Global Seasonal Influenza Disease and Vaccination: A Paradox With Substantial Public Health Implications

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Abstract

Evidence of the global benefits of seasonal influenza vaccination has been collected in a multitude of studies over 50 years, from many countries and under many epidemiological conditions. WHO recommends the use of influenza vaccines for annual vaccination of specific at-risk groups. Despite the global recommendation, there is a wide held belief, including amongst health care professionals, that current influenza vaccines are only modestly effective. Since health authorities use national health data to define and implement national health policies, influenza vaccine effectiveness data often comes from national or local studies which are substantially affected by special and temporal epidemiological circumstances, such as antigenic match, extent of virus circulation, and pre-vaccination immune status of the study population. Still other countries, with insufficient influenza-related disease surveillance systems in place, fail to offer seasonal influenza vaccination, due to insufficient data, exposing persons at serious risk to otherwise preventable influenza infections and avoidable serious health outcomes. Rather than defer implementation of seasonal influenza vaccination, pending better local evidence of influenza vaccine benefits, it is proposed that the pool of available evidence on influenza vaccines, the “global file on influenza vaccines”, should be used as the basis for vaccination policies globally. This would make immediate the benefits from current influenza vaccines, for which the benefit-risk ratio is overwhelmingly favourable. The “global file on influenza vaccines” could be updated every 3-5 years, and could be utilized by health authorities for positive social media interactions and conversations with the public on the health value of seasonal influenza vaccination.

1. Introduction

Unlike for most vaccine-preventable diseases, where immunity from vaccination is long-lasting (several years to a lifetime), seasonal influenza vaccination must be repeated annually to prevent infection with new strains, which are constantly emerging. Annual revaccination poses challenges for achieving and sustaining a high vaccination coverage rate in high-risk groups. But vaccine hesitancy, misinterpretation, and unjustified extrapolation of specific local vaccine effectiveness data, are also major contributors to low vaccination coverage rates for seasonal influenza vaccination.

Outcomes of influenza vaccine effectiveness studies are substantially affected by special and temporal epidemiological circumstances, such as antigenic match, extent of virus circulation and pre-vaccination immune status of the study population. Without documentation or knowledge of these variable study-specific parameters, credible general conclusions about the potential vaccine benefits cannot be drawn from such point estimates. In addition to vaccine effectiveness, vaccine coverage rates also determine the level of reduction in disease burden that can be achieved by public health immunization programs.

Evidence for the global benefits of seasonal influenza vaccination has been collected in a multitude of studies over 50 years, from many countries and under many epidemiological conditions. The overall benefits and risks associated with influenza vaccines are re-evaluated periodically by the WHO[1] and some national health advisory bodies, such as ACIP[2] in the USA. The pool of available evidence on influenza vaccines in various formulations and vaccination programmes, for which the benefit-risk ratio is overwhelmingly favourable, could be labelled the “global file on influenza vaccines”. It is proposed that the implementation of current influenza

immunization recommendations should not be deferred pending better local evidence of influenza vaccine benefits, or until new alternative vaccines are available, but rather that the current "global file on influenza vaccines" should be used as the basis for implementing seasonal influenza vaccination policies globally. This would make the benefits from current influenza vaccines immediate. Every 3-5 years, updates of the "global file on influenza vaccines" can be used to identify the potential need for adaptation of the current global - or national - policies.

Acceptance of - and compliance with - recommended immunization policies are influenced by scientific evidence but also by the mechanisms that underlie vaccine hesitancy. The internet is increasingly promoting doubts about vaccine benefits and fears over vaccine safety. Global and national health authorities are challenged to maintain a trustworthy reputation while acting as strong advocates of vaccination and opposing disinformation. Positive interaction and conversation with target audiences on social media may therefore become an important tool for public health authorities and experts with an interest in disease control and management. The "global file on influenza vaccines", would allow for more general evidence-based conclusions on the benefits of influenza vaccination, and could underpin communications on the public health value of seasonal influenza vaccination.

2. Impact of annual influenza virus infections

Even in healthy adults, where the medical consequences of acute influenza infection are usually limited to fever, cough and malaise, and recovery occurs within a week or so, without further sequelae, influenza poses a serious socio-economic burden due to absence from work and loss of productivity.[3] In children under the age of 5

years, persons with underlying medical conditions, and in older adults, influenza poses a serious medical threat due to infection-related complications or exacerbation of underlying non-communicable diseases. In frail or older persons, an episode of influenza infection may result in loss of independence.[4]

The annual burden of influenza-associated disease, hospitalizations and deaths is well recognised and documented.[1,3,5 6] But as the quality of influenza surveillance varies largely between countries, ranging from very poor in some, to highly sophisticated, with linked databases, in others, awareness of disease burden at the community level is also highly divergent. Both the quality of influenza surveillance and awareness of disease burden affect a country's ability, and resolve, to reduce the disease burden.

The literature is clear: influenza infections, and associated disease, occur in all parts of the word.[6] Influenza viruses are not contained by geographical borders and influenza recurs globally every year, albeit with different epidemiological patterns in different parts of the world. Therefore, it is reasonable to assume that countries without, or with limited, surveillance infrastructure to monitor influenza disease, have a similar disease burden to countries in the same geographic region where the disease burden has been well established by sophisticated surveillance systems.

3. Influenza virological surveillance and vaccine composition

The first isolation of influenza virus in humans by Smith, Andrewes and Laidlaw, in 1933,[7] was followed shortly thereafter by the development of a first influenza vaccine in 1944.[8] Since then it has been recognised that influenza viruses constantly undergo antigenic drift, and sometimes shift, which require continuous global virological surveillance to monitor the most recent antigenic changes. The WHO Global

Influenza Surveillance and Response System (GISRS) was established in 1952 to monitor these changes.[9] The GISRS publishes twice-yearly recommendations for vaccine composition, based on the findings from global surveillance.[9, 10]

4. Vaccination policy recommendations and associated dilemmas for policy makers

WHO recommends the use of influenza vaccines for annual vaccination of specific at-risk groups.[1] The most recent recommendations by WHO[1] are based on thorough analysis of all available literature using the GRADE methodology[11] for analysis of vaccine benefits and risks for different at-risk sub-populations.

At a national level, though, health authorities use national health data to define and implement national health policies. Since many countries have insufficient influenza-related disease surveillance systems in place, this may in fact impede the elaboration and implementation of national influenza prevention policies.

This poses a huge public health dilemma, since national borders offer no defence to the threat of influenza: should vaccination be offered based on the global evidence and experience or not because of insufficient national surveillance infrastructure and therefore insufficient national data? Unfortunately, the latter is frequently common practice, exposing persons at serious risk to otherwise preventable influenza infections and avoidable serious health implications.

In a recent WHO paper,[12] providing an overview of countries with existing national recommendations for influenza prevention and control, only 28 – 47% of countries with national influenza vaccination policies target specific high-risk groups. Moreover, national immunization policy was associated with income level, which may also be a proxy for

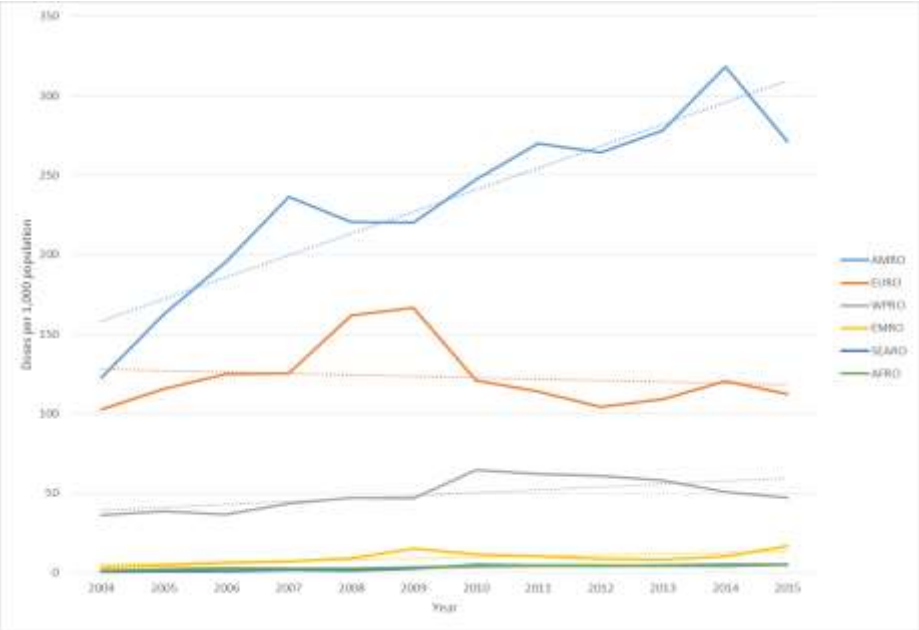
surveillance infrastructure, making it likely that many countries without national vaccination policies have no, or limited, local surveillance data.

Despite the thorough WHO analyses many people, including health care professionals, believe that current influenza vaccines are only modestly effective. This may be one of the reasons why there is poor compliance with the WHO recommendations, as reflected by the current global distribution of influenza vaccines.[12, 13]

5. Uneven global seasonal influenza vaccine distribution

Figure 1 shows the vaccine distribution rates (as proxy of vaccine usage) for six geographical regions in the years 2004 to 2015.[13] Only in the Americas is there an upward trend; in all other regions, rates are stagnating at a modest or low level indicating a huge regional disparity of vaccine usage in the world and a huge annual burden of otherwise avoidable influenza-associated disease. In 1986, Mostow[14] referred to influenza as "a preventable disease not being prevented", a statement still applicable in 2018 in many countries.

Figure 1. Regional trends of seasonal influenza dose distribution per 1,000 population.



6. Vaccine effectiveness: caution about drawing general conclusions on the impact of annual influenza vaccination campaigns

Influenza vaccination programs, on a population level, have been evaluated by estimating the absolute numbers of outcomes prevented by vaccine (e.g., physician visits, hospitalisations, deaths, etc) during epidemics (vaccination impact studies). For example, Kostova et al.[15] and Preaud et al.[16] found that seasonal influenza vaccination prevented, on average, around 10,000 influenza-related cases per million population, for the 2005-2006 to 2010-2011 seasons in the United States and for the 2003-2004 to 2009-2010 seasons in countries of the European Union, respectively. Prevented disease burden, derived from vaccination impact studies, and presented in absolute numbers, is easier to understand and interpret than the relative risk reduction (vaccine effectiveness, see below). However, such studies require the

ability to document diagnostic criteria, and access medical records and death certificates, depending on the outcomes being measured, in addition to requiring surveillance data on epidemiological conditions like virus attack-rate, vaccination coverage, and vaccine effectiveness, in the study population. The health infrastructure and ability to estimate these parameters may not be available in many countries, hampering the assessment of vaccination program outcomes at a local or national level.

One of the parameters needed for vaccination impact studies is vaccine effectiveness (VE), the fraction of influenza cases directly prevented by vaccination. VE is not an intrinsic property of a vaccine, but an outcome of vaccine performance under specific epidemiological circumstances. Ideally, VE is assessed by randomised controlled trials (RCTs), where volunteers are assigned, at random, to receive either vaccine or placebo, and monitored for influenza-related events during the following epidemic period. VE is then calculated from the infection or disease risk rates in vaccinated and unvaccinated persons. Randomisation guaranties that factors modulating VE, but unrelated to vaccine, like the risk of virus exposure, are equally distributed in both groups. As RCTs are ethically debatable, logistically complex, and costly to perform, another study design is increasingly being used nowadays: the observational test-negative case-control trial (tn-CCT). For the latter, the equal distribution of VE modulating factors is not guaranteed, which may increase the chance of a biased result. Epidemiologists and statisticians are still debating the comparability of RCT and tn-CCT.

But however it is assessed, VE is strongly dependent on at least three related factors: the pre-seasonal immunity in the population, due to age-dependent previous exposure to

influenza; the match between the circulating virus and the vaccine strain (which is imperfect in case of antigenic drift and shift); and, the extent of virus circulation. These factors vary extremely in place and time, affecting VE-estimates. Proper interpretation of a given VE-estimate, therefore, requires knowledge of these specific epidemiological factors, which are often not reported and unknown.

Single VE measurements are suitable to evaluate the performance of an influenza vaccine under specific spatial and temporal epidemiological conditions, but they cannot be used to evaluate the performance of a vaccine in general, nor to predict the vaccine performance under different epidemiological circumstances or in the future. Ignoring this may lead to a seriously biased perception of influenza vaccination in the public domain. Generalised conclusions can only be drawn by proper meta-analyses of a large quantity of VE studies under many epidemiological situations in different years at different locations, so that the influence of differing epidemiological conditions can be defined and disentangled.

Similarly, comparisons of new influenza vaccine brands, or types, to existing influenza vaccines, would need to be made in large, properly-sized, clinical trials covering various natural epidemiological conditions.

The importance of considering the epidemiological context of a VE study is manifest by an extensive literature review on the impact of influenza vaccination in the elderly, by Jefferson et al.,[17] in 2010. The authors concluded that: "The available evidence is of poor quality and provides no guidance regarding the safety, efficacy or effectiveness of influenza vaccines for people aged 65 years or older". This conclusion attracted wide media and public attention as evidenced by these headlines in the New York Times, "Doubts Grow Over

Flu Vaccine in Elderly"[18] and in the Daily Mail UK "Flu vaccines 'not worth the bother' says expert".[19] But in 2013, when Beyer et al.,[20] re-analysed Jefferson's literature collection, they identified and adjusted for a number of methodological shortcomings in the original analysis, related to the specific epidemiological factors and concluded: "We regard these findings as substantial evidence for the ability of influenza vaccine to reduce the risk of influenza infection and influenza-related disease and death in the elderly". This is a clear example of the potential for misinterpretation of influenza vaccine effectiveness studies[i].

Furthermore, even when the VE value is as low as 10 to 20%, substantial numbers of cases can be prevented if a high vaccination coverage rate is achieved (Table 1).

i The conclusions from Jefferson et al are often cited as a source of skeptism about the benefits of influenza vaccination in the elderly, whereas the conclusions from Beyer et al often go unnoticed by health care professionals and the lay press.

[ii] Absolute number of prevented cases = Number of population * AR * VC * VE, where AR = attack rate (chance of exposure/infection/disease); VC = vaccine coverage (chance of vaccination); VE = vaccine effectiveness (chance of prevention).

Table 1. Influence of vaccine effectiveness and vaccine coverage rate on absolute numbers of influenza cases prevented at an assumed attack-rate of 10% (moderate season).

Numbers of clinical influenza cases prevented by vaccination at an attack rate of 10% Per million population[ii]				
Vaccine coverage	Vaccine effectiveness			
	10%	20%	50%	70%
10%	1,000	2,000	5,000	7,000
20%	2,000	4,000	10,000	14,000
50%	5,000	10,000	25,000	35,000
70%	7,000	14,000	35,000	49,000

Because of the numerical impact of vaccination programs, even at low VE, the implementation of the WHO recommendations is justified. Furthermore, failing to vaccinate risk groups would be counter to ethical and evidence-based medical practice, given the global evidence of the benefits.

Based on these arguments, national health authorities would be well advised not only to depend on local data to support vaccination policies but rather to also rely on WHO recommendations supported by global data. In parallel, expansion or establishment of influenza disease surveillance capacity would enable countries to supplement global data with national data over time, and to adapt or modify national recommendations and practices accordingly.

7. Global file for influenza vaccines

As argued before, the potential benefits of national influenza vaccination programs cannot be generalised from local single studies. Instead, the evidence for the global benefits of seasonal influenza vaccination has been collected in a multitude of studies over 50 years, from many countries and under many epidemiological conditions. The overall benefits and risks associated with influenza vaccines are re-evaluated periodically by the WHO and published as a "position paper"[1] documenting and articulating influenza immunization policy recommendations. In addition to the WHO recommendations, many countries have National Immunization Advisory Groups that also review the available evidence and formulate national immunization recommendations.

Given the intrinsic unpredictability of influenza epidemiology, the "global file on influenza vaccines" would constitute the 'general' evidence for vaccination recommendations, but not serve to predict the influenza-associated disease burden, nor

to predict the vaccine-preventable burden of disease in a particular year. The nature of influenza epidemiology is such that the reduction of influenza-associated outcomes due to vaccination will be much less in some years than in others. But even in years when vaccine effectiveness is low, vaccination should not be misconstrued to be of little value to public health (see Table 1).

Annual vaccine effectiveness studies should not be conducted for the purpose of assessing the local seasonal benefits of vaccination campaigns in a particular year, but more so to expand and keep the "global file of evidence" updated. Periodic thorough reviews of the literature, perhaps every 3 to 5 years, will allow the general evidence for policy recommendations and practices to be regularly updated.

8. Scientific- and public debates on influenza vaccination: transparency and communication in the public domain

Communications on low vaccine effectiveness values often lead to the perception by medical professionals, and the public, that influenza vaccination may not be effective. This is a frequently cited barrier in vaccination surveys. This "biased" perception is amplified by the fact that scientific and public discussions attract attention mainly in years where low vaccine effectiveness estimates are reported. Such perceptions may contribute to vaccine hesitancy and may undermine implementation of, and compliance with, recommended influenza prevention policies.

It would be more appropriate, and beneficial for public health, to communicate on the evidence from the "global file on influenza", acknowledging the limited predictive value of the evidence for any given influenza

season. The rationale for the use of meta-analyses, which is to draw more general conclusions on the benefits of influenza vaccination, to update the "global file on influenza", and to adapt recommendations for vaccination, would need to be properly and transparently explained by public health authorities and medical professionals.

In September 2017, at the ESWI meeting in Riga (http://eswi.org/influenzaconferences/), a group of influenza experts, the Steering Group on Influenza Vaccination, launched an "Influenza Manifesto".[21] The Influenza Manifesto takes a firm position on the public health benefits of influenza immunization, calling for "more action to increase seasonal influenza coverage rates in Europe to reduce the burden of this disease, and therefore improve citizens' health outcomes and quality of life". It notes that influenza is a life-threatening disease, particularly dangerous for vulnerable groups, and that influenza vaccination is one of the greatest medical achievements of the past century, and can play a key role in the fight against antimicrobial resistance. It goes on to note that given that seasonal influenza vaccination coverage rates remain low in most countries in Europe, and are declining in many, a comprehensive understanding of the safety and benefits of seasonal influenza vaccination is required. The Manifesto calls for the challenges to be addressed with holistic, people-centred, health system-wide approaches. The Steering Group on Influenza Vaccination may prove to be a model for reliable, balanced, and effective communication about influenza and its prevention and appeal to healthcare workers (HCWs) looking for independent information and advice on an appropriate attitude towards influenza immunization.

Increased vaccine hesitancy and distrust of health authorities is also occurring for routine children's immunization programmes in an increasing number of

countries. Vaccination uptake rates are declining, leading to measles outbreaks in countries where the disease had already "disappeared".[22] Health authorities are challenged to maintain trust and confidence in vaccines for diseases that have vanished. Further undermining confidence in vaccination are doubts about vaccine effectiveness. Although measles vaccination is highly effective in a fully susceptible population, vaccine effectiveness in a clinical observational trial would be near 0%, because measles cases would virtually not occur in both vaccinated and unvaccinated persons.

Contributing to the growing vaccine hesitancy, the internet increasingly promotes fears over vaccine safety. The big challenge for global and national health authorities is to maintain a reputation as trustworthy and transparent health care providers, and act as strong advocates of vaccinations to oppose disinformation. Since it is well documented that emotional barriers (or drivers) for behaviour cannot simply be countered with scientific data, behavioural intervention programmes are likely to be more useful[23].

Traditional methods of encouraging target populations to benefit from influenza immunisation programmes have failed to increase uptake in many countries. Positive interaction and conversation with target audiences via internet may therefore become an important tool for public health authorities and experts with an interest in disease control and management. The Influenza Hub (http://influenzahub.com/) partnership was formed to explore alternative ways of reaching audiences and changing behaviour. The assumption behind this project was that social media are both a threat and an opportunity to promote the benefits of vaccination. The strategy was to create a social media campaign to provide targeted information to high-risk groups. The first campaign covering the 65+ population

on Facebook in France and Germany highlights flu severity and impact while addressing wide-ranging questions and using peer-to-peer shareable assets to connect with broader audiences. First results show that the messages are reaching a very active and engaged audience and have increased awareness about the dangers flu and the need for vaccination.

9. Conclusion

Persistent discussions and potential misinterpretation of local VE data for seasonal influenza vaccination has contributed to the erosion of confidence in seasonal influenza vaccination and is detrimental to optimizing the public health benefits of available vaccines. Furthermore, social media are increasingly used to spread misconceptions and fears about the safety and benefits of seasonal influenza vaccination.

To enhance the implementation of seasonal influenza vaccination campaigns, thought leaders and public health authorities would be well advised to resort to the use of evidence compiled in the "global file on influenza vaccines" to design and adapt vaccination programs, and to communicate on the general benefits of seasonal influenza vaccination. Evidence from the "global file on influenza vaccines" is robust and compelling and is generalizable, unlike local data for which context is often lacking. Establishing a convention to favour the use and communication of evidence from the "global file on influenza vaccines" over local data, could go a long way to redress trends in vaccine hesitancy, and allow health authorities to reap greater trusted benefits from seasonal influenza vaccination.

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Conflict of interest

Dr. Abraham Palache is founder of FluPal Consultancy BV, a private company that provides expertise and services to private and public institutions, in the field of influenza and influenza vaccinology. He chairs the Policy, Practice and Communication subgroup (PPC) of the International Federation of Pharmaceutical Manufacturers and Associations' (IFPMA) Influenza Vaccine Supply International Task Force (IVS). He is also a member of the Influenza- and External Affairs Working Group of Vaccines Europe.

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