Invasive Pneumococcal Serotype 3 Disease, Despite Pneumococcal Polysaccharide Vaccine-23

B. Frank Parker1∗, MD; Forest W. Arnold2, DO, MSc

1Department of Internal Medicine, University of Louisville, Louisville, KY; 2Division of Infectious Diseases, Department of Medicine, University of Louisville, Louisville, KY

∗bfpark01@louisville.edu

Recommended Citation: Parker BF, Arnold FW. Invasive pneumococcal serotype 3 disease, despite pneumococcal polysaccharide vaccine-23. Univ Louisville J Respir Infect 2021; 5(1): Article 13.

Abstract

Pneumococcal disease has a high global morbidity and mortality. We report a case of a 63-year old female with a history of vaccination with pneumococcal polysaccharide vaccine-23 (PPSV-23) who was transferred to a tertiary care facility with fever and seizures due to an unknown etiology. The diagnosis of invasive pneumococcal disease (IPD) was based on the identification of Streptococcus pneumoniae in the blood (culture; serogroup 3) and cerebrospinal fluid (antigen) and the finding of purulence under pressure at craniotomy. The pneumococcal vaccine should provide protection from IPD. The findings reported here display that IPD can overcome immunity proffered by the pneumococcal vaccine, especially in patients with multiple comorbidities. This patient who had IPD represents anyone with comorbidities which justify PPSV-23 vaccination, but in whom neither a second PPSV-23, nor a PCV-13 vaccination is recommended prior to the age of 65 years.

Introduction

Historically, vaccination has reduced morbidity and mortality from disease. A vaccine against Streptococcus pneumoniae was developed in 1977 for 14 serotypes. It was expanded to 23 serotypes in 1983 and is known as pneumococcal polysaccharide vaccine (PPSV-23). In 2000, a conjugated version for children was created for 7 serotypes, known as pneumococcal conjugate vaccine (PCV-7). It was only available in Europe. It was expanded to 13 serotypes (PCV-13) in 2010 and available in the US as well. The following year, it was approved for adults. The unconjugated vaccine (PPSV-23) stimulates B-cells which release IgM, while the pneumococcal conjugate vaccine (PCV-13) also recruits helper T-cells for a more robust and longer immune response. For those who are candidates, in general, the PCV-13 is administered first, followed by a PPSV-23 at least one year later, which is repeated again by a PPSV-23 five years later if a patient is asplenic or immunocompromised (Table 1).[1–3] The pneumococcal vaccine has been shown to reduce the rate of deaths due to invasive pneumococcal disease (IPD).[4] The pneumococcal vaccine should provide protection from IPD.

Most pneumococcal infection results in otitis media in children, but it commonly causes pneumonia in adults and can less commonly cause invasive pneumococcal disease, which is a severe complication that may even result in death. The World Health Organization estimates that nearly 2 million people die each year from this disease. Although approximately two thirds of the deaths are among children, many of their infections are linked to adults to whom it is transmitted. A benefit of vaccinating children has been translated to older adults.[5] The following case may represent a population who have less than optimal protection against S. pneumoniae despite being appropriately vaccinated according to the Advisory Committee on Immunization Practices (ACIP). (IRB# 140217, 19.0161)

Presentation

A 63-year-old female with a history of diabetes mellitus and cardiac-related comorbidities, but no asplenia or immunosuppression, was found unresponsive in her home after complaining of an ear ache for three days. The patient was admitted to the outside hospital, obtunded with a temperature of 39.4°C. She required mechanical intubation and ventilation after the onset of
Table 1. Recommendations from the Advisory Committee on Immunization Practices (ACIP) for vaccination criteria with pneumococcal polysaccharide vaccine-23 (PPSV-23) and pneumococcal conjugate vaccine-13 (PCV-13).[1]

| Risk group                  | Underlying medical condition                                                                 | PCV13 Recommended | PPSV23 Recommended | Revaccination 5 yrs after first dose |
|-----------------------------|-----------------------------------------------------------------------------------------------|-------------------|--------------------|--------------------------------------|
| Immunocompetent persons     | Chronic heart disease‡                                                                      | •                 | •                  |                                      |
|                             | Chronic lung disease‡                                                                       | •                 | •                  |                                      |
|                             | Diabetes mellitus                                                                          | •                 | •                  |                                      |
|                             | Cerebrospinal fluid leak                                                                   | •                 | •                  |                                      |
|                             | Cochlear implant                                                                           | •                 | •                  |                                      |
|                             | Alcoholism                                                                                 | •                 | •                  |                                      |
|                             | Chronic liver disease, cirrhosis                                                            | •                 | •                  |                                      |
|                             | Cigarette smoking                                                                          | •                 | •                  |                                      |
| Persons with functional or anatomic asplenia | Sickle cell disease/ other hemoglobinopathy                                                 | •                 | •                  | •                                    |
|                             | Congenital or acquired asplenia                                                           | •                 | •                  | •                                    |
| Immunocompromised persons   | Congenital or acquired immunodeficiency§                                                   | •                 | •                  | •                                    |
|                             | Human immunodeficiency virus infection                                                     | •                 | •                  | •                                    |
|                             | Chronic renal failure                                                                       | •                 | •                  | •                                    |
|                             | Nephrotic syndrome                                                                         | •                 | •                  | •                                    |
|                             | Leukemia                                                                                   | •                 | •                  | •                                    |
|                             | Lymphoma                                                                                   | •                 | •                  | •                                    |
|                             | Hodgkin disease                                                                            | •                 | •                  | •                                    |
|                             | Generalized malignancy                                                                     | •                 | •                  | •                                    |
|                             | Iatrogenic immunosuppression¶                                                              | •                 | •                  | •                                    |
|                             | Solid organ transplant                                                                     | •                 | •                  | •                                    |
|                             | Multiple myeloma                                                                           | •                 | •                  | •                                    |

*All adults aged ≥ 65 years should receive a dose of PPSV23, regardless of previous history of vaccination with pneumococcal vaccine; †Including congestive heart failure and cardiomyopathies, excluding hypertension; ‡Including chronic obstructive pulmonary disease, emphysema, and asthma; §Includes B- (humoral) or T-lymphocyte deficiency, complement deficiencies (particularly C1, C2, C3, and C4 deficiencies), and phagocytic disorders (excluding chronic granulomatous disease); ¶Diseases requiring treatment with immunosuppressive drugs, including long-term systemic corticosteroids and radiation therapy.
generalized seizures and hypoxic respiratory failure. A chest X-ray was abnormal with a left lower lobe infiltrate (Figure 1).

The seizures were treated with phenytoin and levetiracetam. She received empiric intravenous cefepime, vancomycin and fluconazole. Cerebrospinal fluid analysis was consistent with bacterial meningitis—2700 nucleated cells/mL with 96% neutrophils, glucose 138 mg/dL (normal 40–70), and protein 155 mg/dL (normal 10–45). Computed tomography scan of the brain on the second day of admission revealed an area suspicious for subarachnoid bleeding or subdural hematoma. The patient’s respiratory status improved, and she was able to be extubated; however, the fever and seizures continued. Cultures of the cerebrospinal fluid were negative. Two blood cultures revealed *S. pneumoniae*, MIC to penicillin G <0.03. She was then transferred to our tertiary care hospital for further workup and management. She had had a PPSV-23 at age 61.

On initial evaluation, the patient was alert and oriented to person, place, time and situation. She complained of partial hearing loss that was worse on the right, headache, confusion, and intermittent slurred speech with right-sided weakness. Vital signs were stable with a temperature of 36.8°C, blood pressure 131/46 mmHg, pulse 80 beats/min, respirations 20 breaths/min, and SaO₂ 92% on room air. Physical exam revealed a ruptured right tympanic membrane with dried blood present in the external auditory canal. The left tympanic membrane was intact and nearly opaque with minimal fluid. There was dysmetria of the right hand noted in finger-to-nose testing with pronator drift of the right arm. A non-contrasted MRI revealed left subdural hematomas with a small amount of hemorrhage within the lateral ventricle (Figure 2). Contrasted computed tomography scan of the temporal bones revealed bilateral mastoiditis without bony destructive changes. An electroencephalogram showed excessive diffuse slowing of background activity, a nonspecific indicator of cerebral dysfunction.

**Diagnosis and Management**

This patient had multiple concurrent diagnoses on admission: pneumonia, bilateral mastoiditis, meningitis, subdural hematoma, seizure and streptococcal bacteremia. A urinary streptococcal antigen test was applied to the patient’s cerebrospinal fluid obtained from the outside hospital, which was positive. Streptococcal antigen in both urine and cerebrospinal fluid are FDA-approved tests to detect the presence of pneumococcal infection.[6] A repeat MRI of the brain with contrast revealed a new fluid collection versus blood products in the left frontal and parietal sulci and overlying subdural collection (Figure 3). In the setting of bilateral mastoiditis complicated by confirmed pneumococcal meningitis, this collection was considered to be an empyema with concern for developing cerebritis.[7, 8]

The neurosurgeons drilled two burr holes, one frontal and one parietal, over the left convexity, releasing purulent discharge under pressure. The next day, the otolaryngologists performed bilateral myringotomies with aspiration, culture of middle ear fluid and tympanostomy tube placement. After these procedures, her seizures resolved. She was continued on oral levetiracetam for seizure prophylaxis. She was then adminis-
Figure 2. A motion artifact degraded MRI of the brain without IV contrast. T2 FLAIR axial image showing left subdural hematoma measuring 5–6 mm in its greatest axial thickness with localized mass effect and associated scattered subarachnoid hemorrhage.

Figure 3. An MRI of the patient’s brain with IV contrast with axial T1 image (A) and coronal (B) images showing progressed proteinaceous fluid in the left frontal and parietal sulci, with associated mild enhancement and some focal areas of restricted diffusion and overlying subdural collection. Full mastoid air cells are also visible bilaterally (right greater than left) inferior to each ear canal (B).
Invasive Pneumococcal Disease after PPSV-23

Discussion

The proportion of candidates who are immunized is low; in the US, for example, only 32% of adults ≥65 years have been vaccinated with PCV-13.[4] The CDC’s Healthy People 2020 targets are 60% for adult candidates aged 18–64, and 90% for adults ≥65 years.[9]

PCV-13 is recommended to everyone ≥65 years, followed by PPSV-23 6–12 months later.[10] For persons ≥50, PCV-13 may be given if certain risk factors are present (Table 1), followed by PPSV-23 only eight weeks later.[1] A second PPSV-23 may be given prior to age 65 years for asplenia (anatomic or functional) or if immunocompromised. This case raises the question of whether additional comorbidities should qualify a patient for vaccination.

The current patient had IPD despite vaccination. Based on her diagnosis of diabetes, she was a candidate for a PPSV-23, which she received when she was approximately 61 years old. She did not qualify for either a second PPSV-23 or a PCV-13 with her risk factors. Although the FDA approved PCV-13 for adults ≥50 years, ACIP recommends it for adults ≥65 years. The case patient was vaccinated with PCV-13 before leaving the hospital with an intention for a subsequent PPSV-23 vaccination. This may be effective prevention against IPD as well as pneumonia—two diagnoses that the patient may not live through should she acquire them again.[11, 12]

A meta-analysis of randomized controlled trials, comparing the incidence of IPD in patients vaccinated with PPSV-23 versus placebo, found a correlate of efficacy of 74% (95% confidence interval (CI) 56%–85%).[13] It also placed the odds ratio of contracting IPD at 0.26 when PPSV-23 had been given. This means that the odds of acquiring IPD for someone who received PPSV-23 was one-fourth that of someone who received a placebo. A sub-group analysis performed from the meta-analysis found that vaccine efficacy among adults with chronic disease, as in the case patient described, appeared poor in comparison to that in otherwise healthy adults.

Two other studies evaluated response to pneumococcal vaccination. The first included over 2000 patients and showed that overall vaccine efficacy (prevention of IPD) was 48% within the first two years and decreased to 15% by five years, giving an overall vaccine efficacy of only 24% (95% CI 10–36).[14] The second was a surveillance study of pneumococcal epidemiology in the UK, which studied the effect during the use of PCV-7 in children and later during the use of PVC-13.[15] It found a 37% decrease in overall IPD, but there was an increase in IPD due to non-PVC-13 serotypes from 3.85 per 100,000 to 7.97 per 100,000 population (2000–06 versus 2016–17).

The present patient received one PPSV-23 previously; among the 23 serotypes that it includes was the one isolated from her: serotype 3. As she had only received one PPSV-23 more than two years prior to admission, her level of protection would have been expected to be ~3000 mg antibody nitrogen/radioimmunoassay compared to pre-vaccination levels of ~1500 mg Ab N/RIA and 1-month post-vaccination levels of ~4000 Ab N/RIA.[16] Furthermore, pneumococcal conjugate vaccines, like the one she received before leaving the hospital, may offer more benefit than the polysaccharide vaccine PPSV-23 alone.

A study in Germany evaluated the prevalence of IPD and pneumococcal serotypes, including serotype 3, during two periods when conjugated vaccines were prescribed to children.[17] The first period was 2007–10, during which time PCV-7 was used, which does not include serotype 3. The second period was 2010–14, during which time PVC-13 was used, which includes serotype 3. The study showed that the prevalence of IPD due to serotype 3 in adults increased during the first period but remained the same during the second period.

There are challenges to immunizing a population. The first is that physicians may not offer to immunize, or patients may decline immunization. Among 24 patients with IPD in our facility since 2013, at least 10 were not vaccinated (Table 2). The second challenge is under-vaccination. Two patients had incomplete vaccination, in need of PCV-13 and their second PPSV-23 vaccine. The third challenge is administering PPSV-23 before PCV-13. A more robust response has been shown when PCV-13 precedes PPSV-23.[18] Among our 23 patients, only three had a serotype that was not included in either the PCV-13 or PPSV-23 vaccine. The most common serotype was 9V, which is in both pneumococcal vaccines.

This case highlights that patients such as this may benefit from additional pneumococcal vaccinations despite not being indicated by the current ACIP guidelines. There are a few revisions to the indications for pneumococcal vaccinations that should be considered. First, for patients with multiple co-morbidities who qualify for a PPSV-23 and have some degree of immunosuppression, PCV-13 and a second PPSV-23 should also be indicated. Furthermore, all of the conditions that qualify a patient of 19–64 years to be a candidate for PPSV-23 should also qualify a patient for PCV-13. A potential compromise would be for ACIP to lower the age at which it recommends PCV-13 from ≥65 years to ≥50 years to match the approval by the FDA.
Table 2. Serotype and vaccination history among other patients with invasive pneumococcal disease in this hospital over the last seven years.

| Subject No. | Year | Culture Source | Serotype | Prior PPSV-23 | Prior PCV-13 |
|-------------|------|----------------|----------|---------------|-------------|
| 1           | 2013 | Blood          | 11       | N/A           | N/A         |
| 2           | 2013 | Brain abscess  | 3        | N/A           | N/A         |
| 3           | 2013 | Blood, CSF     | 12B      | N/A           | N/A         |
| 4           | 2013 | N/A            | 15       | N/A           | N/A         |
| 5           | 2013 | Blood          | 3        | Yes, 1 of 1   | No          |
| 6           | 2014 | Blood          | 9V       | No            | No          |
| 7           | 2015 | N/A            | 23F      | N/A           | N/A         |
| 8           | 2015 | Blood          | 9V       | N/A           | N/A         |
| 9           | 2016 | Blood          | 9V       | N/A           | N/A         |
| 10          | 2016 | Sputum         | 19F      | Yes, 2 of 2   | Yes         |
| 11          | 2016 | Blood          | 15       | No            | No          |
| 12          | 2016 | Blood, CSF     | 20       | No            | No          |
| 13          | 2016 | Blood          | 22       | No            | No          |
| 14          | 2017 | Blood, CSF     | 19A      | No            | No          |
| 15          | 2017 | Blood          | 9V       | Yes, 2 of 2   | Yes         |
| 16          | 2017 | Blood          | 20       | N/A           | No          |
| 17          | 2018 | Blood          | 35       | No            | No          |
| 18          | 2019 | Blood          | 7        | No            | No          |
| 19          | 2019 | Blood          | 15       | Yes, 1 of 1   | No          |
| 20          | 2019 | Blood, CSF     | 20       | No            | No          |
| 21          | 2019 | Blood          | 9V       | No            | No          |
| 22          | 2019 | Blood, CSF     | 23F      | No            | Yes         |
| 23          | 2019 | Blood, CSF     | 35       | No            | No          |
| 24          | 2019 | Blood          | 12B      | Yes           | Yes         |

Conclusion

This patient had been vaccinated with PPSV-23 as recommended by ACIP but developed pneumonia and IPD due to *S. pneumoniae* serotype 3. She represents one of several people in our hospital, as well as a larger population, who needs disease prevention the most, but in whom neither a second PPSV-23 nor a PCV-13 is recommended prior to age 65 years. Reconsidering which comorbidities justify additional vaccination may be beneficial.

Acknowledgements: We thank Gordon G. Stout, B.S., Research Manager, Pediatric Infectious Diseases Laboratory, University of Louisville School of Medicine, for his assistance.

Received: July 26, 2019

Accepted: January 30, 2020

Published: April 12, 2021

Copyright: © 2021 The author(s). This original article is brought to you for free and open access by ThinkIR: The University of Louisville's Institutional Repository. For more information, please contact thinkir@louisville.edu. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (CC BY 4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Funding Source: The author(s) received no specific funding for this study.

Conflict of Interest: All authors declared no conflict of interest in relation to the main objective of this work.
References

1. Centers for Disease Control and Prevention (CDC). Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2012; 61(40): 816–9. PMID: 23051612.

2. Tromp KM, Campbell MW, Vazquez A. Recent Developments and Future Directions of Pneumococcal Vaccine Recommendations. Clin Ther 2015; 37(5): 926–34. doi: 10.1016/j.clinthera.2015.03.025. PMID: 25913921.

3. Pilishvili T, Bennett NM. Pneumococcal Disease Prevention Among Adults: Strategies for the Use of Pneumococcal Vaccines. Am J Prev Med 2015; 49(6 Suppl 6): S389–90. doi: 10.1016/j.amepre.2015.09.008. PMID: 26305438.

4. Black CL, Williams WW, Warnock R, Pilishvili T, Kim D, Kelman JA. Pneumococcal Vaccination Among Medicare Beneficiaries Occurring After the Advisory Committee on Immunization Practices Recommendation for Routine Use Of 13-Valent Pneumococcal Conjugate Vaccine and 23-Valent Pneumococcal Polysaccharide Vaccine for Adults Aged ≥65 Years. MMWR Morb Mortal Wkly Rep 2017; 66(27): 728–33. doi: 10.15585/mmwr.mm6627a4. PMID: 28704347.

5. Samra Z, Shmuely N, Nahum E, Paghis D, Ben-Ari J. Use of the NOW Streptococcus pneumoniae urinary antigen test in cerebrospinal fluid for rapid diagnosis of pneumococcal meningitis. Diagn Microbiol Infect Dis 2003; 50(3): 244–56. doi: 10.1016/s0732-8893(02)00548-5. PMID: 12729992.

6. Jim KK, Brouwer MC, van der Ende A, van de Beek D. Subdural empyema in bacterial meningitis. Neurology 2012; 79(21): 2133–9. doi: 10.1212/wnl.0b013e3182752d0e. PMID: 23136260.

7. Hsu HE, Shutt KA, Moore MR, et al. Effect of pneumococcal conjugate vaccine on pneumococcal meningitis. N Engl J Med 2009; 360(3): 244–56. doi: 10.1056/NEJMoa0800836. PMID: 19144940.

8. Koedel U, Scheld WM, Pfister HW. Pathogenesis and pathophysiology of pneumococcal meningitis. Lancet Infect Dis 2002; 2(12): 721–36. doi: 10.1016/s1473-3099(02)00450-4. PMID: 12467688.

9. Williams WW, Lu PJ, O’Halloran A, et al. Surveillance of Vaccination Coverage among Adult Populations - United States, 2015. MMWR Surveill Summ 2017; 66(11): 1–28. doi: 10.15585/mmwr.ss6611a1. PMID: 28472027.

10. Tomczyk S, Bennett NM, Stoecker C, et al. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥65 years: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2014; 63(37): 822–5. PMID: 25233284.

11. McLaughlin JM, Jiang Q, Isturiz RE, et al. Effectiveness of 13-Valent Pneumococcal Conjugate Vaccine Against Hospitalization for Community-Acquired Pneumonia in Older US Adults: A Test-Negative Design. Clin Infect Dis 2018; 67(10): 1498–506. doi: 10.1093/cid/ciy312. PMID: 29790925.

12. Bonten MJ, Huijts SM, Bolkenbaas M, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med 2015; 372(12): 1114–25. doi: 10.1056/NEJMoa1408544. PMID: 25785969.

13. Moberley S, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev 2013; 2013(1): CD000422. doi: 10.1002/14651858.CD000422.pub3. PMID: 23440780.

14. Andrews NJ, Wright PA, George RC, Slack MP, Miller E. Impact and effectiveness of 23-valent pneumococcal polysaccharide vaccine against invasive pneumococcal disease in the elderly in England and Wales. Vaccine 2012; 30(48): 6802–8. doi: 10.1016/j.vaccine.2012.09.019. PMID: 23000122.

15. Ladhani SN, Collins S, Djeennad A, et al. Rapid increase in non-vaccine serotypes causing invasive pneumococcal disease in England and Wales, 2000-17: a prospective national observational cohort study. Lancet Infect Dis 2018; 18(4): 441–51. doi: 10.1016/s1473-3099(18)30052-5. PMID: 29395999.

16. Mufson MA. Antibody response of pneumococcal vaccine: need for booster dosing? Int J Antimicrob Agents 2000; 14(2): 107–12. doi: 10.1016/s0924-8579(99)00167-3. PMID: 10720799.

17. van der Linden M, Falkenhorst G, Perincario S, Imöhö M. Effects of Infant Pneumococcal Conjugate Vaccination on Serotype Distribution in Invasive Pneumococcal Disease among Children and Adults in Germany. PLoS One 2015; 10(7): e0131494. doi: 10.1371/journal.pone.0131494. PMID: 26132078.

18. Jackson LA, Gurtman A, Rice K, et al. Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine in adults 70 years of age and older previously vaccinated with 23-valent pneumococcal polysaccharide vaccine. Vaccine 2013; 31(35): 3585–93. doi: 10.1016/j.vaccine.2013.05.010. PMID: 23688527.