Assessing reduced-dose pneumococcal vaccine schedules in South Africa

Pneumococcal conjugate vaccines (PCVs) provide direct protection against disease caused by vaccine-serotype Streptococcus pneumoniae and indirect protection by reducing nasopharyngeal colonisation and subsequent transmission of vaccine-type strains to unvaccinated individuals. WHO recommends PCV administration to infants in a three-dose schedule, with either two primary doses (starting as early as 6 weeks of age) and a booster given at age 9–18 months (2+1 schedule), or three primary doses without a booster (3+0 schedule).1 By inducing higher antibody concentrations during the child’s second year of life, the booster dose might lead to longer protection against colonisation and improved indirect protection, which is crucial for successful PCV programmes.

In countries with mature PCV programmes resulting in effective control of vaccine-type disease, reduced-dose schedules are considered a potentially cost-effective alternative for maintaining protection against pneumococcal disease.2 The advantages are clear: fewer doses of the expensive PCV would lower costs and ease a crowded infant vaccine schedule. In 2020, the UK adopted a 1+1 PCV schedule, with the primary dose given at 12 weeks and the booster dose given at age 1 year. This decision was bolstered by robust disease surveillance data and pneumococcal carriage studies that showed decreased circulation of vaccine-type strains in the community, modelling that suggested a 1+1 schedule can effectively maintain control of vaccine serotypes, and a clinical trial examining the immunogenicity of reduced-dose schedules in UK infants.3–5 In the trial,6 for most PCV13 serotypes, post-booster antibody responses were equivalent or higher among infants who received a single priming dose (1+1 schedule) versus those who received the standard 2+1 schedule. However, fewer primary doses might lessen direct protection against disease before the booster dose. A US study in 2016 showed that the rate of breakthrough infection was higher for infants receiving two versus three primary doses.4 The change in the UK schedule generated concern for infants. Time and robust surveillance will establish whether the 1+1 schedule maintains suppression of vaccine serotypes without increasing invasive pneumococcal disease during early infancy.

For low-income and middle-income countries (LMICs), which bear the greatest burden of pneumococcal disease, the benefits and risks of reduced-dose PCV schedules are heightened. In The Lancet Infectious Diseases, Shabir Madhi and colleagues report results from a randomised, non-inferiority trial investigating the immunogenicity of a 1+1 PCV schedule versus a 2+1 schedule in South African infants.7 South Africa is an upper-middle-income country with a well established PCV programme (PCV7 was introduced in 2009 and replaced by PCV13 in 2011). Robust national surveillance documented substantial declines in invasive pneumococcal disease caused by vaccine serotypes following introduction of PCV into the routine immunisation programme, including among unvaccinated age groups through indirect effects.7

Infants were randomly assigned into six groups, including four that received 1+1 schedules of ten-valent PCV (PCV10) or 13-valent PCV (PCV13), with the priming dose given at either age 6 or 14 weeks, followed by a booster at 40 weeks of age, and two that received the standard 2+1 schedule of PCV10 or PCV13, with doses given at ages 6, 14, and 40 weeks. The primary endpoint, serotype-specific IgG concentrations after the booster dose, reflects the goal of the 1+1 schedule to maintain reduced vaccine-serotype carriage in young children. Consistent with the UK trial, post-booster antibody responses for 1+1 groups were non-inferior to those of the standard 2+1 groups for both vaccine formulations. Evaluation of both PCV13 and PCV10 and two options for timing of the primary dose in a 1+1 schedule expand the utility of the findings.

As anticipated, antibody concentrations were lower after the primary series for the 1+1 groups, identifying a window of reduced immunity before the booster. Delaying the primary dose to 14 weeks of age might improve immunity during this window because pre-booster antibody concentrations were higher when the primary dose was given at that age than when it was given at age 6 weeks. However, pneumococcal colonisation occurs very early in LMICs, and delaying the first dose might increase the time infants are at
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risk. Madhi and colleagues point to surveillance data showing very low incidence of vaccine-type invasive pneumococcal disease in infants younger than 10 weeks, indicative of indirect protection. Higher-valency PCV formulations are on the horizon, and disease caused by the additional serotypes they contain would not immediately be controlled by indirect effects.

A crucial question remains. How do reduced-dose schedules compare with a 2+1 schedule in terms of the effects on pneumococcal carriage? The epidemiology of pneumococcal carriage in LMICs is different from that in high-income countries. Persistent and higher residual vaccine-serotype carriage has been recorded across several sub-Saharan Africa countries, including South Africa, irrespective of PCV formulations and schedules.

In a 2020 study in Malawi, vaccine-serotype carriage was reported for 16.7% of PCV-vaccinated children aged 3–5 years several years after PCV introduction. The South African study did not evaluate carriage; however, PCV reduced-dose trials with carriage as a primary endpoint are underway in Vietnam, India, and The Gambia.

Madhi and colleagues’ study showing non-inferiority of post-booster antibody responses from reduced-dose PCV schedules supports their potential application in LMIC settings. However, several factors, including country-specific epidemiology and serotype distribution, need to be taken into account by countries considering a switch to a reduced-dose PCV schedule to ensure that success of the PCV programme is maintained. Robust surveillance systems capable of detecting increases in invasive pneumococcal disease, including breakthrough infections during infancy, are essential. Achieving high immunisation coverage poses a challenge in many LMICs. High coverage and timely administration of a booster dose are needed to ensure that indirect effects from a 1+1 schedule mitigate potential reductions in individual-level protection. Reduced-dose PCV schedules might not be suitable for infants at increased risk of pneumococcal disease (eg, HIV-exposed infants) or for settings with high residual vaccine-serotype carriage, suboptimal vaccination coverage, or inadequate surveillance systems. Development of clear implementation guidelines for countries considering reduced-dose PCV schedules is warranted.

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