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EDITORIAL

Evaluation of varicella vaccine effectiveness as public health tool for increasing scientific evidence and improving vaccination programs☆,☆☆

Avaliação da eficácia da vacina contra varicela como ferramenta de saúde pública para aumentar as evidências científicas e melhorar os programas de vacinação

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Varicella zoster virus (VZV) is a ubiquitous human herpes virus that is spread worldwide and causes two distinct diseases. These latter are primary varicella infection and herpes zoster, a vesicular dermatomal rash that results from reactivation of the latent virus.

Varicella infection is usually a mild self-limiting illness, characterized by a generalized vesicular rash with fever and malaise. Complications affect around 2%–4% of cases and, in developed countries, hospitalization rates are approximately two to three per 1000 cases among healthy children and eight per 1000 cases among adults, determining about two to three deaths per 100,000 cases.[1,2] Complications are more common at the extremes of age, among people with immune deficiencies and pregnant women, but can also occur among previously healthy people.[2]

Before the introduction of the vaccine, varicella was endemic in the world, with an annual incidence corresponding approximately to the birth cohort of each country. The introduction of varicella vaccine has significantly changed the epidemiology of varicella. The vaccine was firstly produced in Japan in the 1970s but it was introduced in most western countries, including Germany, Sweden, Korea, the United States, and Italy in late 1980s and 1990s.[3] A combined measles-mumps-rubella-varicella (MMRV) live-attenuated vaccine has been also developed and licensed on the basis of non-inferior immunogenicity of the antigenic components compared with simultaneous administration of MMR and varicella vaccines.[4,5] MMRV has been used to enable more streamlined integration with existing childhood vaccination schedules in order to increase vaccination coverage. Several efficacy trials documented that the vaccine was safe and gave a high degree of protection against varicella and, for this reason, the World Health Organization (WHO) recommends that countries in which varicella has an important burden of disease should consider introducing varicella vaccine into the routine childhood immunization schedule, with the first dose given at 12–18 months of age.[6] A recently published post-licensure evaluation of vaccine effectiveness (VE) analyzed 42 articles published between 1995 and 2014 and found that for one dose, VE was 81%

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(95% CI: 78%–84%) against all varicella infections, 98% (95% CI: 97%–99%) against moderate/severe varicella, and 100% for prevention of severe disease.[7] The pooled two-dose VE against all varicella diseases was 92% (95% CI: 88%–95%), with no significant differences between VE and vaccine type or study design. However, it is recognized that there is a need for further studies that assess and monitor varicella vaccination introduction in different areas of the world according to their different epidemiologic scenarios.

According to this mandate, the study carried out by Ribeiro et al. and published in this issue of *Jornal de Pediatria* enriches the current international literature by comparing the frequency of hospitalizations and deaths due to varicella before (2010–2012) and after (2014–2016) the vaccine's introduction in Brazil, which is the most populated country in South America and the fifth most populous in the world, with more than 200 million people.[8] In particular, the authors have intended to analyze the effectiveness of the MMRV vaccine introduction, which took place in September 2013 for infants at 15 months.

Such studies as this have an essential role in increasing evidence-based public health practices and in assessing epidemiological findings that could be of interest for making adjustments, if required, to vaccination programs from a national point of view. The results of the study confirm that in Brazil varicella accounted for a high burden of disease that, in the pre-vaccination era (2010–2012), caused hospitalization rates of 39.6/100,000 in infants aged <1 year and 19.6/100,000 in children aged 1–4 years, and mortality rates of 1.36/100,000 in infants aged <1 year and 0.68/100,000 in children aged 1–4 years, respectively. After MMRV vaccine introduction, significant reductions were observed in both hospitalization rates (−40% in infants <1 year and −47% in children 1–4 years) and mortality rates (−57% in infants <1 year and −49% in children 1–4 years). These results are strongly encouraging since they confirm that varicella vaccination is associated with an immediate reduction of the burden of the disease, evident just after few years from vaccine introduction. The decreased hospitalization and mortality rates should be also considered in the light of the economic and societal burden sustained by all varicella cases, of which they represent only the tip of the iceberg.

However, at a first glance, the findings from Ribeiro et al. could suggest relatively moderate vaccine effectiveness and, thus, for this reason they need to be adequately contextualized. In a recent analysis, our research group found that in Italy, from 2003 to 2018, varicella vaccination effectiveness on reducing hospitalization risk can be of higher impact as well as −80.0% in the <1 year age class and −86.7% in children aged 1–5 years (article submitted for publication).[9,10] Similarly, decreasing hospitalization rate percentages were found in other countries, as Germany (−77.6% in children <5 years) or Spain (-83.5% in children <5 years), Australia (−76.8% in children 1–4 years), Canada (-93.0% in children 1–4 years), and Uruguay (−94% in children 1–4 years).[11–15]

For improving the interpretation of these data, it should be considered that among the different factors that can influence vaccination effectiveness, a main role is played by vaccination coverage and the number of years since the introduction of the vaccination.[16] The higher the contribution of these two factors, the greater the positive effects on the general populations' health. This assumption is further confirmed by considering that in the study by Ribeiro et al. the impact of vaccination was heterogeneous across the country's macro regions, being higher in the regions with higher vaccination coverage as well as South region (VC > 85%). Nonetheless, as stated by the authors, the short post-vaccination period studied may underestimate the indirect effect provided by the vaccination. According to these considerations, in Sicily we have found that increasing varicella vaccination coverage rates (from 40% in 2001 birth cohort to 85% in 2010 birth cohort) were significantly correlated with a progressive reduction of varicella notifications and hospitalization rates.[17]

Notably, Ribeiro et al. found a significant reduction in hospitalization and mortality rates among children aged <1 year and 5–14 years that, in our opinion, should be considered as a probable consequence of herd protection. It is probable that with time the strength of vaccine effectiveness will increase among 5 to 14-year-old children since a growing percentage of these will belong to previously vaccinated birth cohorts.

There is a third important factor that should be taken into careful consideration when evaluating vaccine effectiveness studies, which is the validity of collected data. Under diagnosis and underreporting are still quite frequent in all countries and, particularly, in regions where access to health services can be still precarious, as stated by the authors for some areas of Brazil. Moreover, epidemiological follow-up of Brazilian vaccination coverage is essential to ensure reaching and sustaining vaccine coverage ≥80%, which is the critical threshold necessary to maintain herd immunity and reduce the risk to shift varicella infection to older ages, with an increase of morbidity and mortality despite reduction in total numbers of cases. Further studies investigating the reasons for low vaccination coverage observed in different Brazilian regions could be the need for evaluating possible roles played by anti-vaccine movements or difficulties in vaccination offer by the national health system.

Moreover, as recommended by the WHO, assessing average age of acquisition of varicella infections could suggest the need for considering alternative vaccination strategies such as vaccination (or catch up) of adolescents and adults without evidence of varicella immunity.[6]

Although the study by Ribeiro et al. could have some limitations, mainly related to the retrospective ecological approach, the reported findings strongly confirm that in Brazil varicella has had a significant burden in terms of hospitalization and mortality before the introduction of universal mass varicella vaccination. Moreover, there is the evidence for the vaccine's effectiveness in significantly reducing this burden in the years immediately following its introduction. In the coming years, these data will need to be confirmed and monitored in order to avoid a possible perverse effect due to low vaccination coverage with increase in the number of cases with older age and severe outcome.

Conflicts of interest

The authors declare no conflicts of interest.

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