Towards improved influenza control through vaccination

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Summary

In August 27/2014, SLIPE organized the Master Class “Towards improved influenza control through vaccination”, a panel with international influenza experts who shared their understanding of the disease and the control measures available, focusing on the most recent information about this serious diseases. In this report Dr Falleiros and Dr Bricks summarized the following topics: Global influenza epidemiology, presented by Dr Puig-Barbera; Influenza vaccine recommendations and coverage in Latin American countries, presented by Dr Bricks; Influenza vaccines efficacy and effectiveness, presented by Dr Fedson; Influenza burden and rational for prevention in children, presented by Dr Muñoz; Influenza burden in pregnancy, presented by Dr Ribeiro; Influenza vaccination in health care workers, presented by Dr Macías; Influenza vaccination in the elderly, presented by Dr Ribeiro; Rational to increase vaccination coverage rates Global Influenza Hospital Surveillance Network, presented by Dr Puig-Barbera; Influenza B epidemiology and vaccine strain mismatch in Latin American Region, presented by Dr Bricks; Modeling for quadrivalent influenza vaccines impact, presented by Dr Blank; Rational for quadrivalent influenza vaccines and the clinical development of QIVs, presented by Dr Desauziers and Modelling quadrivalent influenza vaccines impact, presented by Dr Blank.

Key words: Influenza, vaccine, immunization, herd protection.

Palabras clave: Influenza, vacuna, inmunización, protección del grupo de inmunización.

Acknowledges to speakers

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Global Influenza Epidemiology

Influenza is a highly transmissible disease that cannot be distinguished from other acute respiratory infections (ARI). There is no good standard clinical case definition. The surveillance system adopted by WHO is based on information about influenza like illness (ILI), serves as a global alert mechanism for the emergence of influenza viruses with pandemic potential and to identify the strains that will be included in vaccines recommended for North and South Hemispheres (NH and SH) in the next season. Every year, about 10% of the world’s population catch influenza, but the burden of disease is not uniform. There are large variations in the incidence in different regions and seasons and, in tropical regions, influenza virus circulates all around the year. Children, typically are the first group infected, have higher attack rates, and high hospitalization rates, but the majority of deaths are confirmed in elderly and persons with comorbidities. Serious complications and deaths can occur in all age groups, and influenza is responsible for significant economic costs, especially associated with reduction of productivity from missed work days. A and B influenza strains presented continuous evolution and can cause serious diseases in people of all age group, but B strains were associated with disproportional impact in pediatric age group in US. Vaccination is the best way to prevent influenza and its complications. The influenza vaccines are considered safe, with low risk of local and systemic adverse events. In 2012, WHO consider pregnant women as the top priority for immunization, because of confirmed benefits to mother and infants. For other at risk groups (elderly, health care
workers (HCW), persons with comorbidities] there is no specific order for priority⁷.

**Influenza vaccine recommendations and coverage in Latin American countries**

The majority of Latin American countries introduced influenza vaccines in public sector in the last 15 years. In 2013, 40 of 45 countries and territories have politics for influenza immunization, but the recommendations are not uniform. In 2013, 30 (67%) of countries have recommendations for children (5 only for at risk children), 40 (89%) for elderly, 39 (87%) for HCW, and only 26 (56%) for pregnant women³,⁴. The majority of countries recommend the vaccination only for young infants (6-23 months), and the coverage rates are lower for the second dose. The influenza vaccine coverage rates are high for elderly⁴, but very low for pregnant women in the majority of countries, and some impose restrictions for the vaccine use during the first trimester of pregnancy⁴. The coverage rates are also very low in people with co-morbidities, and data are not informed for the majority of countries. In Brazil, only 1 out of seven young adults (20-60 years) with diabetes were immunized in 2014⁷. The same was observed with respect to other chronic diseases, like asthma in children, and obstructive pulmonary and cardiac chronic diseases in adults⁶,⁷. The first results of REVELAC-I, a study to evaluate the effectiveness of influenza vaccine in children and elderly, developed in collaboration with CDC and Ministry of Health of 8 Latin American countries demonstrated that influenza vaccination prevented more than 50% of hospitalizations confirmed by influenza in children < 5 years of age (52%) and elderly (57%)⁹. There most relevant challenges for the future are: to improve the coverage rates in at risk groups, to identify the most relevant factors associated with acceptance or refuse of the vaccine for HCW and pregnant women, the logistics to complete 2 doses in children, and for the acquisition and distribution of the vaccine in the region, the use of NH and SH vaccines in some countries, and the necessity of improve surveillance and communication among people involved in epidemiologic studies, laboratory program and the scientific community¹.

**Influenza vaccines: efficacy and effectiveness**

The estimation of efficacy and effectiveness in clinical trials and observational studies depend on the definitions for influenza cases and influenza seasons. If we adopt highly specific criteria (like ILLI confirmed by lab tests), the number of cases detect will be lower as compared with criteria with lower sensitivity (ex. upper respiratory infection without lab confirmation). So, a vaccine with lower vaccine efficacy (VE) can prevent more cases as compared with a vaccine with higher VE, depending on the criteria used. Case test-negative studies can avoid unmeasured confounding in observation studies to estimate vaccine effectiveness, but also have limitations. It is necessary to implement standardized protocols to better evaluate the impact of the disease, especially in hospitalized cases. In elderly people, clinical trials and observational studies clearly demonstrate the benefits of influenza vaccination⁹.

**Influenza burden and rationale for prevention in children**

Children are primary vectors of influenza and play a pivotal role in transmission to other children, family members and other close contacts, and in community¹⁰,¹¹. As compared to adults, children are more likely to become infected with influenza, are the first group to become ill with influenza during seasonal outbreaks, shed greater quantities of virus and for a longer time, have more opportunities to infect others because of social contacts, and have a high risk for hospitalization, even without any other risk factor¹². Even with lower mortality rate as compared to elderly, the burden of influenza in children is high in terms of morbidity, number of medical visits. Children frequently receive antibiotics to treat flu complications that are very common, especially in those < 5 years of age. Children immunization can reduce substantially the number of outpatient visits for influenza like illnesses, the number of children admitted to intensive care units, and also reduces household illness and mortality in the community. The potential indirect effect of reducing influenza among person who have close contact with children and the community, including the elderly and other population at risk, is an additional benefit¹³-¹⁶.

**Influenza burden in pregnancy: rationale for protecting mothers and babies**

During pregnancy, there are many immunologic and physiologic alterations that increase susceptibility to influenza and its complications. Influenza risks for pregnant women grew from the first to third trimester and are also higher in the first 4 weeks post-partum (4 times higher risk of mortality)¹⁷-¹⁹. The results of a case-control study with 49 pregnant women who died and 185 controls that survived after hospital admission with SARI due to Influenza A (H1N1) in São Paulo state were presented. The median age of pregnant women in both groups was 25 years; and more than 80% of cases and controls did not have any co-morbidity. The risk of death was 2.37 higher in the second trimester and 4.45 in third trimester⁵⁰ WHO recommends that pregnant women receive the vaccine in any trimester of pregnancy, but there are barriers to the vaccine acceptance related to ethical issues, concerns
about vaccine risks to the mother or to the baby, and rules for inserts. However, vaccination of pregnant women can protect the mother and the baby. In a case-control study, the mothers immunized during pregnancy had 30% lower incidence of incidence of ILI, and their babies had 62.8% lower risk of hospitalization associated with influenza until 24 weeks after birth. About 10% of infants hospitalized because of influenza needs intensive care and 75% do not have any risk factor. The review of the risks of adverse obstetric events in pregnant women vaccinated with inactivated influenza vaccine in US revealed that the risks of eclampsia, pre eclampsia, proteinuria and urinary infection were similar in vaccinated and non-vaccinated groups. Among 74,000 women immunized during the pregnancy it was observed a significant reduction in gestational diabetes. There are also substantial evidence the vaccine do not cause malformation or other problems to the concept. By the other side, high fever in the first trimester caused by influenza can damage the fetus and cause miscarriage, and influenza in second and third trimester has been associated with high risk of low birth weight and prematurity. Pregnant women immunization is safe and can reduce the risks of miscarriage and low birth weight in about 25%. Vaccination of pregnant women benefits the mother and their babies and it is necessary to improve the coverage rates.

**Rational and ethics of influenza vaccination in health care workers**

Multiple studies confirm that symptomatic and asymptomatic infected healthcare workers transmit influenza to their patients, and health care associated influenza outbreaks are well documented. Vaccination of HCWs is recommended by WHO and PAHO to reduce transmission, employee illness and absenteeism and to protect high-risk patients; however vaccination rates reported remain low. A study from Argentina demonstrated that 69.6/100,000 HCWs were hospitalized with SARI during pandemic, and the OR was 3.1 (95% CI 2.3-4.1) as compared to general population (20.3/100,000). The most common barriers to vaccination are related to concerns about vaccine effectiveness and safety; medical contraindications such as “egg allergy”, religious beliefs and conscientious objection, inconvenience and fear of injections, underestimation of the person’s susceptibility to the infection and of the potential to spread it further and belief that the disease may be mild. Despite of consistent recommendations, dedicated efforts, vaccine availability free of charge, publicity (including posters and flyers), education, incentives and rewards, and mobile vaccination teams, the coverage rates for HCW are very low in US and Europe (30-50%) and there are hot debates about if it should be mandatory, because involves not only individual protection but also indirect protection for high risk patients.

**Rational and impact of influenza vaccination in the elderly**

The impact of the introduction of seasonal influenza vaccination among persons older than 60 years of age after the introduction of influenza vaccine in 1999 in the State of São Paulo was presented. The number of deaths due to pneumonia and influenza (P&I) and the respiratory hospitalization rates were analyzed from 1994 until 2009, and adjusted by influenza seasonality and vaccination coverage during this period. After vaccine introduction, it was observed 57% of reduction in deaths, representing almost 1,000 deaths by year, and 70% of reduction in hospitalization rates (more than 3,700 hospitalizations by year). Lower impact was also observed in young adults (25% of reduction in deaths and 48% of reduction in hospitalization).

**Rational to increase vaccination coverage rates?**

In the majority of European countries, influenza vaccine coverage rates are inferior to 75%, the target established by European Council in 2009. The drivers and barriers towards vaccination varies among different groups, but, in general, individuals support a preventive measure if they believe that the disease is serious and that they are at risk of disease, and that the measure is effective and without risk for them. Doctors recommendations are the strongest motivator for parents to immunize children and pregnant women receive the shot, but many doctors have also concerns about influenza immunization, as demonstrated by low coverage rates in HCW. There is a need for determining ways to improve seasonal influenza coverage rates among recommended groups. Better awareness of disease and its severity, motivation of physicians to recommend vaccination, reminding systems to the public and strong official recommendations with monitoring systems are measures essential to improve vaccination.

**Global Influenza Hospital Surveillance Network (GIHSN)**

The GIHSN is a partnership between Sanofi Pasteur, Fondation Mérieux and several public institutions, each one coordinating a number of hospitals that adopted a standardized protocol to analyze severe cases of influenza, to document the burden of severe influenza, to raise awareness about influenza morbidity and to evaluate vaccine effectiveness in preventing influenza hospitalizations. In 2013/2014, China, Russia, Turkey and Spain centers...
were included. In the Northern Hemisphere, influenza circulated for 24 weeks (EW49/2013-WE20/2014) and resulted in severe outcomes in at risk groups. Flu A(H1N1)pdm09 was related to a significant risk of admission with influenza in obese, and all influenza strains were associated with higher risk of hospitalization in at risk people, including pregnant women. It was observed large variation on strains circulating in different countries, and been vaccinated reduced in about 30% the risk of hospitalization, but influenza vaccine coverage was low. For 2014/2015 season, GIHSN will include information from Brazil and Mexico.

**Influenza B epidemiology and vaccine strain mismatch in Latin America region**

Before the pandemic, data about influenza circulation in Latin America countries were scarce. A meta-analysis of 31 articles published from 1980-2008 revealed that influenza B was identified in only 14% of ILI cases, but in 21% of hospitalized cases. There was great variation in A and B circulation among neighboring countries, and in some years, the B strain was identified in more than 50% of cases. After 2009, on average, influenza B was identified in about 20% of cases in PAHO region, with lower reporting in Central America (9%) and higher in Caribbean (23%). In Brazil, before and after pandemic, the prevalence of B strains was 25%. Influenza B strains affect people of all age groups and seems to have higher disproportional impact in children, adolescents and young people. After pandemic many countries implemented the surveillance for SARI in the region and introduced RT PCR for diagnosis. Recently, some countries are also introducing in PAHO information about B lineages. Data from Brazil and Argentina revealed that in Latin America there was mismatch between B strains in circulation and those included in the vaccine recommended for SH, similar to those observed in US, Europe and Australiа. Influenza B in Latin America is frequent (up to 70% in some countries and years), unpredictable, varies from one country to another, from one year to another and from one region to another, even in the same country. Influenza B strains caused outbreaks among people in crowded conditions, like military and tourists. To choose the best vaccine for Latin America region, it is necessary to improve influenza surveillance, including information about B lineages and mismatch in our region.

**Rational for quadrivalent influenza vaccines (QIV) and clinical development**

Constant and rapid genetic evolution is a hallmark of influenza viruses, and Influenza vaccines must evolve accordingly to maintain level of protection against disease. The first influenza vaccine, licensed in 1933, was monovalent. It was substituted by bivalent vaccine in 1942, and by trivalent influenza vaccines (TIVs) in 1978. Since 2001, influenza B Victoria and Yamagata lineages have co-circulated globally, but TIVs contain only 1 B strain. In addition, in 6 of the last 12 seasons, the B-lineage strain selected by the WHO/CDC did not match the circulating B-lineage strain.

There is low antibody cross-reactivity between influenza B lineages and high levels of protection against influenza B should not be expected from vaccination in years when a mismatch of B lineage occurs. The need to address this B strain mismatch and to explore the possibility of adding an additional B component to the seasonal influenza vaccine was first raised in 2007 by the FDA’s Vaccines and Related Biological Products Advisory Committee (VRBPAC). In US, in 2013, 3 QIV were already licensed. The safety and immunogenicity profiles of QIVs are similar to licensed TIVs. QIV demonstrated superior immunogenicity compared to TIV for the additional B strain and thus provides superior coverage against influenza. QIV introduction will contribute to the reduction of morbidity and mortality associated with influenza virus infections and is expected that QIV will improve public confidence in influenza vaccine by reducing the frequency of vaccine mismatch. The WHO and major regulatory agencies are paving the way for a shift to QIVs, and in US the acceptance of QIV in 2013 was higher than expected, especially for children, that suffer a disproportional impact in terms of deaths. Replacement of TIV by QIV will ultimately be the decision of national health authorities taking into consideration any WHO recommendations. QIV represents a logical next step to fit with the current epidemiology, and an improved standard of care for all age groups.

**Modeling QIV impact: implications for vaccination policy**

Influenza outbreaks have a high public health and economic burden and modeling shows that QIV could reduce clinical burden of influenza outbreaks, could substantially reduce incidence of influenza B cases, and might be cost-effective, as demonstrated in US. Data regarding the relative cost-effectiveness of new vaccine products will be an important criterion for decision-makers to consider the introduction of QIV as a new standard of immunization against influenza.

**Discussion and conclusions**

The discussion among experts, coordinated by Dr Falleiros and Dr Fedson emphasized that vaccination is the
best way to protect against influenza and its complications. Even considering the moderate efficacy of TIV vaccines in at risk groups, the coverage rates with TIV should be improved in our region, considering the recent information about vaccine safety, effectiveness and benefits from herd protection. Because of the limited cross-protection and the difficulties to predict what lineage B will circulate in the next season, it is expected that the introduction of QIV in Latin American countries can protect better the population.

References


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