Serotype replacement in invasive pneumococcal disease has been observed after widespread use of the 7-valent pneumococcal conjugate vaccine (PCV7). Replacement is dominated by penicillin-nonsusceptible serotype 19A in several countries. Antibiotic selection pressure has been proposed to interact with immunization, leading to rapid replacement. In Norway, where prescription of antibiotics is limited, post-PCV7 replacement by serotype 19A is dominated by penicillin-susceptible clones. Hence, serotype 19A replacement occurs, although it is not driven by antibiotic selection pressure.
The post-PCV7 increase of serotype 19A in Norway was dominated by penicillin-susceptible strains. The increase was driven mainly by expansion of CC199. Strains with intermediate susceptibility to penicillin were only sporadically identified within this CC. CC199 has also been found to dominate the post-PCV7 increase of serotype 19A in the United States (11, 13), although the relative contribution of this CC has appeared to decrease since 2005 (2). In the United States, however, the emergence of CC320

![FIG 1 Incidence rate of IPD caused by serotype 19A in children aged less than 5 years and in the population aged 5 years or more. The overall incidence rate of penicillin-nonsusceptible (PNSP) serotype 19A IPD is shown by the broken curve. The 7-valent pneumococcal conjugate vaccine was introduced in the national immunization program in 2006, as shown with the shaded column.](#)

**TABLE 1 Clonal distribution and nonsusceptibility profiles of serotype 19A isolates recovered from IPD patients in 2005, 2007, and 2009**

| Clonal complex and sequence type (no. of isolates) | No. (%) of isolates in: 2005 | 2007 | 2009 | Nonsusceptibility profile a (no. of nonsusceptible isolates) in: 2005 | 2007 | 2009 |
|--------------------------------------------------|-----------------------------|------|------|-------------------------------------------------|------|------|
| CC199 (66)                                       | 10 (83.3)                   | 10 (62.5) | 46 (83.6) | PNSP-MLS-TC (1) | PNSP (2) | PNSP (1) |
| ST199 (47)                                       | 7 (58.3)                    | 8 (50.0) | 32 (58.2) | 0              | 0              | 0 |
| ST667 (7)                                        | 1 (8.3)                     | 2 (12.5) | 4 (7.3)   | 0              | 0              | 0 |
| ST2220 (10)                                      | 2 (16.7)                    | 0      | 8 (14.5)  | 0              | 0              | 0 |
| ST6958 (1)                                       | 0                           | 0      | 1 (1.8)   | 0              | 0              | 0 |
| ST416 (1)                                        | 0                           | 0      | 1 (1.8)   | 0              | 0              | 0 |
| CC276 (4)                                        | 0                           | 0      | 4 (7.3)   | 0              | 0              | 0 |
| ST276 (2)                                        | 0                           | 0      | 2 (3.6)   | 0              | 0              | PNSP-M-TC (2) |
| ST3772 (2)                                       | 0                           | 0      | 2 (3.6)   | 0              | 0              | PNSP-MLS-TC (2) |
| None c (13)                                       | 2 (16.7)                    | 6 (37.5) | 5 (9.1)  | PNSP-MLS-TC (1) | 0 |
| ST63 (2)                                         | 1 (8.3)                     | 1 (6.3) | 0        | 0              | PNSP-MLS-TC (1) | 0 |
| ST172 (1)                                        | 0                           | 1 (6.3) | 0        | 0              | PNSP (1)       | 0 |
| ST320 (1)                                        | 1 (8.3)                     | 0      | 0        | PRP-MLS-TC (1) | 0 |
| ST847 (1)                                        | 0                           | 1 (6.3) | 0        | 0              | 0              | 0 |
| ST416 (1)                                        | 0                           | 0      | 1 (1.8)  | 0              | 0              | MLS-T (1) |
| ST3017 (2)                                       | 0                           | 0      | 2 (3.6)  | 0              | 0              | 0 |
| ST3546 (2)                                       | 0                           | 1 (6.3) | 1 (1.8)  | 0              | MLS-T (1)     | MLS-T (1) |
| ST3615 (1)                                       | 0                           | 1 (6.3) | 0        | 0              | PNSP-M (1)    | 0 |
| ST3710 (1)                                       | 0                           | 1 (6.3) | 0        | 0              | PNSP-T (1)    | 0 |
| ST5954 (1)                                       | 0                           | 0      | 1 (1.8)  | 0              | 0              | 0 |
| Total no. of isolates                            | 12                          | 16     | 55       | 2               | 7              | 7 |

a Nonsusceptible phenotype (benzylpenicillin MIC > 0.064 μg/ml); MLS, macrolide-lincosamide-streptogramin resistance phenotype (high-level resistance to erythromycin, MIC ≥ 128 μg/ml, and clindamycin, MIC ≥ 128 μg/ml); TC, tetracycline resistance phenotype (MIC > 2.0 μg/ml); PRP, penicillin resistance phenotype (benzylpenicillin MIC > 2.0 μg/ml); M, efflux-mediated macrolide resistance phenotype (low-level resistance to erythromycin [MIC range, 1.0 to 64.0 μg/ml] and susceptibility to clindamycin).

b Isolates in this group were not associated with a clonal complex.
accounted for the major increase in penicillin-resistant strains; ST320 is a double-locus variant of the globally dispersed Taiwan19F-14-ST236 clone, and the majority of CC320 strains in the United States are penicillin resistant. CC320 was not identified in the United States prior to vaccine introduction. CC320 has also been identified in France and Spain (8, 9) and was found to dominate the pre-PCV7 increase of serotype 19A in South Korea (3). In Norway, however, a single isolate of ST320 was identified in 2004, before the introduction of PCV7.

In 2009, CC276 emerged as the dominating contributor to penicillin nonsusceptibility among serotype 19A strains in Norway. ST276 is a single-locus variant of the Denmark14-32-ST230 clone. This CC has been identified in the United States, although its relative contribution to serotype 19A replacement has been modest. In southern Europe, however, expansion of CC276 has been found to dominate the serotype 19A increase, with moderate contribution from CC199 (1, 8, 9).

The clonal characteristics of serotype 19A replacement appear to differ among study sites. In Norway, penicillin-susceptible strains dominated and the major increase was caused by expansion of CC199. However, the emergence of intermediate susceptible strains belonging to the Denmark14-32-ST230 complex, a CC reported to dominate in southern Europe, was observed. Thus, regional differences in circulating clones are evident. Use of antibiotics in Norway is limited by a restrictive prescription policy (6, 12). Thus, selection by antibiotic pressure is likely of minor importance for serotype 19A replacement in our setting. However, multidrug-resistant strains have been identified, although sporadically, and a shift toward a higher proportion of nonsusceptible strains among serotype 19A strains may occur over time. An increase similar to that of serotype 19A has been observed in Norway for serotype 22F, a serotype also predominantly penicillin susceptible. The mechanisms underlying the increase of susceptible clones of non-vaccine serotypes are not fully understood. Both serotypes 19A and 22F were relatively uncommon among asymptomatic carriers both before and after vaccine introduction in Norway (16), and the invasive disease potential is apparently altered in the post-PCV era. The success of certain serotypes and clones thus remains to be explained.

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