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EDITORIAL

Pneumococcal conjugate vaccine and changing epidemiology of childhood bacterial meningitis☆,☆☆

Vacina pneumocócica conjugada e variação da epidemiologia de meningite bacteriana infantil

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Since the inclusion of *Haemophilus influenza* type b (Hib) conjugate vaccine (HibCV) into childhood immunization programs, there has been virtual elimination of Hib meningitis in high- and low-income countries.[1,2] This resulted from immunization of young children, which not only conferred direct protection against invasive Hib disease among immunized children, but also indirect protection of unvaccinated individuals, due to the interruption of transmission of the bacterium within communities through targeted vaccination of young children.[3] Subsequent to HibCV immunization of children, *Streptococcus pneumoniae* emerged as the leading cause of bacterial meningitis in most countries, albeit second to *Neisseria meningitidis* (32%) in some countries, such as Brazil.[4] The study by Hirose et al., published in this issue of the Journal, suggests that further changes in the epidemiology of childhood meningitis in Brazil are likely to occur, since the introduction of the 10-valent polysaccharide-Protein-D protein conjugate vaccine (PCV10) into the public immunization program in March of 2010.[5] Using the Notifiable Diseases Information System on reported cases of pneumococcal meningitis for the Brazilian state of Paraná, Hirose et al. document a reduction by approximately 60% in the incidence of pneumococcal meningitis and a 76% reduction in the incidence of death due to pneumococcal meningitis in children younger than 2 years. This occurred within two-years of introducing PCV10 into the public immunization program of Brazil; the authors performed a comparison with the pre-PCV10 era.

Although these observations are encouraging, it is important to interpret the findings in the context of the limitations and possible biases that are inherent to passive reporting systems, including variability in completeness and accuracy of capture of cases over time. This could inadvertently bias the findings from ecological studies using such administrative databases, either through overestimation of the impact of PCV (should reporting have been suboptimal following PCV introduction) or underestimation of its effect (should there have been enhanced reporting of cases in the post-PCV era). One way of addressing this limitation is to analyse for other diseases recorded in such systems, which are less likely to have been affected by the intervention under investigation and which themselves are not subject to temporal changes. In this regard, it would have been useful to analyse the trends in incidence of other causes of bacterial meningitis, such as Group B *Streptococcus* (GBS), which although mainly affecting infants < 3 months of age, is expected to remain largely unchanged.[6,7] Such a ''dummy'' analyses would help to verify the stability in documentation of bacterial meningitis cases in the reporting system. Similarly, reporting on the trends of incidence by vaccine-serotype and non-vaccine serotype (excluding those for which there could be cross-

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protection or are known to be associated with temporal variability) would further strengthen the interpretation of the current results. In contrast, trends in meningitis due to *Neisseria meningitidis* would have been less useful as a ''dummy'' variable analysis, as it is subject to natural temporal changes and could also be affected by introduction of vaccines recently developed against this bacterium.

Also, although the current study details the proportion of pneumococcal meningitis cases that were due to the PCV10-serotypes prior to the PCV10 era (58%) and during the PCV10-era (46%), the results were not analyzed specifically in relation to vaccine serotype-specific changes in incidence of meningitis, possibly due to the fact that serotyping was only performed in < 50% of isolates. Furthermore, the study is unlikely to have had sufficient number of cases of meningitis by individual serotypes to determine whether there was uniform protection against all serotypes, or whether the changes were specific to some serotypes, such as 1 and 5. These serotypes could undergo natural year-on-year incidence fluctuation. Serotype 1 in particular is a major cause of pneumococcal meningitis in some settings;[8] although included in PCV10 (and PCV13), it could have rapidly declined due to natural fluctuations in its incidence, which was only coincidentally temporally related to PCV introduction.

As such, whilst the decline in incidence of pneumococcal meningitis that was temporally related to PCV10 childhood immunization in this ecological study is promising, the results need to be corroborated by additional vaccine effectiveness studies in the same setting. Such studies have recently been forthcoming from Brazil, including a multi-centred case-control study on invasive pneumococcal disease (IPD) that included meningitis cases.[9] In the latter study, Domingues et al. reported that PCV10 immunization using the three dose primary series (at 2, 4, and 6 months of age) and a booster dose at age 12 months was associated with a 84% reduction (95% CI: 66-92) in PCV10 serotype IPD and notably also a 78% reduction (95% CI: 41-92) in vaccine-related serotypes (6A and 19A), whose immunological cross-reactivity had been reported from earlier immunogenicity studies.[10] This indicates that the PCV10 formulation effectively prevented IPD due to at least 12 serotypes, including serotype 19A (VE: 82%; 95% CI: 11-96). Serotype 19A previously emerged as a major serotype that caused ''replacement disease'' following the introduction of the 7-valent polysaccharide-CRM_{197} protein conjugate vaccine (PCV7) into immunization programs of some high-income countries, which was largely due to clonal expansion of pre-existing antibiotic-resistant strains.[11] Additionally, clonal expansion of other non-PCV7 serotypes, including serotypes 1, 3, 7F, 22F, and 33F, were observed in United Kingdom following PCV7 immunization.[12] The effectiveness of PCV10 against IPD is further corroborated by a cluster randomized control trial of PCV10 undertaken in Finland, in which vaccine efficacy was 100% for the 3+1 dosing schedule and 93% for a two-dose primary series followed by a booster dose.[13]

Despite the limitations of the study by Hirose et al., the results are nevertheless consistent with the impact that PCV7 childhood immunization had on vaccine-serotype meningitis in high-income countries. A recent review on the effect of PCV7 on pneumococcal meningitis in European and North American countries demonstrated reductions of vaccine serotype meningitis of 59% within one year of introduction in the United States, and of up to 100% in some countries among the age groups targeted for vaccination.[14] In addition, many studies reported a decline in incidence of vaccine-serotype meningitis among the age groups that were not targeted for vaccination. In the United States, this decline among PCV unvaccinated age-groups was of slightly lower magnitude (59% to 65% reduction) compared to that observed in children younger than 1 year (83% reduction) ten years following PCV7 introduction.[15] This reflects some ongoing transmission of the vaccine-serotypes even in countries such as the United States, and possibly a lag in indirect protection materializing relative to the direct effect among the age groups targeted for vaccination. Similarly to HibCV, the indirect effect of PCV immunization of children, who are the main age group reservoir of pneumococcal colonization and source of transmission in communities, is related to vaccination reducing their risk of acquiring vaccine-serotype nasopharyngeal colonization.[16] Consequently, there is interruption of the transmission of vaccine-serotypes in the community and reduced acquisition of these serotypes even among unvaccinated individuals, thus protecting them from developing IPD (including meningitis).[3] Although the study by Hirose et al. did not analyze the effect of childhood PCV10 immunization on the incidence of pneumococcal meningitis among PCV-unvaccinated age groups, the findings by Hammitt et al., from Kenya, support that PCV10 (similarly to PCV7 and PCV13) result in indirect community protection against pneumococcal colonization (and consequently likely against disease).[17]

Despite the success in reducing the incidence of pneumococcal meningitis, it remained a leading cause of bacterial meningitis in the United States (58%) seven years following PCV7 introduction, albeit being second to GBS in those < 18 years.[7] Also, the case fatality proportion of pneumococcal meningitis has remained unchanged in the United States and in the United Kingdom in the era of PCV immunization (14% to 16%),[7,12,18] as well as in the study by Hirose et al., when comparing the pre-PCV (31%) to the PCV-era (19%, $p = 0.25$). Furthermore, a high rate (63%) of neurological sequelae among children surviving pneumococcal meningitis persists, regardless of whether it was due to PCV7 vaccine-serotypes.[18] As further reductions in pneumococcal meningitis are expected since the transition from PCV7 to the PCV13 formulation in many countries, the incidence of pneumococcal meningitis is likely to decline further in countries where PCV13 (or PCV10) vaccination has been widely implemented. This change is already being observed in the United States, within one year of transitioning from PCV7 to PCV13 for immunization, with a further 57% reduction observed in IPD due to PCV13 serotypes compared to the era of PCV7 utilisation.[19] The reduction in pneumococcal meningitis was, however, lower than the decrease observed in vaccine-serotype bacteremia, pneumonia, and mastoiditis.[19] With the further decline in pneumococcal meningitis, it is expected that GBS will now become the leading cause of bacterial meningitis in the United States among the pediatric population, albeit concentrated in infants younger than 3 months.[7] Although a trivalent GBS polysaccharide protein conjugate vaccine is currently in

phase II clinical studies,[20] the target for such a vaccine is the immunization of pregnant women, aimed at increasing the transplacental transfer of capsular antibody to the fetus; this is subsequently expected to protect young infant against GBS (group B streptococcal) meningitis and other invasive GBS disease.[21]

Although pneumococcal meningitis is among the least common forms of severe pneumococcal disease, it remains a disease with high proportions of fatality and neurological sequelae. The PCV vaccines have now been established to prevent vaccine-serotype meningitis. Considering the higher incidence of pneumococcal disease and much higher mortality associated with pneumococcal meningitis (35%) in children from low-income countries,[22] expediting the introduction of PCV into all low-middle income countries in a cost-effective and sustainable manner should be prioritized.

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Conflicts of interest

The author declares no conflicts of interest.

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