Prevention of pneumococcal diseases: the challenge remains

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Streptococcus pneumoniae (pneumococcus) is a leading cause of pneumonia that kills almost a million children worldwide annually, mostly in African and Asian countries.[1] By 2015, 129 countries have introduced pneumococcal conjugate vaccines (PCVs) that have substantially reduced child morbidity and mortality.[2] However, post-vaccine surveillance has shown the emergence of diseases caused by non-vaccine serotypes as well as serotype replacement in nasopharyngeal colonisation.[3] Although an impact of vaccination on invasive pneumococcal disease has been observed in young children (particularly those younger than 2 years, even after many years of pneumococcal conjugate vaccine implementation) the emergence of non-vaccine serotypes with antibiotic resistance has become a new global threat to the control and prevention of pneumococcal diseases.[3,4]

In *The Lancet Global Health*, Shrijana Shrestha and colleagues[5] present much needed data on the effect of the 10-valent pneumococcal conjugate vaccine (PCV10) in Nepal. There is a paucity of such vaccine impact data from low-income and middle-income countries. Nepal included PCV10 in its national immunisation programme in 2015 by adopting a dosing schedule of two primary doses at 6 weeks and 10 weeks and one booster at age 9 months. Between the periods of 1·5 years before and 4·5 years after PCV10 introduction, the study compared serotype distributions of pneumococci in nasopharyngeal colonisation of healthy children, children with pneumonia, and children with invasive pneumococcal diseases. The prevalence of overall PCV10 vaccine serotypes decreased substantially in both healthy children (by 75%, adjusted prevalence ratio [aPR] 0·25 [95% CI 0·19–0·33] in urban children in 2019; and by 72%, aPR 0·28 [0·19–0·37] in rural children in 2018) and in children with pneumonia (by 82%, aPR 0·18 [95% CI 0·07–0·50] in 2019) among those younger than age 2 years in the post-vaccine period. The number of children with invasive pneumococcal diseases was found to be suddenly higher in 2019, and authors suspected that the increased detection was due to the calibration of the Bactec machine. However, most of the children were older than 5 years, and the sudden increase in 2019 was observed only for serotype 1. Therefore, an outbreak of serotype 1 might have been a possibility, and this might have occurred even in the post-vaccine period because a similar pattern was observed in children older than 5 years and adults in Ghana after 3 years of introduction of PCV13 in 2015–16.[6]

Surveillance of the long-term impact of PCVs on colonisation and pneumococcal diseases needs to continue. We expect that the vaccine serotypes will further decrease in Nepal as the vaccination programme matures; however, the decrease might plateau in the near future with persisting residual vaccine serotypes as seen in The Gambia after 10 years of introduction of PCVs.[7] The proportion of residual persisting vaccine serotype is higher in low-income and middle-income countries than in high-income countries because of various hosts and vaccine-related factors (eg, age of children, pre-vaccine carriage prevalence, susceptibility to colonisation, vaccine efficacy, vaccine schedule, and catch-up campaign).[8] Studies on alternative vaccine schedules or an additional booster dose probably answer the question as to whether the residual vaccine serotype colonisation can be reduced in low-income and middle-income countries.[7]

Emergence of non-vaccine serotypes after introduction of PCVs, along with increased antibiotic resistance in these serotypes, has become a global threat.[3,4] Therefore, documenting the emergence of non-vaccine serotypes and investigating their resistance patterns is essential. Because higher valent vaccines are being developed to control the present non-vaccine serotypes, pneumococci seem to evolve quickly to adapt with humans by increasing their serotype diversity at the initial phase of vaccine pressure and then establishing themselves as few pathogenic dominant non-vaccine serotypes resulting in a new evolutionary equilibrium.[9] Further studies are needed to understand the emergence of non-vaccine serotypes and their long-term implications. Use of novel molecular serotyping methods based in microarray or real-time PCR systems might reveal multiple serotype colonisation and infections that might help to further understand vaccine effectiveness and pneumococcal evolution.[10,11]

In conclusion, introduction of PCVs has a positive impact on reducing pneumococcal disease burden worldwide, including in low-income and middle-income countries; however, the challenge with pneumococci remains, as they are evolving fast to adapt in the post-vaccine period.

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1 McAllister DA, Liu L, Shi T, et al. Global, regional, and national estimates of pneumonia morbidity and mortality in children younger than 5 years between 2000 and 2015: a systematic analysis. *Lancet Glob Health* 2019; **7:** e47–57.

2 Wahl B, O'Brien KL, Greenbaum A, et al. Burden of Streptococcus pneumoniae and haemophilus influenzae type b disease in children in the era of conjugate vaccines: global, regional, and national estimates for 2000–15. *Lancet Glob Health* 2018; **6:** e744–e57.

3 Waight PA, Andrews NJ, Ladhani SN, Sheppard CL, Slack MP, Miller E. Effect of the 13-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in England and Wales 4 years after its introduction: an observational cohort study. *Lancet Infect Dis* 2015; **15:** 535–43.

4 Lo SW, Gladstone RA, van Tonder AJ, et al. Pneumococcal lineages associated with serotype replacement and antibiotic resistance in childhood invasive pneumococcal disease in the post-PCV13 era: an international whole-genome sequencing study. *Lancet Infect Dis* 2019; **19:** 759–69.

5 Shrestha S, Gurung M, Amatya P, et al. Effect of the of 10-valent pneumococcal conjugate vaccine in Nepal 4 years after introduction: an observational cohort study. *Lancet Glob Health* 2022; **10:** e1494–504.

6 Kwambana-Adams BA, Asiedu-Bekoe F, Sarkodie B, et al. An outbreak of pneumococcal meningitis among older children (≥5 years) and adults after the implementation of an infant vaccination programme with the 13-valent pneumococcal conjugate vaccine in Ghana. *BMC Infect Dis* 2016; **16:** 575.

7 Usuf E, Bottomley C, Gladstone R, et al. Persistent and emerging pneumococcal carriage serotypes in a rural Gambian community after 10 years of pneumococcal conjugate vaccine pressure. *Clin Infect Dis* 2021; **73:** e3825–35.

8 Lourenço J, Obolski U, Swarthout TD, et al. Determinants of high residual post-PCV13 pneumococcal vaccine-type carriage in Blantyre, Malawi: a modelling study. *BMC Med* 2019; **17:** 219.

9 Stockmann C, Ampofo K, Pavia AT, et al. Clinical and epidemiological evidence of the red queen hypothesis in pneumococcal serotype dynamics. *Clin Infect Dis* 2016; **63:** 619–26.

10 Valente C, Hinds J, Gould KA, Pinto FR, de Lencastre H, Sa-Leao R. Impact of the 13-valent pneumococcal conjugate vaccine on Streptococcus pneumoniae multiple serotype carriage. *Vaccine* 2016; **34:** 4072–8.

11 Dhoubhadel BG, Suzuki M, Ishifuji T, et al. High prevalence of multiple serotypes of pneumococci in patients with pneumonia and their associated risk factors. *Thorax* 2022; published online April 26. https://doi.org/10.1136/thoraxjnl-2021-217979.