

**Challenges inferring pneumococcal conjugate vaccine impact from bacterial surveillance data**

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To the editor:

Pneumococcal conjugate vaccines (PCVs) have greatly reduced pneumococcal disease in children <5 years of age in low- and middle-income countries where infant immunization rates were high (>80%) and sufficient time had passed since introduction into national infant immunization programs.<sup>1-3</sup> Nakamura and colleagues presented surveillance data from 58 countries in the WHO-coordinated Global Invasive Bacterial Vaccine-Preventable Diseases Surveillance Network on pediatric bacterial meningitis in children <5 years, which detects *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae* bacteria.<sup>4</sup> They described the pneumococcal serotype distribution before and after PCV introduction. They stated that “Pneumococcus was the most common pathogen detected from pediatric bacterial meningitis cases... despite increasing use of highly effective PCVs”, that 50% of post-PCV pneumococcal meningitis was vaccine-type (VT) and concluded that “The continued occurrence of both vaccine-type and nonvaccine-type [pneumococcal] meningitis cases suggests a role for both increased PCV coverage and higher-valent PCVs”. Although the authors intentionally did not estimate impact because of many stated limitations, one might infer from this that PCV impact was subpar. But evaluating impact is complicated and requires additional post-introduction evidence, including evaluating the change in incidence over time and incorporating indirect effects, including what is happening with non-VT disease. In the following, we describe several issues that may bias impressions of impact when relying only on serotype and pathogen distribution data even for high-performing PCV programs.

**Not accounting for impact of other vaccines:** The number of pneumococcal cases was compared to meningococcal and *H. influenzae* cases, but meningococcal and Hib vaccines were also introduced. If those vaccines eliminated the most common meningococcal and *H. influenzae* types associated with

invasive disease, then the *relative* number of pneumococcal cases compared to meningococcal or Hib cases could *increase* even if the absolute number of pneumococcal cases also decreased following PCV introduction.

**Including age-ineligible cases:** Post-PCV cases could be unvaccinated because they were too young or too old to receive PCV when it was introduced. Analyses that are conducted after recent (e.g.,  $\leq 3$  years) PCV introduction and evaluate all cases  $< 5$  years of age include such vaccine-ineligible children, especially as most countries do not have catchup programs for older age groups. Restricting cases to those who were vaccine-age-eligible removes this bias.

**Time since PCV introduction is too short for maximal impact:** It takes a minimum of 5 years since PCV introduction for all children  $< 5$  years of age to have a chance to be immunized, and can take 5-7 years post-vaccination to achieve a stabilized serotype distribution.<sup>5,6</sup> The serotype distribution changes prior to this time because VTs are gradually being eliminated due to direct and indirect (herd immunity) effects, and non-VT replacement disease may increase as carriage of non-VT serotypes replaces VT carriage. Catch-up programs that vaccinate more than the birth cohort can shorten this time period to reach full coverage<sup>2</sup>.

**Pooling all post-PCV cases underestimates impact:** The years with the greatest impact are the furthest out from PCV introduction and have the fewest number of cases because the annual number of VT cases declines over time. Thus, analyses that pool all post-PCV cases are comprised mostly of unvaccinated VT cases from the early years, biasing estimates towards both larger case counts and VT cases.

**Serotype distribution alone does not convey impact:** Comparing the proportion of vaccine-type disease before vs after PCV introduction cannot directly measure the magnitude of PCV impact and may lead to misperceptions. To illustrate, if pre-PCV there were 10 VT cases and 1 non-VT case (i.e., 11 cases total, 91% VT) and we eliminated 9 of the 10 VT cases (i.e., 90% vaccine effectiveness), there would be 1 nonVT and 1 VT case remaining (i.e., 50% VT). Thus, in this example of 90% effectiveness and 82% impact (i.e., 9 of 11 cases prevented), the proportion VT changed from 91% to only 50%.

Evaluating vaccine impact is difficult to infer from serotype and pathogen distributions alone. Rigorous incidence-based approaches that consider vaccine uptake, vaccine-age-eligibility, sensitivity of case detection, standardization of methods over time and known denominators provide the best evidence but are resource intensive. Invasive bacterial disease surveillance is more affordable and, if interpreted with caution and within its limits, is still valuable for monitoring progress, and increases in value when long-term. However, even the most basic surveillance can be difficult in resource constrained settings.<sup>7</sup> Although the evidence to estimate impact must come from incidence data, we agree with Nakamura et. al that higher immunization coverage and higher valency PCVs will increase that impact on meningitis and all invasive pneumococcal disease.<sup>1,2</sup>

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