Playing "Whack-a-Mole" With Pneumococcal Serotype Eradication

Douglas S. Swanson, MD, Christopher J. Harrison, MD

In this issue of *Pediatrics*, Lee et al[1] report surveillance data from Massachusetts communities regarding *Streptococcus pneumoniae* (SPN) colonization during the pneumococcal conjugate vaccine (PCV) era. Nasopharyngeal (NP) colonization is thought to precede SPN disease, so it is a reasonable measure of circulating (and potentially disease-producing) pneumococcal strains. Three aspects are notable: (1) shifting serotypes of known invasive pneumococcal disease (IPD) producers; (2) risk factors for colonization; and (3) evolving antibiotic resistance.

Excluding HIV-associated pneumococcal deaths, global estimates attribute ∼11% of all deaths in children 1 to 59 months of age to SPN disease.[2] SPN remains a concern for US practitioners, causing both IPD (eg, meningitis, pneumonia, and bacteremia) and noninvasive disease (eg, acute otitis media [AOM] and sinusitis). Practitioners likely see at least 1 child per week for whom SPN bacteremia, pneumonia, or meningitis is a concern. A preventive vaccine targeting the most common IPD strains seemed a reasonable strategy to reduce disease burden and ease providers' fears of missing an impending severe IPD case.

Introduced in 2000, 7-valent PCV (PCV7) markedly decreased IPD among PCV7 recipients,[3–6] and also among non-PCV7 recipients through herd immunity.[4,5,7] Pneumonia,[8] AOM,[9,10] tympanostomy tube procedures,[11] and NP colonization[12] also declined. However, non-PCV7 serotypes emerged to colonize and cause disease (serotype replacement).[13–15] Serotype 19A was a major culprit sustaining both IPD and difficult-to-treat noninvasive infections, adding to the problem of high-level multidrug resistance.[16,17] In 2010, 13-valent PCV (PCV13) included the main post-PCV7 replacement serotypes and was successful in reducing IPD from the 6 added PCV13 serotypes, including 19A[18–20] and multidrug-resistant strains.[20,21]

Lee et al's[1] data confirm that PCV7 and PCV13 caused a rapid but transient decrease in NP colonization, followed by increasing colonization due to newly emerged replacement serotypes. One concern is whether some replacement serotypes could have invasive disease potential. For example, post-PCV7, there was increased severity of IPD from non-PCV7 serogroup organisms among children in the Intermountain West of the United States.[22] Although Stockmann et al[23] identified an initial increase in diversity of IPD serotypes after PCV7 and PCV13, the diversity soon reversed, presumably because of selective competition and the emergence of new dominant strains. They hypothesize that these new strains could cause increased IPD, especially in vulnerable populations. Thus, post-PCV13 serotype 35B may become the equivalent of post-PCV7 serotype 19A.

But occult bacteremia has nearly disappeared and meningitis is less frequent. Despite this, the authors report ongoing risk factors for colonization with potential IPD strains. These risks, described previously in

Division of Infectious Diseases, Children's Mercy Kansas City, University of Missouri-Kansas City, Kansas City, Missouri

DOI: https://doi.org/10.1542/peds.2017-2034

Accepted for publication Aug 9, 2017

Address correspondence to Douglas S. Swanson, MD, Infectious Diseases, Children's Mercy Kansas City, 2401 Gillham Rd, Kanas City, MO 64108. E-mail: dswasnon@cmh.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: Children's Mercy Kansas City has received research support from Pfizer Inc for which Drs Swanson and Harrison are investigators.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: Drs Swanson and Harrison conducted pneumococcal research that was supported by funding from Pfizer Inc, New York, a manufacturer of pneumococcal conjugate vaccine.

COMPANION PAPER: A companion to this article can be found online at www.pediatrics.org/cgi/doi/10.1542/peds.2017-0001.

To cite: Swanson DS and Harrison CJ. Playing "Whack-a-Mole" With Pneumococcal Serotype Eradication. *Pediatrics*. 2017;140(5):e20172034

smaller short-term studies, offer targets for action. The risk factor of young age can be addressed by on-time PCV13 administration to provide protection as soon as possible. Advising fewer hours at daycare can reduce pathogen exposure and frequency of upper respiratory tract infections (2 other risk factors). Educational efforts to restrict second hand smoke exposure and minimize antibiotic use can also decrease the risk for SPN NP colonization. Of these, judicious antibiotic use and on-time PCV13 are actions providers can impact the most.

The authors' data[1] confirm the rise and fall of antibiotic resistance, particularly in the multidrug-resistant 19A strain, which peaked from 2008 to 2010. By 2014, only ~5% of SPN were penicillin nonsusceptible, but new replacement strains increased ceftriaxone and macrolide nonsusceptibility. Indeed, serotype 35B accounted for >80% of ceftriaxone nonsusceptibility. Interestingly, the nonsusceptible 35B strains appear to have originally had 9V capsules. They switched to a 35B capsule post-PCV13,[24] confirming the concerns of some experts that SPN could change its capsule under antibody pressure like people change their clothes for different weather. The considerable macrolide nonsusceptibility, likely due to past azithromycin exposure, is important given azithromycin's overuse for outpatient pneumonia[25] and AOM.[26]

Is there a better strategy? From the pool of >90 SPN serotypes, new types emerged after each PCV was implemented. More serotypes in a multivalent PCV will not likely solve this problem because of limits on the number of new serotypes that can be added. Auxiliary PCVs that address only emerging non-PCV13 serotypes may be possible. However, the time and/or resources to reformulate and obtain Food and Drug Administration approval make this strategy seem like playing a game of whack-a-mole.

To overcome the phenomenon of serotype replacement, vaccine strategies need to expand beyond serotype specificity by identifying antigens common to all SPN, regardless of serotype. Meanwhile, studies like this one by Lee et al,[1] that monitor pneumococcal seroepidemiology will inform treatment and vaccine strategies. The hope that IPD and antibiotic resistance would disappear after widespread use of PCV vaccines has yet to be realized.

Yet there is progress. Shifts back to less penicillin resistance may soon preclude the need for high dose amoxicillin for AOM, and the near absence of occult SPN bacteremia may drastically reduce empirical ceftriaxone for fever without a focus. To assist providers in ongoing vigilance for the now less frequent IPD, algorithms based on new epidemiologic data are in development and should decrease the number of "sepsis workups" performed.

ABBREVIATIONS

AOM: acute otitis media
IPD: invasive pneumococcal disease
PCV: pneumococcal conjugate vaccine
PCV7: 7-valent pneumococcal conjugate vaccine
PCV13: 13-valent pneumococcal conjugate vaccine
NP: nasopharyngeal
SPN: *Streptococcus pneumoniae*

REFERENCES

1. Lee GM, Kleinman K, Pelton S, et al. Immunization, antibiotic use, and pneumococcal colonization over a 15-year period. *Pediatrics*. 2017; 140(5):e20170001
2. O'Brien KL, Wolfson LJ, Watt JP, et al; Hib and Pneumococcal Global Burden of Disease Study Team. Burden of disease caused by *Streptococcus pneumoniae* in children younger than 5 years: global estimates. *Lancet*. 2009;374(9693):893–902
3. Kaplan SL, Mason EO Jr, Wald ER, et al. Decrease of invasive pneumococcal infections in children among 8 children's hospitals in the United States after the introduction of the 7-valent pneumococcal conjugate vaccine. *Pediatrics*. 2004;113(3 pt 1):443–449
4. Poehling KA, Talbot TR, Griffin MR, et al. Invasive pneumococcal disease among infants before and after introduction of pneumococcal conjugate vaccine. *JAMA*. 2006;295(14):1668–1674
5. Whitney CG, Farley MM, Hadler J, et al; Active Bacterial Core Surveillance of the Emerging Infections Program Network. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. *N Engl J Med*. 2003;348(18):1737–1746
6. McIntosh EDG, Reinert RR. Global prevailing and emerging pediatric pneumococcal serotypes. *Expert Rev Vaccines*. 2011;10(1):109–129
7. Lexau CA, Lynfield R, Danila R, et al; Active Bacterial Core Surveillance Team. Changing epidemiology of invasive pneumococcal disease among older adults in the era of pediatric pneumococcal conjugate vaccine. *JAMA*. 2005;294(16):2043–2051
8. Griffin MR, Zhu Y, Moore MR, Whitney CG, Grijalva CGUS. U.S. hospitalizations for pneumonia after a decade of pneumococcal vaccination. *N Engl J Med*. 2013;369(2):155–163
9. Eskola J, Kilpi T, Palmu A, et al; Finnish Otitis Media Study Group. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. *N Engl J Med*. 2001;344(6):403–409
10. Grijalva CG, Poehling KA, Nuorti JP, et al. National impact of universal childhood immunization with pneumococcal conjugate vaccine on outpatient medical care visits in the United States. *Pediatrics*. 2006;118(3):865–873

11. Poehling KA, Szilagyi PG, Grijalva CG, et al. Reduction of frequent otitis media and pressure-equalizing tube insertions in children after introduction of pneumococcal conjugate vaccine. *Pediatrics*. 2007;119(4):707–715

12. Pelton SI, Loughlin AM, Marchant CD. Seven valent pneumococcal conjugate vaccine immunization in two Boston communities: changes in serotypes and antimicrobial susceptibility among *Streptococcus pneumoniae* isolates. *Pediatr Infect Dis J*. 2004;23(11):1015–1022

13. Hicks LA, Harrison LH, Flannery B, et al. Incidence of pneumococcal disease due to non-pneumococcal conjugate vaccine (PCV7) serotypes in the United States during the era of widespread PCV7 vaccination, 1998-2004. *J Infect Dis*. 2007;196(9):1346–1354

14. Huang SS, Hinrichsen VL, Stevenson AE, et al. Continued impact of pneumococcal conjugate vaccine on carriage in young children. *Pediatrics*. 2009;124(1). Available at: www.pediatrics.org/cgi/content/full/124/1/e1

15. Pilishvili T, Lexau C, Farley MM, et al; Active Bacterial Core Surveillance/Emerging Infections Program Network. Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. *J Infect Dis*. 2010;201(1):32–41

16. Moore MR, Gertz RE Jr, Woodbury RL, et al. Population snapshot of emergent *Streptococcus pneumoniae* serotype 19A in the United States, 2005. *J Infect Dis*. 2008;197(7):1016–1027

17. Kaplan SL, Barson WJ, Lin PL, et al. Serotype 19A is the most common serotype causing invasive pneumococcal infections in children. *Pediatrics*. 2010;125(3):429–436

18. Gounder PP, Bruce MG, Bruden DJ, et al. Effect of the 13-valent pneumococcal conjugate vaccine on nasopharyngeal colonization by Streptococcus pneumoniae–Alaska, 2008-2012. *J Infect Dis*. 2014;209(8):1251–1258

19. Lee GM, Kleinman K, Pelton SI, et al. Impact of 13-valent pneumococcal conjugate vaccination on Streptococcus pneumoniae carriage in young children in Massachusetts. *J Pediatric Infect Dis Soc*. 2014;3(1):23–32

20. Moore MR, Link-Gelles R, Schaffner W, et al. Effect of use of 13-valent pneumococcal conjugate vaccine in children on invasive pneumococcal disease in children and adults in the USA: analysis of multisite, population-based surveillance. *Lancet Infect Dis*. 2015;15(3):301–309

21. Dagan R, Juergens C, Trammel J, et al. Efficacy of 13-valent pneumococcal conjugate vaccine (PCV13) versus that of 7-valent PCV (PCV7) against nasopharyngeal colonization of antibiotic-nonsusceptible *Streptococcus pneumoniae*. *J Infect Dis*. 2015;211(7):1144–1153

22. Byington CL, Samore MH, Stoddard GJ, et al. Temporal trends of invasive disease due to *Streptococcus pneumoniae* among children in the intermountain west: emergence of nonvaccine serogroups. *Clin Infect Dis*. 2005;41(1):21–29

23. 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(5):619–626

24. Chochua S, Metcalf BJ, Li Z, et al. Invasive serotype 35B pneumococci including an expanding serotype switch lineage, United States, 2015-2016. *Emerg Infect Dis*. 2017;23(6):922–930

25. Handy LK, Bryan M, Gerber JS, Zaoutis T, Feemster KA. Variability in antibiotic prescribing for community-acquired pneumonia. *Pediatrics*. 2017;139(4):e20162331

26. Grijalva CG, Nuorti P, Griffin MR. Antibiotic prescription rates for acute respiratory tract infections in US ambulatory settings. *JAMA*. 2009;302(7):758–766

Playing ''Whack-a-Mole'' With Pneumococcal Serotype Eradication

Douglas S. Swanson and Christopher J. Harrison

Pediatrics 2017;140;
DOI: 10.1542/peds.2017-2034 originally published online October 4, 2017;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Playing ''Whack-a-Mole'' With Pneumococcal Serotype Eradication

Douglas S. Swanson and Christopher J. Harrison

Pediatrics 2017;140;
DOI: 10.1542/peds.2017-2034 originally published online October 4, 2017;