Influenza vaccines really work? Keeping apart the true from the false

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A yearly seasonal flu vaccine is the best preventive method we have against influenza at this time. Even then, vaccination adoption is hampered by on-going discussions about safety and effectiveness. In order to dot the I's and cross the T's at the fifth ESWI influenza conference, a dedicated SPI track focused on these important aspects of influenza vaccination.

1. The reality of flu vaccine use in priority groups

Opening speaker, Diane Gross, of the World Health Organization (WHO) Regional Office for Europe, set the scene by commenting on the reality of flu vaccine use in priority groups. Influenza vaccines were first introduced in 1940s. They still offer the best means to prevent influenza, but vaccine effectiveness varies every year and by target group. WHO provides recommendations regarding priority groups for influenza vaccination: pregnant women, young children between 6 and 59 months, the elderly, the chronically sick, healthcare workers, and residents of institutions for the elderly and the disabled. Gross: “The majority of these groups are at high risk of severe disease and death. Currently, the greatest emphasis is given to pregnant women. In 2012, the Strategic Advisory Group of Experts (SAGE) said that if countries start an influenza programme or update their existing programme, pregnant women should be

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included. Pregnant women are at a high risk of severe disease or death, especially in combination with an underlying condition such as asthma, diabetes or obesity. Flu infection during pregnancy may also increase the risk of pre-term birth, low birth weight, stillbirth and the need for an emergency caesarean. Furthermore, as a positive side effect, vaccination of the mother can reduce infection in infants until the age of 6 months. Young children are targeted because of their higher rates of disease, clinic visits and hospitalizations when compared with adults. Because of their contact with family members and other children, they also play a critical role in sustaining influenza transmission. Vaccines are safe and effective, but less effective in children under the age of 2 years. Also the elderly and the chronically sick are more likely to develop severe health issues or fatal disease. In the elderly, hospitalization rates due to influenza are high and recovery from infection is long. Influenza outbreaks in recovery homes for the elderly or the disabled are common. Healthcare workers are considered as a target group for a different reason: the risk of transmitting the infection to vulnerable patients. Given the fact that vaccination is safe and effective, vaccination may reduce staff absence rates and morbidity and mortality rates in patients."

"Countries have to figure out how to incorporate these target groups in their flu programs," says Gross. However, national member states cannot be obliged to follow WHO recommendations. Consequently, vaccination rates in these risk groups still remain suboptimal. WHO organized an electronic survey on vaccine programs, vaccine uptake, and monitoring policies in the 2011/2012 season. Gross: "53 countries were invited to participate in the Vaccine European New Integrated Collaboration Effort (VENICE) Survey, of which 48 responded. From these respondents, 44 countries said that they had vaccines available. All recommend vaccination for the elderly and the chronically sick. Healthcare workers were also recommended for vaccination, with the exception of Denmark, Sweden and Finland. With regard to pregnant women, there is more variability. Very few have recommendations in place for this target group. Some countries have recommendations for some pregnant women, and some have no recommendations at all. The latter goes for France, the Netherlands, Norway, Finland, Poland, Austria, the Czech Republic, Slovakia, Romania, Bulgaria and Turkey. But there is also good news: the number of

EU countries with recommendations in place has been going up. With regard to recommendations for young children, Eurasia is split into two parts, with recommendations largely absent in the western part and the eastern part generally recommending vaccination for all children older than 6 months or for some age groups."

Collecting accurate information about vaccine uptake remains hampered by the absence of monitoring systems. Less than 50% of the countries with vaccination recommendations for pregnant women, the chronically sick, residents of long-term care facilities, and healthcare workers actually monitor the uptake. Monitoring is mainly focused on the uptake in children and the elderly, although the number of countries doing so is still far from optimal. According to Diane Gross, failure to monitor vaccine uptake means that it is difficult to assess progress. "Of the 41 countries that replied to the survey and had recommendations for the elderly, only 28 provided data for the 2011/2012 season. The majority of countries did not reach 50% of the target population. Only one country—the Netherlands—achieved the 75% uptake goal set by the WHO."

However, the evidence that is available suggests, firstly, that the low uptake of vaccines in key target groups in some countries is now mainly due to a lack of awareness amongst the risk groups themselves. Safety concerns and a lack of positive recommendation from medical providers for the elderly and the pregnant are subsidiary factors. Secondly, in order to raise vaccine uptake rates, it is necessary for people in target groups to have easy access to vaccination. At the same time, it is important to be aware that the limited evidence of the effect on mortality in countries with high coverage leads to a loss of public confidence. "Despite the strong evidence of the burden and its severity, vaccine uptake remains low," says Gross. "Monitoring adverse events is important if we want to increase trust. We need to build a body of evidence."

Is there no danger of overcomplicating matters? With so many risk groups, it is difficult for countries to organize the implementation of all the various recommendations. A simpler approach, like

the one the United States employs with its universal recommendation, might possibly make things easier to absorb; for example, in Europe. Gross: “Universal recommendations could be very useful, especially from a complexity point of view. For some countries simplification might help. But even then, the prioritizing of certain groups might still be necessary.”

2. The effectiveness issue in elderly patients

The vaccination controversy is primarily about safety and effectiveness. Policy makers want certainty. But if even the scientists are unable to provide conclusive answers, it is hardly surprising that the policy makers remain confused. And, if the evidence is not convincing, why have governments not stopped recommending vaccination for the elderly? These were the basic questions posed by Jonathan Van-Tam of the University of Nottingham.

The root cause of the inability to deliver simple answers to these questions lies in the relationship between biological vaccine efficacy and vaccine effectiveness. This relationship is a complex one. The situation is further complicated by the fact that vaccination effectiveness estimates are also influenced to a large degree by the extent of virus circulation, the co-circulation of other pathogens, and measurement biases induced by the original study design. Van-Tam: “If you have mass vaccination, you suppress the circulation of the virus itself. When the virus is not circulating, the vaccine cannot protect against a non-existent entity and thus vaccination effectiveness will tend towards zero and the studies will be underpowered. Vaccination effectiveness estimates will also vary according to the study outcome. It is very easy to misdiagnose influenza. If laboratory-confirmed influenza infection is the outcome, then the study will be as accurate as it possibly can be. If, on the other hand, syndromic illness is the outcome, or complications, or mortality, without virus confirmation, then these outcomes, being non-specific for influenza, will include outcomes that are not due to influenza and are therefore not vaccine preventable, so that ‘effectiveness’ estimates are reduced, often significantly.”

Early last year, influenza vaccination benefits for the elderly were questioned by the Cochrane Collaboration. Van-Tam: “With its review of 75 eligible studies, comprising 100 datasets, 14 different outcomes and 4 sub-groups, Cochrane adopted a highly stratified approach. Some errors were made in the assignment of studies to virus circulation or non-circulation periods. The mosaic of results led to a lack of overall interpretability.” Cochrane not only reported that it was “unable to reach clear conclusions about the effects of vaccines in the elderly,” but also said that influenza vaccine is more effective in frail old people living in an assisted nursing environment than the elderly living in the community—a conclusion that makes no sense from a biological perspective. In the lay press, this message was further simplified and abbreviated to “elderly people living in the community should expect no benefit from influenza vaccination,” providing fodder for those who say that science and vaccines cannot be trusted.

In order to carry out their review, the Cochrane statisticians chose 75 articles from a database of 4000 publications, using mainly observational studies, to perform 100 single meta-analyses, according to various vaccine types, study designs, populations, and outcome case definitions. The Cochrane data analysis did not always successfully distinguish between seasons with high, mild, or no circulation of an influenza virus. Nor did it always accurately distinguish between vaccines with a good or a poor match for the influenza strain circulating at that time. Another weakness was the fact that the analyses were guided mainly by formal statistical criteria and not by biological criteria.

Encouraged by the invitation of the Cochrane authors to produce “any alternative interpretation” of the evidence, a group of scientists comprising Walter E.P. Beyer, Janet McElhaney, Arnold Monto, Jonathan Nguyen-Van-Tam, Ab Osterhaus, and Derek J. Smith conducted a new collaborative study based on the same data used by Cochrane, but applied an alternative and simpler framework of analysis. Van-Tam: “We took the same 75 eligible studies and first corrected the assignment errors of studies to circulation periods. The outcomes were then re-plotted on the basis of simple, policy-relevant scenarios: laboratory-confirmed influenza, syndromic influenza-like illness, complications and periods of virus and no virus circulation.”

With an efficacy against laboratory-confirmed influenza of around 50%; against ILI without virus confirmation of around 40%; and against influenza-related fatal and nonfatal complications of around 30% (with large dispersion), the “Cochrane re-arranged” study now provides a valid alternative view on the evidence of effectiveness of influenza vaccines in the elderly. Biological vaccine efficacy against infection is between 50 and 70%.

3. The safety issue

There is not only confusion about vaccine effectiveness. Safety is also an issue. Seasonal trivalent influenza vaccines may cause reactions at the injection site, such as redness, pain, and swelling. Systemic reactions can also occur, but these are usually mild and self-limited: fever, general malaise, myalgia, and ocular or respiratory symptoms, such as red eyes, a hoarse voice, or a cough, especially with aerosol vaccines. Other and rarer side effects include the Guillain–Barré syndrome and there were also reports of febrile seizures in Australia in 2010.

Arguments against vaccination regularly cite their so-called lack of safety, frequently associating a number of contentious health issues with vaccination and also claiming that seasonal vaccination can actually cause serious illnesses instead of preventing it. In order to deal with these exaggerations and misinterpretations, which cause anxiety or make existing anxiety even worse, it is necessary to reframe opinions with objective findings.

“Safety issues may have a considerable impact on vaccine uptake in vulnerable populations, which emphasizes the urgent need for risk monitoring and the benefits it can yield. Once people have a negative idea of vaccination, it is difficult to change,” says Miriam Sturkenboom of the Department of Medical Informatics at the Erasmus Medical Centre in Rotterdam. In 2014, the European Medicines Agency issued a new guidance document on the subject of safety. This document said that: “Pharmaco-vigilance systems for influenza vaccines need the capability to rapidly detect and evaluate new safety

concerns each season." Sturkenboom: "The new surveillance request should mitigate risks before the peak period of seasonal immunization. This is important, because mass immunization takes place over a relatively short period of time. There is also a multiplicity of seasonal c-vaccine products on the market. Any change in production processes might affect the immune response. The early mitigation of risk is also important because of the expansion of target groups to pregnant women and children. The objective of the new guidance is to rapidly detect a clinically significant change in reactogenicity; in other words, local, systemic or allergic reactions. Companies are expected to report their results within 1 month following the start of influenza vaccination."

The pandemic H1N1 influenza vaccine was responsible for one of the major safety surveillance issues of the last years, after the Guillain–Barré syndrome concern with the swine flu virus in 1976. Both the adjuvanted and non-adjuvanted pandemic H1N1 vaccines were licensed with fast track procedures. As a result of this fast tracking, safety data were limited. The non-adjuvanted H1N1 vaccines were expected to have a similar safety profile to the seasonal influenza vaccines. "The concern about GBS was one of the key elements of the pandemic risk management programme," says Sturkenboom. The active surveillance of Guillain–Barré showed a global study difference between adjuvanted and non-adjuvanted vaccines. Most of the studies showed a significantly increased risk. But stratification between adjuvanted and non-adjuvanted vaccines indicated that the risk was highest for the non-adjuvanted vaccines. In Europe and Canada, where oil-in-water adjuvants were used to increase response and save on antigens, there was no increased risk. In the United States, where non-adjuvanted vaccines were used, the risk increased. Sturkenboom: "The question is whether this augmented risk is due to the non-adjuvanted vaccine itself or its lower effectiveness compared to the adjuvanted vaccine. It also continues to be very difficult to adjust for the fact that the wild type influenza virus has an effect that can cause the Guillain-Barré syndrome."

4. Awareness bias

Just signalling a potential problem may also increase the number of problem cases reported. For example, there was an unexpected increase in the occurrence of narcolepsy cases in Sweden and Finland during the pandemic. The first suggestion that narcolepsy—a chronic sleep disorder characterized by overwhelming daytime drowsiness and sudden "attacks" of sleep—might be associated with the Pandemrix vaccine was made in Finland in February 2010. From August 2010 onwards, the issue received regulatory attention and each time new news broke the number of Google hits on the term "narcolepsy" peaked. Likewise, the number of spontaneous reports by physicians detecting a Pandemrix-narcolepsy association also suddenly increased.

Narcolepsy is a disease that in other circumstances takes a long time to be diagnosed accurately. The lag time average between onset and diagnosis is 10 years. Sturkenboom: "It is very clear that as soon as there is a lot of talk about narcolepsy, people with similar problems will seek medical attention more quickly. So you can expect a shortening of the time between onset and diagnosis. But if you want to study the possible relationship between the vaccine and the safety issue, in this case narcolepsy, you don't want to get mixed up in the media-effect. For patients, it is very difficult to remember the exact moment when their sleeping problem started. Everybody will say that it started after vaccination, not in the least so that they can file a claim. One methodological solution to potential awareness bias is to exclude all cases diagnosed after the start of the attention wave."

Many studies were conducted to determine whether the association was real or media-inspired. "Several studies show strong associations, leading to a general belief that there is a causal association. But all in all, the findings remain inconclusive. No study has properly addressed potential detection bias. And several studies suffer from ascertainment bias. For this reason, additional studies are needed that avoid detection and awareness bias," says Sturkenboom. The supposed association has already had a negative effect on vaccination uptake in Finland, especially in children aged from 6 to 35 months. Compared to 2009–2010 or even the 2008 and 2007 flu seasons, vaccine uptake has dropped by half, and is now well below 20%. The vaccination rate in the elderly has also been declining in the post-pandemic years.

5. Nothing is ever 100%

Vaccines really work. But the individual degree of effectiveness in a person always depends on who is vaccinated and how well the vaccine matches the circulating flu strain. This is inevitable, given the complex relationship between biological vaccine efficacy and the real world context. Vaccines trigger the immune system. The resulting protection effectiveness always depends on the ability of the immune system of the vaccinated person to respond. As a consequence, for some people—the elderly, children younger than 2 years, and the sufferers of certain chronic illnesses—flu shots might not work as well as for healthy young adults. This continues to be the biggest difficulty in encouraging more vaccination: at the present time, influenza vaccination cannot guarantee 100% effectiveness and safe result—and this is what is needed to silence the critical voices. “Very few things in medicine are 100% safe and effective, just as very few things in communication are 100% safe and effective,” says John Parrish-Sprowl from the Global Health Communication Centre at the Indiana University, School of Liberal Arts, USA. “Looking for the perfect message is simple and elegant, but its existence depends on certainty, which in today's world is an illusion. Besides, the more potential risks that the state and the doctors present to the public, the more people are going to stick to the idea that not vaccinating is the right choice.”

“Vaccines are widely recognized by health authorities and the medical community as a major tool for achieving public health successes, such as the eradication of smallpox. Yet for many individuals, this is not sufficient evidence for them to embrace vaccination wholeheartedly. They doubt the benefits of vaccines, worry about their safety and question the need for them. We refer to this attitude as vaccine hesitancy. An attitude of vaccine hesitancy differs from an action of vaccine refusal. Even those who are vaccinated can harbour hesitancy towards certain aspects of vaccination. The policy concern is that hesitancy soon becomes refusal, as suggested by both theory and experience. This could lead to the emergence of unvaccinated clusters, in which disease outbreaks could occur. Moreover, people not only make a decision about vaccination for themselves; they also talk about it. Vaccine hesitancy is an

increasing global phenomenon. And research consistently suggests that just providing accurate scientific information will not stop this trend, much less reverse it."

6. Health communication strategy

"We will have to come up with something different," Parrish-Sprowl continues. "Communication should never be limited to giving the naked scientific facts and figures. Public health communication needs to shift its perspective from 'talking at people' to 'talking with people'. Scientists have to understand that there is no such thing as one-way communication. Even so, the transmission model still persists, because intellectual history has led to the development of the practices that maintain this pattern of behaviour. It always works to some degree, and so we keep trying to perfect it. This is a mistake." Communication is inherently relational, which means that in order to be listened to, you first have to relate to your public. "We must engage in conversation with the public. We need dialogue, both electronic and face-to-face. And when necessary, the trajectory of this conversation should be adjusted to maintain the trajectory towards our goal."

Various changes need to be implemented in health communication strategies for vaccines: a change in the communication strategic planning process; collaboration with others, such as healthcare workers, community leaders, and teachers; greater focus on training and the development of new conversational skills; a different allocation of resources; and new metrics of evaluation. Parrish-Sprowl: "The internet and social media enable large-scale conversations. People are discussing issues in many different ways, the ways they prefer. We can observe these conversations and, more importantly, be pro-active in them. But this pro-active social media strategy needs to be combined with a face-to-face-strategy. In the UK, visiting nurses are sent into houses to explain to people how they can use medical technology. We know intuitively that face-to-face conversations are better for dealing with people's fears. Research supports this approach. It is not about what is said, but about how it is said. Everybody knows

how communication works. But as soon as we become professionals, we forget. One of the challenges is to remember what we already know."

7. SPI lessons learned

Despite the strong evidence for the burden and its severity, vaccine uptake remains low. And the collection of accurate information about vaccine uptake is still hampered by the absence of monitoring systems.

Universal recommendations could be very useful, especially from a complexity point of view. But even then, the prioritizing of certain groups may still need to be possible.

With an effectiveness against laboratory-confirmed influenza of around 50%; against ILI without virus confirmation of around 40%; and against influenza-related fatal and nonfatal complications of around 30% (with large dispersion), the "Cochrane re-arranged" study now summarises evidence of the effectiveness of influenza vaccines in the elderly. Biological vaccine efficacy against infection is between 50 and 70%.

Safety issues may have a considerable impact on vaccine uptake in vulnerable populations, which emphasizes the need for the rapid benefits of greater risk monitoring.

Communication should never be limited to giving the naked scientific facts and figures. Scientists must engage in conversation with the public. There must be dialogue, both electronic and face-to-face. The internet and social media enable conversations to be conducted on a wide scale. Having said this, research confirms that face-to-face conversations are better for dealing with people's fears.

Conflict of interest

Gross: none declared.

Van-Tam: Between October 2007 and September 2010, *ad hoc* paid consultancy to several influenza vaccine manufacturers (Sanofi-Pasteur MSD, Sanofi-Pasteur, GlaxoSmithKline plc, Baxter AG, Solvay, Novartis). Former employee of SmithKline Beecham (now part of GSK) 2000–2001. Travel expenses to attend 5th ESWI meeting provided by ESWI.

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