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Title

The changing epidemiology of pneumococcal diseases: New challenges after widespread routine immunization

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4 Though the use of the pneumococcal conjugate vaccines (PCVs) has reduced the incidence of
5 pneumonia and invasive diseases around the world, widespread vaccine use has resulted in serotype
6 replacement (1). Serotype replacement describes the shifting burden of invasive pneumococcal
7 disease, from vaccine serotypes to other serotypes not covered by the vaccine, which may,
8 paradoxically, increase disease burden (2). This has created new challenges like detecting non-vaccine
9 pneumococcus strains, identifying changes in disease transmission patterns, and raised questions
10 about adapting immunization strategies.

11

12 Pneumococcal diseases are most commonly caused by 10 to 13 bacterial serotypes and current
13 vaccines are designed to work against these. The remaining 80 serotypes are usually considered rare,
14 but after widespread vaccine-use, they are seen more often. The best serotype test is time-consuming
15 and expensive, requires highly trained technical staff, and is difficult to scale up to process large
16 numbers of samples (3). This results in less testing, so the true burden of non-vaccine serotypes is
17 unknown. Recently, the field of pneumococcal diagnostics has shifted towards molecular-based
18 techniques utilizing the voluminous data from the Global Pneumococcus Sequencing Project
19 (<https://www.pneumogen.net/gps/>). Multiplex-PCR tests are especially promising because they can
20 identify non-vaccine serotypes, are easy to use, and samples can be processed in huge batches (4).

21

22 The transmission pattern of pneumonia is also changing. Pneumococcus colonizes the nasopharynx,
23 while 30-80% of healthy children carry the bacteria, (5) and colonization rates are highest in developing
24 countries (5). Since children are known reservoirs for disease-causing serotypes, controlling infection in
25 this age group is crucial to public health. In countries with mature immunization programs, the vaccine
26 serotypes are rarely seen in infants and younger children and pneumonia incidence has declined 22%
27 across the population (6). Nonetheless, in some countries, such as the UK, a recent epidemiologic
28 assessment found increased incidence of invasive diseases not covered by the vaccine (7). The
29 increase in disease burden among the elderly was 4% after 10 years of sustained high childhood
30 immunization coverage (7). This is a group not targeted by routine PCV immunization, but was expected
31 to benefit from high immunization coverage in children through herd immunity.

32

33 Our understanding that pneumococcal disease is controlled through the herd effect has been thrown
34 into question. In most high-income countries, the herd effect becomes almost immediately apparent
35 after the vaccine is introduced, but in developing countries the effect is more gradual (8). In high-income
36 countries, serotype replacement seems to erode the effectiveness of a vaccine after long-term use,
37 illustrated by the growing number of cases of invasive disease in adults. It is too early to tell if this is the
38 case in developing countries since the vaccine was newly introduced and the program has not matured
39 (8). We also do not know if transmission patterns will change since, as yet, there is little adult

40 nasopharyngeal data from developing countries. We can expect more data in the future because many
41 countries have set-up nationwide surveillance monitoring of the post-routine immunization period.

42

43 We need more studies to determine the optimal vaccine schedule for pneumococcal vaccines, as the
44 Strategic Advisory Group of Experts for Immunization pointed out in their latest meeting (October 2017)
45 (9). All countries have chosen different vaccine products, targeted different age groups, and has
46 established campaigns or phased-introduction and/or varying schedules. Given the wide variation in
47 routine immunization programs in different countries, it is difficult to evaluate specific outcomes of
48 interest like nasopharyngeal carriage, herd immunity, duration of protection, and transmission dynamics
49 (8, 10). However, policymakers need to know the optimal dosing schedule so they can set the number
50 of doses and shot schedules, as these factors guide implementation and determine costs for
51 immunization programs.

52

53 The epidemiology of pneumococcal diseases will change as the pathogen evolves in response to
54 vaccine-induced population immunity. Non-vaccine serotypes will likely dominate transmission cycles
55 among carriers. When non-vaccine pneumococci become more invasive, we will see a higher proportion
56 of them in those who present with the disease. Newer serotypes will also evolve in response to vaccine-
57 induced herd immunity, raising new challenges for serotyping testing, for predicting disease
58 transmission patterns and optimizing immunization schedules. All these challenges must be met if we
59 want vaccination programs to provide continued benefits to the population.

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