful unless there is a specific methodological issue in the analysis that they are questioning. The paucity of robust data with sufficient power to provide brand specific VE estimates is the key issue and further analyses suggested by the sort of questions above is not going to help with this.