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Editorial

Influenza: A preventable infection in different populations

Gripe: una infección prevenible en diferentes poblaciones

Seasonal influenza is a preventable infectious disease, mainly involving respiratory symptoms caused by the influenzavirus, which is moderately infectious and has a worldwide distribution. Influenza viruses belong to the *Orthomyxoviridae* family and have a single-stranded segmented RNA genome. The influenzaviruses are classified into types A, B, and C on the basis of their core proteins. There is also evidence of a fourth type D, but it does not seem to affect humans.[1] Type A viruses are further subdivided according to their glycoproteins envelope on the virus surface with haemagglutinin (HA) (H1–H8) or neuraminidase (NA) (N1–N11) activity. Characteristic of many RNA genome viruses, influenzavirus undergoes high mutation rates and frequent genetic reassortment (combination and rearrangement of genetic material) leading to variability in HA and NA antigens. Minor changes in the protein structure in influenza A strains («antigenic drift») occur frequently, enabling the virus to cause repetitive influenza outbreaks by evading immune recognition. Major changes in the influenza type A HA antigen («antigenic shift») are caused by reassortment from different influenza A subtypes, such as between animal and human subtypes, and in rare events, such shifted viruses can result in strains capable of causing large regional or global pandemic outbreaks. Type B viruses cause somewhat less severe disease and tend to cause fewer complications than some type A viruses. Type B does not have subtypes but two antigenically distinct lineages: Victoria and Yamagata. Influenza B and C viruses mainly affect humans, whereas influenza A viruses infect a range of mammalian and avian species. Only type A and B cause human disease of any concern. At any given time there may be a mix of influenza viruses circulating in the human population. Since the most recent influenza pandemic in 2009, seasonal influenza has consisted of variable mixes of influenza A(H3N2), A(H1N1)pdm09, which caused the 2009 pandemic, and the two B virus lineages.

Influenza is predominantly spread via droplets and contact, or indirectly via respiratory secretions on hands, tissues, etc. Aerosol transmission can also play a part in spread of the virus.[2] Influenza occurs all over the world, with an annual global attack rate estimated at 5–10% in adults and 20–30% in children.[3] Influenza is associated with considerable economic burden arising from healthcare costs, lost days of work or education, and general social disruption across all age groups. In addition, secondary bacterial pneumonia is a frequent complication of influenza infection, particularly in elderly people and individuals with certain chronic diseases, resulting in a significant level of morbidity and mortality. Therefore, infection by influenza virus has accompanied humanity from time immemorial, producing annual epidemics that can cause severe infection, mainly in the elderly, pregnant women, or in those with previous comorbidities.

Each year, seasonal influenza is responsible for up to 50 million symptomatic cases in the European Union/European Economic Area (EU/EEA), and 15,000–70,000 European citizens die of causes associated with influenza. Despite the usually short duration of illness, the annual economic and healthcare burden of influenza is substantial.[4] In the last few decades, we have witnessed a huge development in the diagnostic, preventive, and therapeutic tools for influenza virus infection that have demonstrated their usefulness in reducing the incidence, morbidity, and mortality of this infection.[5]

Vaccination is the most effective measure to prevent severe disease caused by influenza. Influenza vaccines are safe, effective, and the principal measure for preventing influenza and reducing the impact of epidemics. Protection against clinical disease is mainly conferred by serum antibodies, whereas mucosal IgA antibodies contribute to resistance against infection. HA is the major antigenic target of neutralizing antibodies. However, due to antigenic drift and antigenic shift, the protective effect of antibodies induced by one strain may be reduced or lost as a function of time, resulting in individuals being relatively or completely unprotected against the new strains in circulation.[3] It is very important to characterize the influenza virus in order to prepare vaccines for the next year. The World Health Organization (WHO) reviews the world epidemiological situation twice annually, once for the southern hemisphere and once for the northern hemisphere, and if necessary recommends new vaccine strain(s) in accordance with the available evidence. Seasonal influenza vaccines are designed to protect against 3 or 4 influenza viruses (trivalent vaccines and quadrivalent vaccines, respectively), containing a mixture of influenza A and B strains. Of the 2022–2023 reports, 84% were type A viruses, with A(H3N2) and A(H1N1)pdm09 viruses being detected in equal proportions overall, following a rise in the proportion of A(H1N1)pdm09 viruses detected in recent weeks. Since December, the proportion of type B viruses has risen from 6% to 16% and all 3371 viruses (9% of the

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total) ascribed to a lineage have been B/Victoria.[6] The vast majority of viruses with collection dates in 2023, for which sequences have been deposited in GISAID's EpiFluTM database, have HA genes that fall in the V1A.3a.2 subgroup with defining HA1 A127T, P144L and K203R amino acid substitutions. B/Austria/1359417/2021-like (V1A.3a.2) viruses have been retained as the vaccine virus recommendation for both 2023 southern hemisphere and 2023–2024 northern hemisphere influenza seasons.

Two types of influenza vaccines are available, an inactivated (killed) preparation that is injected and an attenuated influenza vaccine normally delivered nasally.

Among healthy adults, influenza vaccine provides protection, even when circulating viruses do not exactly match the vaccine viruses. However, among the elderly, influenza vaccination may be less effective in preventing illness but reduces the severity of the disease and incidence of complications and deaths. Vaccination is especially important for people at high risk of influenza complications, and for people who live with or care for the people at high risk.[7] Since 2012, the WHO has recommended the vaccination of children aged between 6 months and 5 years, pregnant women at any stage of pregnancy, elderly individuals (aged more than 65 years), individuals with chronic medical conditions and health-care workers.[7] Besides this, the Interterritorial Council of the National Health System (Consejo Interterritorial del Sistema Nacional de Salud) also details the target population groups for influenza vaccination in the latest document published.[8]

Influenza is a highly prevalent infectious disease, which causes a significantly high number of hospitalizations, medical visits and antibiotic consumption in children. The most frequent complications are mainly respiratory, such as bronchial obstruction and pneumonia, and also acute otitis. In addition, there are other rare complications, such as encephalitis or myocarditis, these can be serious and cause after effects or even death.[9] In Spain, influenza surveillance reports by the National Epidemiology Centre and the Carlos III Health Institute show the importance of the burden of influenza in normally healthy children. The data shows that in children under 15 years of age, those younger than 5 years have had the highest burden of disease in recent seasons, reaching a high level of incidence during the peak week of the epidemic wave (May 2020).[10] This group presented the highest cumulative incidence rates of influenza (6244.7 cases/100,000 population), even higher than individuals over 64 years old (545.4 cases/100,000 population) as recorded in the previous two seasons.[11] On the other hand, the population under 5 years of age has high rates of influenza and it is estimated (based on data from 7 seasons) that there are 50,000 confirmed cases of influenza per year in Primary Care, 4000 hospitalizations, 800 serious cases, 250 admissions to Intensive Care Unit and 8 in-hospital deaths. Lethality is minimal in children under 15 years of age, but 95% of deaths are under 5 years of age.[9] As said previously, although the WHO has recommended vaccination in children under 5 years of age since 2012, it is really implemented in few countries today. Eleven European countries (Austria, Denmark, Slovakia, Slovenia, Finland, Ireland, Italy, Latvia, Malta, Poland, and the United Kingdom) have introduced annual universal vaccination of this population. Some countries such as Finland, United Kingdom and Canada have included the paediatric population in their routine immunization schedules[12,13]; others such as the United States include the entire population from the age of 6 months under a universal vaccination recommendation. However, in most countries, healthy children are not included as a target group in vaccination policies. In Spain, the flu vaccine is recommended for children with conditions of high risk of serious illness from 6 months of age, reaching a coverage of 15–20% depending on the season.[9]

Orrico-Sánchez et al. reviewed the available evidence on the efficacy/effectiveness of influenza vaccination in healthy children < 18 years of age through a non-systematic search of studies conducted between 2010 and 2020. Despite the high variability in results due to differences in design, vaccine type and season included in the 41 selected studies, statistically significant studies show efficacy values for the influenza vaccine of between 25.6% and 74.2%, and effectiveness from 26% to 78.8%. Although a systematic review would be necessary to corroborate the evidence, the study published in this number suggests that paediatric vaccination is generally an effective measure for preventing influenza in healthy children in line with international organisms' recommendations.[14]

In this sense, the Spanish Public Health Commission published in October 2022 a document whose objective was to evaluate the incorporation of systematic vaccination against influenza in the child population between 6 and 59 months. The epidemiology of the disease, the characteristics of the vaccines, the recommendations at the international level and in neighbouring countries, as well as the ethical-legal aspects and acceptance of their incorporation were reviewed. Finally, after reviewing the cost-effectiveness of systematic vaccination against influenza, it is proposed to recommend it in the child population between 6 and 59 months. In order to facilitate logistics and achieve better vaccination coverage, the administration of a single dose of vaccine is recommended for healthy children (6–59 months), including those who are vaccinated for the first time. Nevertheless, in the child population with risk conditions, the administration of two doses in their first vaccination is recommended. The recommendation for vaccination is maintained for children over 59 months of age with risk conditions and their close contacts. In Spain, there are four inactivated vaccines and one attenuated vaccine for use in children. All of them have been shown to be effective and have an acceptable safety profile. The effectiveness (approximately between 40% and 80%) varies depending on the vaccine used and the circulating subtypes, and is higher when hospitalised and in younger children. Although the two-dose regimen shows greater effectiveness, the better acceptance of one dose makes it necessary to consider the administration of a single dose also in children who are vaccinated for the first time.[9] In fact, flu vaccination will be added to the schedule for children in all the Spanish regions in 2023–2024 seasons. Currently, three regions (Murcia, Galicia and Andalusia) added flu vaccination in 2022–2023 seasons.

In addition, the results of a UK study are compatible with the universal paediatric live attenuated influenza vaccine (LAIV) programme reducing the incidence of group A streptococcal infection (GAS) and invasive group A streptococcal infection disease among children and support attaining high uptake of childhood influenza vaccination. They found overall reductions in incidence rates of GAS and scarlet fever were observed within most of post-LAIV programme seasons when assessing the impact of the LAIV programme among the targeted (2–4 years and 5–10 years) and non-targeted groups using incidence rate ratios from Poisson regressions.[15]

Another WHO recommendation is the development of alternative platforms,[16] such as the production of vaccines from viral cultures in mammalian cells; since the flu vaccine is usually obtained from embryonated eggs and there may be drawbacks due to laboriousness and limited production. In Spain, a vaccine of viruses grown in MDCK (Flucelvax), canine kidney cells, with an adequate immunogenicity and safety profile, is on the market. This was recommended to pregnant women in the 2019–2020 seasons in 4 autonomous communities. However, this group of women is not represented in clinical trials. For this reason, a study carried out by Carreras et al. describes the adverse events reported

with this vaccine in pregnant women and in the group of women aged 16–64 years. The reporting rate of adverse events after vaccination in pregnant women was 4.02/100,000 doses administered, and in non-pregnant women aged 18–64 years it was 5.9/100,000 doses administered. The rate of adverse events reported was 8.04 and 17.74, respectively. No spontaneous abortions, prematurity or foetal malformations were reported. This analysis suggests the safety in pregnant women of the influenza vaccine obtained from cell cultures.[17]

A recent systematic review described that vaccinated women had a lower probability of foetal death, both from the seasonal vaccine (relative risk 0.73); and the H1N1pdm09 vaccine (relative risk 0.69). No association was found between the vaccine and abortions. In addition, review of VAERS claims for cell culture influenza vaccine in pregnant women finds no differences with other influenza vaccines.[18] In conclusion, the quadrivalent influenza vaccine obtained in cell culture has not shown safety problems, with a declaration rate similar to that of non-pregnant women of the same age group.

Influenza morbidity and mortality in pregnancy is similar to that of other risk groups. However, in the first quarter of pregnancy, influenza has been associated with an increase in heart malformations, cleft lips, and neural tube defects and, during the second and third quarters, with a greater number of abortions and premature births. Vaccination of pregnant women provides a triple beneficial effect: protection of the mother, the neonate and the infant. In contrast, vaccination coverage in Spain in this population group is low, although it has been increasing exponentially in the last years from 29.4% (2017–2018 seasons) to 61.9% (2020–2021 seasons).[19]

It is also important to note that vaccination coverage in Spanish health-care workers was low in the previous SARS-CoV2 pandemic (31.1, 35 and 39% in 2017–2018, 2018–2019 and 2019–2020 seasons respectively). Fortunately, the coverage increased in 2020–2021 seasons to 62.0%.[19] Despite the increase, it is not enough to protect the healthcare worker and to reduce the risk of hospital-acquired influenza in patients. Hospitals with active vaccination programmes for their employees have achieved reductions in the incidence of influenza in staff of up to 88% and a reduction in mortality and complications of this infection in patients close to 50%. Recent studies show that hospital-acquired influenza ranged from 4 to 23%,[20] depending on hospital-infections surveillance, flu strains or vaccination coverage. Hospital-acquired influenza is a problem that is increasing epidemiological interest, because it has been associated with high morbidity and mortality and increased economic costs due to increased hospital stays.[3] Therefore, it is important to focus on the evaluation of hospital-acquired influenza and the consequences. Regarding the differences between hospital and community-acquired influenza, Mangas-Moro et al. analyze the characteristics of patients with nosocomial flu, to compare them with patients with community-acquired influenza to study possible differences and to identify possible risk factors associated with this type of flu.[20] The first important finding of this study is that patients with hospital-acquired influenza were younger. Second, the study shows a longer hospital stay, history of chronic pulmonary pathologies, immunodeficiency, risk of bacterial superinfection and admission to the intensive care unit. In the light of these findings, individuals with chronic medical conditions, mainly young people with immunodeficiencies, should be vaccinated.

In summary, vaccination has been shown to have many benefits, including reducing the risk of flu-like illness, hospitalization, and even the risk of flu-related infant death. Therefore, increasing vaccination coverage in risk groups is the focus of the authorities and they project new changes that will improve mainly in childhood. On the other hand, the elderly, pregnant women and young people with chronic diseases should be vaccinated. In addition, health-care workers have an important role in reducing hospital-acquired influenza to protect themselves and patients.

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