D4.6 Guideline for interpretation of influenza vaccine effectiveness results

DRIVE 777363
DEVELOPMENT OF ROBUST AND INNOVATIVE VACCINE EFFECTIVENESS

[WP4 – Framework for analysis and study reports]

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Abbreviations

CI	Confidence interval
DRIVE	Development of Robust and Innovative Vaccine Effectiveness
EMA	European Medicines Agency
EU	European Union
GP	General practitioner
ILI	Influenza-like illness
IVE	Influenza vaccine effectiveness
NHS	National Health Service (United Kingdom)
OR	Odds ratio
PCR	Polymerase chain reaction
RR	Relative risk
RT-PCR	Real-time polymerase chain reaction
SAP	Statistical Analysis Plan
SARI	Severe acute respiratory infection
TND	Test-negative design
VE	Vaccine effectiveness
VE%	Vaccine effectiveness expressed as a percentage
WHO	World Health Organization
WP	Work Package

1. Background

One of the objectives of the DRIVE (Development of Robust and Innovative Vaccine Effectiveness) project is to interpret the results of influenza vaccine effectiveness (IVE) studies and communicate their significance to various stakeholder groups.

There are some unique challenges related to estimating and communicating the impact of influenza vaccines. Their effectiveness (unlike that of most other vaccines) varies from season to season due to changes in the circulating viruses and the corresponding reformulations of the vaccine. Effectiveness also depends on other variables including characteristics of the vaccinated person, and vaccination programmes differ in which population groups are being targeted for vaccination. In addition, a variety of study designs are used to estimate IVE: each with their own strengths, limitations and statistical considerations that may influence the observed vaccine effectiveness.

Both naturally occurring variation in vaccine effectiveness and questions related to study design and analytical methods must be considered when evaluating and communicating IVE. This document provides guidelines for interpretation of influenza vaccine effectiveness estimates.

2. Interpreting IVE results

The factors to be considered when interpreting IVE estimates are divided here into external and study-specific factors. Among the former are the annual vaccine composition recommendations by the World Health Organization (WHO) and their eventual match to the circulating viruses. The latter comprise different factors that may influence the IVE estimate of a given study or meta-analysis.

2.1 External factors

Pattern of virus circulation and vaccine match

The pattern of circulation of influenza viruses is not uniform across Europe; it differs in time and place. The WHO attempts to capture this by defining global influenza transmission zones (WHO 2011), and differences are observed even on regional level within countries. The fact that the vaccine viral strain composition for trivalent and quadrivalent vaccines is the same for all of the northern hemisphere for the entire season, yet different viral types and subtypes may circulate at different times in different places, needs to be taken into account when interpreting vaccine effectiveness results. How well the circulating strains match the vaccine strains will have an effect on the observed VE; additional determinants such as egg adaptation of the vaccine viruses are under investigation.

There is a need to consider IVE figures in context with the available molecular epidemiology data. For this purpose, it is helpful to stratify IVE estimates by virus type and subtype/lineage, and possibly clade, whenever possible. This will allow the comparison of vaccine effectiveness against matching vs. unmatching strains of the virus.

Waning protection within season

Concerns have been raised about intraseasonal waning of the protection conferred by influenza vaccination (Puig-Barbera, 2017). Potential explanations underlying waning protection of influenza vaccination have been discussed in the literature. One explanation is an intraseasonal evolving mismatch among the circulating viruses, but also the timing of vaccination, persistence of host

seroprotection in general as well as the effect of immunosenescence especially in the elderly are being studied (Belongia, 2015). Current knowledge is still too limited for thorough understanding of the mechanisms.

There have been several attempts to quantify the waning effect of influenza vaccination during a season. Two methods have been proposed; firstly, to look at time between vaccination and disease onset and secondly to look at the calendar period of vaccination. To understand the size of the intraseasonal waning effect, a stratified analysis is suggested. The challenge is choosing the number of strata and the cut-off point(s). Sullivan et al. (2014) showed that a small shift of the cut-off point could already have a major effect on the early and late VE estimates.

Even though methods are proposed to quantify the effect of waning immunity, it is important to consider all possible explanations for this effect when interpreting the VE estimates from different strata. When the wild virus significantly drifts during the flu season, that should at least be considered as part of the explanation. The effect is then likely to be seen across all age groups. Immunosenescence is typically related to elderly people and might be a possible explanation if the waning effect is only seen in the older age group. Lastly, the type of influenza vaccine used could be an explanation of the size of the waning effect. High-dose and adjuvanted vaccines are believed to be more immunogenic than normal dose non-adjuvanted vaccines (Young, 2017) and a difference in the waning effect might be seen between these types of vaccines.

Another point to consider is that also the unvaccinated may encounter circulating influenza viruses during the season (with or without symptoms) and thus gain protection, or boosting of pre-existing immunity, from these natural encounters. Cumulative natural encounters in the population increase towards the end of the season, and immunity from these may be cross-protective and long-lasting relative to vaccine-induced immunity. Thus, the difference in disease susceptibility between the vaccinated and unvaccinated decreases during the season, leading to decrease in the VE estimate.

Repeated vaccinations

With numbers of annual influenza vaccinations increasing, the effect of repeated vaccination has gained interest. It has been postulated that repeated vaccinations can cause positive or negative interference (Smith et al. 1999). Some studies have found signals of negative interference (Skowronski et al. 2016), but a meta-analysis (Ramsay et al. 2017) found no overall evidence that prior season vaccination impacts current season VE negatively. Nevertheless, more research on the subject is needed, and many studies look at the effect of vaccination in one or more previous seasons.

2.2 Study-specific factors

Study setting & population

It is important to relate VE% to the population that was studied. Many IVE studies take place in a healthcare setting (e.g. a GP practice, hospital or a long-term care facility); the age and comorbidities of study subjects vary accordingly. A hospital setting generally reflects more severe forms of influenza as a GP setting.

Other studies use population-based registries of influenza diagnoses and vaccination information; in these cases, the source population and the swabbing practice may be broader and less well defined. In many cases, population groups will be underrepresented or absent from the study, e.g. due to differences in health-seeking behaviour.

Most studies consider the age group of the included subjects, and may present the VE estimates stratified by age and comorbidities. Vaccine effectiveness is typically better with children and healthy adults than with the elderly. However, even lower VE may be meaningful in the latter group since the incidence of serious outcomes such as hospitalization and death is greater, and vaccination is presumed to lower the severity of influenza illness even when it does not prevent it.

Study design

Cohort studies

When analysing findings from cohort studies, particularly if data are drawn from administrative databases, it is important to assess to what extent the vaccination records are expected to be complete (e.g. general practice databases may not capture vaccinations administered at other settings such as vaccination clinics). Completeness of data on outcomes should also be evaluated; identifying the outcome of interest could be a challenge, e.g. if cohort members can have access to multiple different health care providers (WHO 2017).

Attention should be paid to healthcare seeking bias, which happens in case of differences in healthcare seeking behaviour between vaccinated and unvaccinated subjects, which could overwhelm a true vaccine effect. Vaccinated individuals may be more likely to seek care when experiencing acute respiratory infection-related symptoms or the opposite situation may occur, i.e. vaccinated patients may have less severe disease and thus be less likely to seek medical care. The WHO recommends researchers to determine the care-seeking patterns of the proposed study cohort. Researchers should be able to evaluate the proportion of outcomes that may be missed due to seeking care outside of study facilities or at home self-treatment.

Case-control studies

In case-control studies attention should be paid to possible misclassification of vaccination status, especially when data regarding influenza vaccination are not collected through electronic medical records/registries. Another potential source of bias is the selection of the controls. They should be selected in such a way that the vaccine distribution among them is the same as that in the population that gave rise to the cases. If, for example, hospital-based controls are selected among cases hospitalized for a vaccine-preventable infection, vaccine distribution may be different from that of cases.

The test-negative design

The TND design it is widely used as a method that allows minimizing confounding due to differences in healthcare seeking behaviour between vaccinated and unvaccinated individuals. However, the design is susceptible to other forms of bias. A source of bias may be represented by misclassification of disease in case influenza tests with imperfect sensitivity and specificity are applied. Findings from a study by Jackson and Rothman showed that when disease misclassification occurs, IVE estimates from the TND method are more biased than those from cohort or case-control designs (Jackson & Rothman 2015). However, the relative increase in bias is small when using highly sensitive and specific tests such as RT-PCR for diagnosing influenza, and the advantages in control of confounding by means of the TND method are likely to outweigh the bias due to outcome misclassification.

Outcomes studied

Non-specific outcomes, such as ILI and all-cause mortality, are sometimes used in IVE studies but lack laboratory-confirmation. Only a fraction of these outcomes are likely to be attributable to influenza. Interpreting IVE against these outcomes as a proxy for IVE against influenza disease leads

to an underestimation of IVE. Influenza virus causes a wide range of clinical disease and sequelae, therefore patients fulfilling ILI and SARI definitions and patients routinely swabbed by clinicians because of suspicion of influenza do not represent all influenza patients, and the hidden disease burden remains large. It should be noted that even a low VE against non-specific outcomes may indicate much higher absolute reduction in the disease burden than a high VE against a specific outcome (Palmu et al. 2015).

Vaccine type used

Valency

Two types of formulations are available. The conventional trivalent vaccine contains both circulating influenza A viruses (H1N1 and H3N2 subtypes) and one influenza B virus. However, since trivalent vaccines have been shown to be less effective in case mismatches between the influenza B vaccine component and the circulating B strain occur, quadrivalent vaccines have been made available to provide a broader protection against circulating influenza B viruses (ECDC 2018). The quadrivalent vaccines contain both influenza B lineages.

Split and subunit vaccines

Split vaccines consist of disrupted virus particles whereas subunit vaccines contain the major influenza virus surface glycoproteins hemagglutinin (HA) and neuraminidase (NA), while lacking inner antigens and lipopolysaccharides. They are commonly used in TIV formulations, although they are now available for QIV vaccines as well.

Intradermal vaccines

Beyond the standard intramuscular split vaccines, an intradermal influenza split vaccine is being administered in some countries in adults (this vaccine is recommended from 18 years). The aim of the intradermal administration is to improve the immune response by activating other arms of the immune system. The high density of antigen presenting cells in the skin allows for antigen dose-sparing in adults (9 mg HA), whereas the elderly still need a normal dose of 15 mg HA.

Adjuvanted vaccines

Adjuvanted inactivated vaccines contain HA and NA purified antigens adjuvanted with MF59 (an oil-in-water emulsion which consists of biodegradable squalene oil droplets stabilized by non-ionic surfactants) or AS03 (squalene and α-tocopherol). Studies indicate a better protection conferred by adjuvanted vaccines in the elderly (Domnich et al. 2017, Chada et al. 2017). Adjuvanted vaccines are generally recommended for the elderly and high-risk patients. Therefore, patients who receive adjuvanted vaccines are generally older, with comorbidities and with reduced functional status.

Intranasal vaccine

Intranasal vaccines contain the live-attenuated influenza virus, they have been approved in the EU/EEA for children and adolescents (2-17 years of age). All live attenuated influenza vaccines currently available are quadrivalent combination vaccines containing two influenza A strains and two influenza B strains as per the WHO recommendations.

Dosing

In unprimed populations, such as children younger than 9 years and never vaccinated against influenza in the past, two doses split-virus and subunit vaccines are recommended to achieve adequate immunogenicity.

Specificity / granularity

As vaccine effectiveness differs from population to population (e.g. across age groups and depending on the presence of chronic conditions), VE results that are stratified by some of these factors are generally more informative than a single VE figure for the whole population. However, the granularity of the possible estimates is subject to the available sample size which in turn depends on both the severity of the season and the capacity of study sites to enrol patients in the study. Brand-specificity is a special case of granularity (please see *Sample size and confidence intervals,* below and also the sample size calculations in the DRIVE core protocols D7.1 & D7.2).

When a single VE percentage is used to describe the effectiveness of a vaccine in a large and varied population, the information should be considered in relation to the characteristics of that population, e.g. age distribution. Many surveillance systems capture predominantly older influenza patients which may drive the collective VE estimate towards lower values.

Sample size and confidence intervals

Sample size

Optimal sample size for single sites in a brand-specific vaccine effectiveness study depends on the study design (cohort design requires a larger sample size than case-control), influenza attack rate among unvaccinated persons (lower sample size with higher attack rate in cohort studies), the influenza vaccine coverage (overall, type-specific and brand-specific) and the vaccine effectiveness itself (if VE is low, sample size will need to be larger to detect the effect).

For discussion of sample size in the DRIVE perspective, please see the sample size calculations included in the core protocols (D7.1 – D7.2).

Confidence intervals

The uncertainty surrounding VE estimate is determined both by the variability of the data and the sample size. The less variation in the data and the larger the sample size, the lower the uncertainty around the VE estimate. Uncertainty is expressed using confidence intervals (CI). A 95%CI means there is 95% confidence that the interval will cover the true population VE.

VE estimates that are based on studies with low sample size and estimates with wide confidence intervals should be interpreted with caution.

Statistical analysis

The statistical analysis of VE data must be consistent with the design of the study and should adjust for confounding (see below). The analysis of the data of a nested case-control design, for example, depends on the how the controls were sampled (by cumulative sampling or by density sampling). Another example is that in the analysis of the data of a case-cohort design the possible overlap between cases and controls (i.e. cases that were also sample as controls) must be allowed for. Confounding can be adjusted for either by multiple regression or by propensity scoring. In the first

approach confounding is eliminated by including confounders as covariates in the regression model. Propensity scoring is an alternative to multiple regression to estimate the effect of treatments in observational studies. The goal is to balance observed covariates between treatment groups in order to mimic what happens in a randomized study. The two analysis methods yield similar results.

For the DRIVE approach to statistical analysis, please see the DRIVE *Statistical Analysis Plans*.

Bias and confounding

Bias occurs if the estimated VE differs systematically from the true VE. In VE studies there are many potential sources of bias. Examples are, amongst others, measurement error, selection bias and confounding. If the specificity of the diagnostic test for influenza infection is imperfect, the VE will be underestimated. Selection bias occurs when the subjects selected in the study are not representative for those eligible for the study. Confounding is a special type of bias, a mixing-up of effects, which distorts the relationship between vaccination and the risk of infection, and which therefore must be eliminated. A factor is a confounder if it is a cause of both vaccination and infection. 'A is a cause of B' should be interpreted in the non-strict sense that there is a statistical relationship directed from A to B. Thus, if the likelihood of being vaccinated increases with age, then age is said to be a cause of infection. Confounding can be reduced either in the design phase of the study, by matching or by making the source population more homogenous, or during the statistical analysis phase, by means of regression or propensity scoring. Not all types of bias can be eliminated in the statistical analysis. Measurement bias and selection bias, for example, cannot be eliminated statistically. These biases are best avoided during the design phase of the study.

For more information on bias and confounders, please also see DRIVE D4.1: *Methodology guidelines for concerted analysis of data and control of confounding factors* and the upcoming systematic review of bias and confounding under DRIVE task T2.1.

Crude VE estimates

A crude vaccine effectiveness estimate is an estimate that is not adjusted (corrected) for confounding. Sullivan and Cowling (Sullivan et al. 2015) point out that a crude VE estimate express the correlation of vaccination with influenza, but may not be an accurate estimate of the causal effect of vaccination on the risk of influenza.

Pooling of several individual studies

Pooled estimate

In the aggregate-data meta-analysis, VE estimates from individual sites are combined into a weighted average of the individual estimates. The major advantage of a meta-analysis is the increased power it has compared to individual studies (i.e. the probability to detect an effect of vaccination if such an effect is present).

Between-study heterogeneity

Statistical heterogeneity refers to the variability between influenza vaccine effectiveness estimates in studies included in the aggregated data meta-analysis that goes beyond variability expected due to chance (Cochrane 2011). Sources of heterogeneity include bias, true underlying differences in vaccines effectiveness from country to country (e.g. due to differences in population or influenza strain circulation), bias, chance, and methodological factors. The pooled estimate has been calculated using a random-effects model, which assumes VE can vary due to underlying difference in vaccine

effectiveness and chance (Riley et al. 2011). To minimize the impact of differences in methodology on multicentre VE estimates, protocols should be harmonized.

An indication for the heterogeneity among estimates from different study sites is obtained by calculating I2. The I2 statistic is to be interpreted as the proportion of total variation in the estimates of treatment effect that is due to heterogeneity between studies. Low, moderate and high levels of heterogeneity correspond to I2 values of 25%, 50% and 75%, respectively. Generally, the lower the heterogeneity, the more meaningful the pooled estimate as a description of vaccine performance. In case I2 is high, it is worthwhile to explore sources of heterogeneity.

3. Communicating IVE results

The interpretation of vaccine effectiveness results goes hand in hand with communicating them to various stakeholder groups including healthcare professionals, decision-makers, regulators, media and the general public. To understand the communications methods and needs, DRIVE Work Package 5: *Communication and dissemination of results* has developed a web-based survey directed at the "level 1" stakeholders identified in D5.1: *Communication of a detailed stakeholder map for the DRIVE Project,* which includes the identification, grouping and layering of all stakeholders. In addition to the information gained by the survey, the materials provided by public health authorities such as the NHS, ECDC and CDC have been analysed. In 2018–2019, DRIVE will continue to gather information of the different stakeholder groups' needs and seek input from regulatory agencies and the public health community.

3.1 Describing VE verbally

Vaccine effectiveness may be defined as the fraction of influenza cases directly prevented by the vaccination (and not by other, indirect vaccine effects such as herd immunity). It is often described by a percentage (VE%): if in a population 15% of the unvaccinated people become infected with influenza compared to 6% of the vaccinated people, then the vaccine effectiveness is (15%-6%)/15% = 60%.

While VE% point estimates and corresponding confidence intervals are often used in scientific communications and within the public health community, it is important to communicate their meaning also in lay terms. However, a single set of guidelines to translate VE% into words may be difficult to establish, e.g. because the expected VE differs across groups of vaccinees (e.g. young vs. elderly adults) and because the uncertainty represented by confidence intervals needs to be taken into account. An indicative guideline for verbalizing VE% point estimates, with the reservations outlined above, is presented in Table 1.

VE point estimate (%)	Interpretation
0 – 30	"low"
31 – 50	"moderate"
51 – 75	"good"
76 – 100	"very good"
Table 1. Indicative guideline for verbalizing VE% point estimates.	

Other approaches to describe the impact of a vaccine include averted cases (e.g. influenza infections, hospitalizations or deaths) or the number needed to vaccinate (NNV) to avoid one outcome. Presented this way, the information may be more concrete and easier to understand. However, additional information besides VE% (incidence of the event in question, vaccine coverage) is needed to provide these figures, and these may not be routinely or reliably available.

Whatever the chosen metric, it is not necessarily meaningful to evaluate the effectiveness of influenza vaccines on the same scale as with other vaccines. Even if the seasonal IVE would not be satisfactory during some years, the long-term effect of the vaccination will save lives especially in the vulnerable groups.

3.2 Presenting VE graphically

For communication purposes, clear infographics may be preferable to lengthy verbal descriptions. Examples of influenza infographics produced by public health authorities for a variety of stakeholders are listed below; however, many of these focus on trends in the circulation of influenza viruses or the burden of influenza; vaccine effectiveness is not necessarily included.

- ECDC (https://ecdc.europa.eu/en/seasonal-influenza/surveillance-and-disease-data/seasonal-overviews; https://ecdc.europa.eu/en/seasonal-influenza/prevention-and-control/vaccination-infographic)

- FluNewsEurope (http://flunewseurope.org/)

- EuroMOMO (http://www.euromomo.eu/)

- CDC (https ://www.cdc.gov/flu/resource-center/freeresources/graphics/infographics.htm)

- THL (www.influenssa.fi; https://thl.fi/documents/605812/3528827/Tietoa+influenssasta_infograafipdf.pdf/6a24818a-3826-44b8-b79c-55a73de5062d)

The scientific communications of DRIVE will use forest plots (Figure 1) to describe pooled influenza vaccine effectiveness estimates. This is a conventional way of presenting the results of a meta-analysis; however, the value of other types of graphical presentation will be explored during the course of the project.
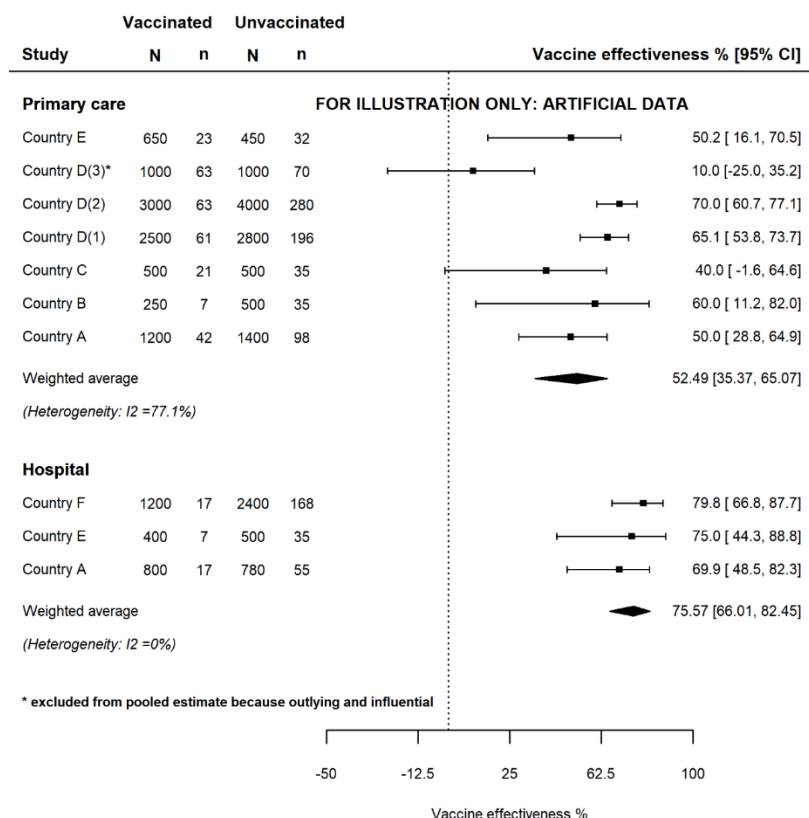
Figure 1. Forest plot describing meta-analyses of IVE by health care setting (artificial data for illustrative purposes).

3.3 Communicating to specific target groups

Some recommendations of communicating IVE (e.g. the use of clear and concise language) are true for all stakeholders; others are more specific to the various stakeholder groups.

Public health institutes

Public health institutes (PHIs) have often a crucial role in informing vaccination policy and providing guidance to clinicians, and need vaccine effectiveness results to fulfill these tasks. Some, but not all, carry out their own vaccine effectiveness studies.

Based on the results of the DRIVE communications survey, information communicated by the PHIs comprises the burden of influenza illness, the benefits of influenza vaccines in general, and in some cases, IVE results in particular. The target groups for communication range from social and health care professionals to medical schools, media and the general public. The communication methods include publications in peer reviewed journals, national and international conferences, direct weekly reports, and websites. Some public institutions offer separate information pages for general public and health professionals, and display the VE% only on the professionals' section. Nevertheless, they use various phrases to communicate that while the vaccine does not offer perfect protection, there are several reasons to get it all the same (milder illness that otherwise etc.). Some stress the number of flu-related deaths in children. Many offer links to scientific articles.

Some PHIs that have answered the DRIVE communications survey have highlighted unanswered needs in IVE results (e.g. unavailability of IVE by age group, IVE of different vaccine types and brands,

or IVE according to geographic area and severity of influenza).

Decision makers

Ministries of health and comparable political bodies are expected to share many of the same information needs as public health institutes. Especially in countries where vaccine purchases are centrally organized, the decision makers need vaccine effectiveness estimates for cost-effectiveness calculations and to direct vaccination programmes. (See also DRIVE D3.1: *Report on the sources for usage of specific influenza vaccine brands and accessibility* for country-to-country differences in vaccine purchase and delivery systems.)

When communicating IVE to decision-makers, economic scenarios and the aspect of saved resources (in terms of e.g. averted hospitalizations and sick leaves) may be more relevant than with other stakeholders.

Healthcare professionals

In most countries, healthcare professionals such as doctors and nurses have a major role in providing vaccines and carrying out vaccination programmes. In order to perform these roles, they need to be aware of the incidence and potential severity of the influenza illness.

In addition to providing vaccine effectiveness figures, it is also important to address other issues such as perceived concerns over vaccine safety. Easy-to-understand measures of vaccine effectiveness and tools such as infographics may help in communicating the benefits of influenza vaccination to patients.

Table 2. Summary: Interpreting IVE estimates

Consider the characteristics of the study

- Study setting & population
- Study design
- Outcome studied
- Stratifications used

Assess the strengths and limitations of the study

- Generalizability
- Sample size & confidence intervals
- Completeness of information
- Bias and confounding

Consider the vaccines used & vaccine match

- Vaccine type
- Vaccine viral strain composition (WHO recommendation)
- Pattern of virus circulation using surveillance data

Translate the IVE estimate into concrete terms

- Verbal description
- Infographics
- Outcomes averted (infections, medically attended visits, hospitalizations, deaths)
- Cost-effectiveness
- In relation to other published estimates

Adapt the communication to the specific needs of the audience.

General public and media

The general public – representing all stakeholder groups outlined above as well as the targeted groups for influenza vaccination (that differ somewhat between countries) – are the people to finally make the choice of whether to get vaccinated. The media, on the other hand, can be an important partner in communicating influenza-related messages including vaccine effectiveness.

When communicating to the media or the general public, some PHIs choose to not emphasize the exact vaccine effectiveness figures focusing rather on the more general messages of protecting oneself and others through vaccination. The use of clear (and sometimes colloquial, e.g. "flu jab") terminology is important.

The ability of media to spread influenza-related messages is often greater than the that of public institutions. News stories often capture stories of human interest; therefore, it can be useful to liaison with healthcare professionals "in the field" who can tell how the seasonal epidemic is being experienced on the local level. News stories also tend to seek novel or unexpected angles to the influenza epidemic.

Regulators

After the pilot season of 2017/18, DRIVE will engage in dialogue with the European Medicines Agency and other relevant regulatory agencies. This section will be updated accordingly.

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