Progress towards reduced-dose pneumococcal vaccine schedules for children in Africa

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Pneumococcal conjugate vaccines (PCVs) have been available for more than 20 years[1] and incorporated into the childhood immunisation programmes of 168 countries. Although they have been remarkably successful at reducing the burden of pneumococcal disease globally,[1] there remain concerns about the sustainability of PCV programmes given the emerging threats and competing public health interests. Importantly, PCV remains the most expensive vaccine in childhood immunisation programmes, and between 2009 and 2020 Gavi, the Vaccine Alliance spent more than US$4 billion on PCV alone. In 2021, all but nine African nations had introduced PCV, with the high cost being a major barrier to introduction.

Given cost considerations, there is an ongoing debate on the optimal number of PCV doses and the best time to schedule them for children.[2] So far, the UK is the only country to have transitioned to a reduced dose (1+1) schedule. The rationale was based on a population achieving near elimination of vaccine-serotype pneumococcal disease as well as vaccine-serotype nasopharyngeal carriage. At the time when England and Wales switched to a 1+1 schedule, 13-valent PCV (PCV13) vaccine-serotype carriage in children younger than 5 years was below 3%,[3] and disease incidence across all age groups was very low at 1·9 per 100 000 population.[4]

In South Africa, the seven-valent PCV (PCV7) was introduced in April, 2009, and replaced with PCV13 in 2011, making it the oldest PCV programme in sub-Saharan Africa. South Africa is also the only country in sub-Saharan Africa to have introduced PCV using a 2+1 schedule with two primary doses plus a booster given at 9 months.[5] By 2017, South Africa had achieved an 80% reduction in vaccine-serotype carriage and a 90% decline in pneumococcal disease.[6]

What Courtney P Olwagen and colleagues present in *The Lancet Child & Adolescent Health* is compelling evidence that South Africa might be in a position to transition to a reduced-dose (1+1) PCV schedule.[7] The authors evaluated the effects of two 1+1 schedules (with the priming dose at 6 weeks or 14 weeks of age and booster at 9 months of age) compared with the 2+1 schedule (two priming doses at 6 weeks and 14 weeks of age and a booster at 9 months of age) for both ten-valent PCV (PCV10) and PCV13 formulations on the carriage of vaccine-serotype and non-vaccine-serotype *Streptococcus pneumoniae* in an open-label randomised-controlled trial with six groups and involving 600 infants in Soweto, South Africa.[8] The authors also investigated the non-inferiority of both 1+1 schedules compared with the 2+1 schedule based on the serotype-specific antibody concentrations and the proportion of children achieving antibody levels above the putative correlates of protection.

Olwagen and colleagues observed that before receiving the PCV13 booster dose, infants aged 9 months on the 6-week 1+1 schedule were significantly more likely to carry vaccine serotypes than children in the 2+1 group (odds ratio [OR] 2·56 [95% CI 1·13–5·78]; p=0·024). Although it did not reach statistical significance, the odds of vaccine-serotype colonisation among infants aged 18 months were twice as high in the PCV13 6-week 1+1 than in the PCV13 2+1 group. Furthermore, the PCV13 6-week 1+1 group did not meet the non-inferiority criteria for serotype-specific anticapsular antibody concentrations. These findings raise important questions about whether a PCV13 6-week 1+1 schedule adequately suppresses the circulation of vaccine serotypes in the first year of life and how well the booster dose extends protection into the second year of life in South Africa.

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By contrast, infants aged 15 months in the PCV13 14-week 1+1 group had significantly lower vaccine-serotype carriage than infants in the 2+1 group (OR 0·61 [95% CI 0·38–0·97], p=0·037), 6 months after the booster dose, with the greatest reductions observed for serotype 19F. This could be because infants aged 14 weeks can mount more robust and longer-lasting vaccine-induced immune responses than those aged 6 weeks.

With vaccine-serotype carriage at 10–20%, a key question is whether South Africa has sufficiently controlled vaccine serotypes[6] to reduce PCV doses and potentially also delay the first dose by 2 months. Would interventions to accelerate PCV impact and further reduce vaccine-serotype colonisation, such as catch-up campaigns, be necessary before transitioning to a reduced-dose schedule? Does transient reduction translate to sustained reductions or maintenance of pneumococcal disease across populations?

The authors reported that the PCV10 14-week 1+1 group met the non-inferiority criteria compared with the PCV10 2+zzz1 schedule. However, the practical and policy implications of this result in favour of PCV10 for countries currently using PCV13 warrant further investigation.

A notable limitation is that the intervals between the 9-month, 15-month, and 18-month visits are too long to effectively assess highly dynamic pneumococcal acquisition in children.[9] Another important consideration is the high burden of HIV in South Africa. This population was excluded from the trial, even though they are more susceptible to pneumococcal infections and have frequent, high-density, and prolonged pneumococcal colonisation.[10] Robust longitudinal studies with frequent sampling in a more diverse and representative population are necessary to assess the impact of reduced-dose schedules on pneumococcal acquisitions before transitioning.

This timely study provides key evidence that a reduced-dose PCV schedule could be within arm's reach in an African country. The long-term sustainability of PCV programmes for the world's poorest countries, as pointed out by Olwagen and colleagues, might indeed depend on being able to determine the minimum PCV doses needed to maintain control of pneumococcal disease. More clinical trials in Africa, including the one currently being conducted in The Gambia (International Standard Randomised Controlled Trial Number 15056916), are needed to determine the cost-effective and optimal strategies for maintaining protection against pneumococcal disease specific to this setting.

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