Future Perspectives for Influenza Prevention – A Global Paradox

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Introduction

According to WHO, vaccines are the cornerstone for the control of influenza. Therefore, this global health organization, and many national health authorities, recommend annual immunizations against influenza. The WHO runs a global surveillance system to monitor the continuously changing influenza viruses to identify and recommend each year the best possible vaccine composition for both the Northern- and the Southern Hemisphere.

Influenza surveillance, epidemiological and vaccine research is, relatively, quite new in Asia, and, as a consequence, much of our knowledge of the epidemiology of influenza disease and the vaccines used to protect against it is derived from research carried out in the western world.

In more recent years, particularly since the emergence of the highly pathogenic H5N1 avian influenza virus in the late 1990s, interest in influenza and influenza control has been aroused in developing countries in South East Asia.

For many years, developed countries in the western world have recommended the use of influenza vaccines for certain groups, who were believed to be at increased risk of complications associated with influenza infections. Over time, these countries developed different strategies to advocate vaccine usage and implement vaccination guidelines.

Although influenza immunization implementation strategies need to fit the country-specific circumstances, the collective experience gained during the last 60 years of usage may offer guidance for other countries which may decide to initiate active influenza prevention policy.

In this article, we discuss seasonal influenza disease and control measures as recommended by WHO and many national health authorities. The article provides data to demonstrate the current discrepancy between the target rates for seasonal immunization of elderly and at-risk patients and the actual influenza vaccine distribution rates. This “influenza paradox” is discussed in the context of 1) global efforts to improve vaccine uptake rates, 2) global and regional health initiatives, such as the global action plan for non communicable diseases and healthy ageing and 3) global pandemic influenza preparedness.
Seasonal Influenza prevention in the past

The global annual disease burden associated with influenza infections is well documented in the literature. Local annual epidemics may be as variable and unpredictable as the influenza viruses causing them. In some years, epidemics can have a serious impact whereas in other years the impact may be much less. WHO estimates that, on average, 3 – 5 million cases occur on an annual basis and 250,000 -500,000 people, mostly elderly, may die as a direct or indirect consequence of an influenza infection. Particularly, older people and patients with chronic underlying disease may experience serious complications and become hospitalized. In many cases, these patients are treated for the clinical condition for which they are hospitalized, without recognizing the underlying viral influenza infection which may have exacerbated their condition. Therefore, clinicians may not always recognize the impact influenza infections may have had upon their patients.

For the same reasons, the protective effectiveness of influenza vaccines is difficult to assess based on purely clinical grounds. Many symptoms of influenza infections are similar to symptoms caused by other, non-influenza pathogens. Obviously, influenza vaccines will protect only against disease caused by the influenza viruses and not by other pathogens causing influenza-like illnesses.

Recognizing the annual burden of influenza disease for people and populations, WHO has, since the 1950’s, been maintaining its Global Influenza Surveillance and Response System (GISRS). This group of specialist scientists is tasked with identifying the most commonly circulating influenza viruses and ensuring the best possible antigenic match in the annual influenza vaccines. The GISRS makes recommendations on the appropriate vaccine compositions for both the Northern and the Southern Hemispheres each year. Although antigenic mismatches can occur occasionally, for most years there is a good antigenic match between the epidemic and vaccine strains, indicating the success of this global program.

The method of growing influenza virus, form which to produce a vaccine, in eggs was developed in the late 1940’s and the vaccines so produced have been investigated and used extensively over the last 65 years. Despite the methodological complexities involved in measuring the benefits of the vaccines on society, the safety and efficacy of the vaccines in preventing serious influenza associated complications, hospitalizations and deaths, particularly of the elderly have been extensively documented in the literature. Recommendations of the WHO (1, 2) and other Health Authorities are based on this documented scientific evidence and represent a strong foundation to advocate and implement seasonal influenza vaccination.

Unfortunately, in many countries, inactivated influenza vaccines are seriously under-utilized despite the global and publically driven efforts of WHO and other health organizations and institutes. The documented evidence, as basis for immunization recommendations, is not always fully appreciated and is sometimes debated. As a consequence, many people at-risk of complications associated with influenza infections, such as the elderly and those with chronic conditions, are not vaccinated and afforded potential protection against negative impacts on their health. On a societal level, the burden imposed by these infections and complications represent an avoidable cost for the healthcare system and budget.

Based on such considerations, the World Health Assembly has adopted a resolution calling for a vaccination rate of 75% of the elderly by the year 2010. From available global vaccination distribution data and published uptake rates, these target rates are not yet met in many countries, although over the period 2004-2009, the global vaccine usage increased by 70% to a total volume of 450 million doses. In Europe, new target vaccine uptake rates have been formulated to reach 75% uptake by elderly and at-risk patients in 2015.

Global efforts to improve seasonal influenza prevention in the future

As outlined above and depicted in Figure 1, there is a clear need to improve the level of seasonal influenza prevention in many countries. Improved seasonal influenza control measures, by fully implementing current recommendations, are important for individual at risk patients but also for global, regional and national pandemic preparedness efforts. As the H1N1 pandemic experience has demonstrated, pandemic control is very much linked to existing vaccine- and antiviral production capabilities and existing health infrastructures before the pandemic.
WHO’s Global Action Plan–II (GAP–II)

In 2006, the WHO launched its first Global Action Plan (GAP-I) in anticipation of an emerging pandemic. In 2011, the WHO started a consulting procedure to define its follow-up Global Action Plan for the next 5 years (GAP-II). Increasing uptake rates of seasonal influenza vaccines is one of the three main pillars of the GAP program with the aim to respond to the direct need of annual disease prevention for patients and society as well as indirect needs to be better prepared for future pandemics.

One of WHO’s key GAP-I objectives was to facilitate and support initiatives to create local influenza vaccine production capacity in some developing countries. Today, such facilities have been realized in countries such as Thailand, Korea, India, and Indonesia. It is of interest to note that, in many of these countries, the distribution rates of seasonal influenza vaccines are low. To achieve the full benefits of these local production facilities at a future influenza pandemic, it is important that these facilities routinely produce influenza vaccines in volumes which are relevant for pandemic containment. The WHO-recommended increased seasonal vaccination uptake rates will provide a realistic economic basis for the new production facilities to be sustainable.

Global Pandemic Influenza Preparedness Framework Agreement (PIPFA)

In addition to WHO’s GAP-II program, an international agreement was reached in 2011 between WHO, World health Assembly member states and industry to ensure global “sharing of influenza viruses and access to vaccines and other benefits” to strengthen the global infrastructure for pandemic influenza preparedness. As part of this process, WHO’s GISRS will be strengthened and access to pandemic vaccines for middle- and low-income countries will be secured, according to the principles laid down in the global Pandemic Influenza Preparedness Framework Agreement.5

Factors to understand the influenza paradox and examples for solutions

Although recommendations and global initiatives are indispensable to guide and...
drive health programs, the success of these programs heavily depend on their acceptance and implementation in countries by the relevant stakeholders. If influenza is often poorly recognized and considered a "hidden disease", one can easily understand the barriers to fully comply with the vaccination recommendations and the programs to increase vaccine uptake rates. It seems that there is a gap between well documented epidemiological and vaccine data and the personal “experience” of physicians and at risk individuals. It seems apparent that awareness and knowledge of the annual burden of influenza disease in specific population segments and the benefits and (minimal) risks of the vaccines may not be sufficiently high in important groups such as policy makers, nurses, physicians and the ‘at risk’ patient populations.

Many studies have been done to understand factors contributing to the phenomenon of the “influenza paradox”. A number of these factors appear to be perceptions about the disease and the vaccines which are often not based on evidence, but merely on subjective opinions and behavior patterns.

In a sub-analysis of a recently reported study on the influenza vaccine distribution rates in 157 countries, it was found that reimbursement for patients and public awareness campaigns and communications by national Health Authorities were the two policy actions which were highly correlated with vaccine distribution rates. Formal recommendations per se, although a prerequisite to support vaccination campaigns, were not found to be correlated with vaccine distribution rates.

**Healthcare workers and influenza prevention**

In many countries in Europe and most likely in other countries as well, at risk individuals are vaccinated if advised by their physicians. Hence, these healthcare providers are instrumental for the implementation of programs to increase vaccine uptake rates. Global, regional and national efforts to achieve these goals should therefore be a focus of both, education about the disease and its control measures as well as behavioral aspects.

Healthcare workers are included in many of the existing vaccination commendations by WHO and national Health Authorities. Vaccine uptake rates in healthcare workers have increased in recent years, particularly in the USA. However, generally speaking, in many countries there is not yet an acceptable level of vaccination amongst these professionals which bear a special responsibility for patients’ safety.

As influenza infections belong to the group of nosocomial infections, there is an increased tendency, particularly in the USA, to consider influenza vaccination for employees as a patient safety consideration. Many programs and initiatives have been tried in institutions to increase vaccination rates amongst healthcare workers on a voluntary basis. In general, these efforts had some positive effect, and stimulated uptake rates somewhat but not to acceptable levels and many times the results were not sustainable.

Today, an increasing number of healthcare institutions in the USA are taking a leadership position and require their employees to be vaccinated against influenza as part of the internal infection control and institutional quality programs.

**Link between International health initiatives and influenza immunizations**

Recently, a number of important global health initiatives were initiated such as the Global Action Plan for Non-Communicable Diseases (NCDs) which primarily focus on diabetes, respiratory illness, cardiac disease and cancer. In addition, there are various initiatives looking at maternal and child health as well as healthy aging. Although these initiatives are not focused on influenza disease, annual immunizations against influenza infections fit very well with the overall objectives of these health programs.

Patients with diabetes, acute and chronic respiratory disease, cardiac disease and the elderly in general, are all known to be at increased risk of influenza infections which often can provoke deterioration of their underlying medical conditions. Influenza immunization of these patients, according to current recommendations will therefore protect these vulnerable patients against influenza-induced disease and exacerbations of their underlying disease. Thus, annual influenza prophylaxis will contribute to the positive management of these important non-communicable diseases and contribute to health initiatives to address these diseases and promote healthy aging. Incorporating influenza immunization into these programs could protect patients and reduce the overall burden on healthcare systems.

**Conclusion and Recommendations**

Despite the availability of safe and effective influenza vaccines and independent recommendations for their use by WHO and other Public Health Authorities, influenza still constitutes a “preventable disease not being prevented”.

The successful implementation of global efforts and initiatives to increase seasonal vaccine uptake rates and pandemic preparedness depends on alignment of all respective stakeholders at national and local levels.

Educational programs, public campaigns of independent health authorities, reimbursement and institutional leadership to promote influenza prophylaxis will be beneficial to patients and society and support global and national efforts for pandemic preparedness and contribute to public health. Countries within the Asian region have a real opportunity to successfully implement effective influenza immunization programs early-on and leverage many of the public health studies and experiences which are available today.
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Dr. Palache received his MSc degree in Biochemistry at the University of Amsterdam in 1980. After graduation, he initiated his professional career as a Clinical Research Associate at Solvay Pharmaceuticals in the Netherlands. He gained a lot of experience in clinical development of new drugs in various fields. Prior to his current position, he held different ‘Clinical Group-leader’ functions. In such position he directed the clinical development program of Solvay’s new cell-cultured influenza vaccine (MDCK), which was registered in 2001 in the Netherlands.

He was an Influenza Research Fellow at the Dutch National Influenza Centre: Erasmus University, Rotterdam (chair: Professor A. Osterhaus), where he received his PhD in Medical Science in 1991.

He is a co-founder of the European Scientific Working Group on Influenza (ESWI, 1992).

Since 2001, he is member of the Public Health Working Group of the Association of the European Vaccine Manufacturers (EVM) and in 2005, he joined the Influenza Working Group, which he co-chairs since January 2009.

In 2003, he became founding member of the Influenza Vaccine Supply International Task Force (IVS) and since 2004, he chairs the Policy Practice and Communication subgroup (PPC) of the IVS. In 2006, he joined the APACI (Asian Pacific Advisory Committee Influenza) group as Solvay Biologicals representative.

Dr. Palache is the author of over 50 papers most of which were published in peer-reviewed medical scientific journals. He is co-author of the Rapid Reference book Influenza which is published by Elsevier in 2006 and has been translated in four languages.