Antibiotic use and resistance of *Streptococcus pneumoniae* in The Netherlands during the period 1994–1999

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Antibiotic use in The Netherlands during the period 1994–1999 is described in relation to the resistance of routine isolates of *Streptococcus pneumoniae*. The average antibiotic use in the study period was 3.4 defined daily doses per 1000 persons per day (DDD/1000/day) pencillins, 0.066 DDD/1000/day \(\beta\)-lactams other than pencillins, 2.3 DDD/1000/day tetracyclines and 0.71 DDD/1000/day trimethoprim and sulphonamides, without apparent rise or decline. In contrast, the use of macrolides doubled from 0.51 DDD/1000/day in 1994 to 1.0 DDD/1000/day in 1997 and stayed at 1.07 DDD/1000/day in 1998 and 1999. In 1994 the first pneumococci isolated from patients showed 0.7% resistance to penicillin (intermediate plus full resistance), 2.5% to erythromycin, 4.2% to co-trimoxazole and 4.7% to tetracycline. In 1999 first isolates showed 1.5% resistance to penicillin, 3.8% to erythromycin, 4.4% to co-trimoxazole and 6.6% to tetracycline. The modest but significant rise in the resistance to erythromycin may have been caused by the increased use of macrolides in the years 1994–1997. The rise in resistance to penicillin seemed not to be related to increased \(\beta\)-lactam use.

**Introduction**

The resistance of *Streptococcus pneumoniae* to penicillin and macrolides has increased in recent years in several European countries such as Spain, but is still low in Denmark and The Netherlands. Here we describe the resistance of *S. pneumoniae* to penicillin, erythromycin, co-trimoxazole and tetracycline, and the use of pencillins, macrolides, sulphonamides and trimethoprim, and tetracyclines in The Netherlands from 1994 to 1999.

**Materials and methods**

During 1994–1999 the results of all routine susceptibility determinations of *S. pneumoniae* were obtained from nine regional public health laboratories, in Enschede, Haarlem, Leeuwarden, Nijmegen, Tilburg, Goes, Arnhem, Heerlen and Rotterdam, which cover c. 30% of the Dutch population. The date of isolation, date of birth and the gender of the host patient, their location (clinic, outpatient clinic, nursing home or general practice) and the site of isolation (blood, CSF, skin, pus, respiratory tract) were recorded for each isolate. The data were forwarded to the National Institute of Public Health and the Environment at least yearly. Susceptibility data for penicillin, erythromycin, co-trimoxazole and tetracycline or doxycycline were analysed only for laboratories that had tested at least 75% of their routine isolates. Resistance was defined by the following breakpoint concentrations of the respective antibiotics, 0.06 mg/L penicillin, 0.25 mg/L erythromycin, 0.5 mg/L trimethoprim plus 9.5 mg/L sulfamethoxazole and 1 mg/L tetracycline or doxycycline.

Data on the use of antibiotics in The Netherlands during the period 1994–1999 were obtained from the Foundation for Pharmaceutical Statistics (The Hague). This database contains the total number of prescriptions and defined daily doses (DDDs) for each drug supplied by 1125 of the 1600 Dutch pharmacies to patients outside hospitals. These data were recalculated to DDD per 1000 persons per day using demographic data from the Central Bureau of Statistics. The data were analysed using Microsoft Excel. Trends in resistance percentage were tested by a Mantel Haenszel \(\chi^2\) test.

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Results

Use of antibiotics

Penicillins and tetracyclines were the antibiotics most often used in the Netherlands during 1994–1999. The use of most classes of antibiotics was fairly stable. The average use was 3.4 DDD/1000/day penicillins (Figure 1), 0.066 DDD/1000/day β-lactams other than penicillins, 2.3 DDD/1000/day tetracyclines and 0.71 DDD/1000/day trimethoprim/sulfamethoxazole. In contrast, the use of macrolides doubled from 0.51 DDD/1000/day in 1994 to 1.0 DDD/1000/day in 1997 and stayed at 1.07 DDD/1000/day in 1998 and 1999 (Figure 2).

Resistance

The number of first isolates per year of *S. pneumoniae* (one per patient) decreased from 4733 in 1994 to 3580 in 1999. The average number of repeat isolates per year was 1789 ± 207. The penicillin resistance of first isolates doubled from 0.70% to 1.5% during the period of investigation (*P* < 0.0001; Figure 1). The percentage of penicillin resistance in repeat isolates increased significantly from 0.73% to 3.3% (*P* < 0.0001). Resistance to erythromycin of first isolates increased from 2.5% to 3.8% (*P* < 0.0001), but levelled off in 1998–1999 (Figure 2). The resistance to erythromycin of repeat isolates was slightly higher and increased to 4.3% in 1999 (*P* = 0.0007). The percentage resistance to co-trimoxazole of first isolates remained stable, 4.2% in 1994 and 4.4% in 1999, but the resistance of repeat isolates rose from 4.6% to 7.1% (*P* = 0.022) (Figure 3). The tetracycline resistance of first isolates increased from 4.7% to 6.6% (*P* = 0.0011), but the resistance of repeat isolates remained stable and was 6.0% in 1999 (Figure 4).

The low use of tetracycline and doxycycline in children was associated with a lower percentage of tetracycline resistance (*P* < 0.0001) (Table 1). The mean percentage of penicillin resistance of isolates from normally sterile compartments, blood and pus (0.60%), was lower than the percentage (1.0%) of isolates from exposed body sites, respiratory tract and skin (*P* = 0.04).

The pattern of co-resistance of first isolates to penicillin, tetracycline, co-trimoxazole and erythromycin was determined if the susceptibility to all four antibiotics had been tested (*n* = 10 489). The frequency of the patterns of co-resistance is given in Table 2. Strains with combined resistance to two or more antibiotics were more frequent than expected if resistance traits were distributed evenly amongst all pneumococci.

![Figure 1](image1.png)

**Figure 1.** Use of penicillins (DDD/1000 persons/day; open bars, left axis) and resistance to penicillin in first (■) and repeat isolates of *S. pneumoniae* (▲) (right axis).

![Figure 2](image2.png)

**Figure 2.** Use of macrolides (DDD/1000 persons/day; open bars, left axis) and resistance to erythromycin in first (■) and repeat isolates of *S. pneumoniae* (▲) (right axis).

![Figure 3](image3.png)

**Figure 3.** Use of trimethoprim and sulfonamides (DDD/1000 persons/day; open bars, left axis) and resistance to co-trimoxazole in first (■) and repeat isolates of *S. pneumoniae* (▲) (right axis).
Antibiotic use and pneumococcal resistance

Discussion

The use of antibiotics for respiratory tract infections is relatively low in The Netherlands, according to the restrictive guidelines of the Dutch Society of General Practitioners for the treatment of acute otitis media and other infections of the upper respiratory tract. This restricted use may explain why the percentage of resistance of \textit{S. pneumoniae} to penicillin and other antibiotics is still low.

We found that the resistance of pneumococci to erythromycin followed an increase in the use of macrolides with a time lag of 2–3 years. Such a time-lag has been observed before in a Finnish study describing a relationship between macrolide consumption and erythromycin resistance in \textit{Streptococcus pyogenes}.8

Penicillin resistance of pneumococci rose from 0.70% in 1994 to 1.5% in 1999 subsequent to the increase in the use of macrolides. Similar observations led Goldstein9 to conclude that increased use of macrolides or co-trimoxazole might enhance the percentage of penicillin-resistant pneumococci. However, only 28% of the penicillin-resistant strains in our survey were also resistant to erythromycin. So the increased use of macrolides alone cannot explain the increase in penicillin resistance.

We found the resistance of repeat isolates (second and subsequent isolates from the same patient) to be higher for all investigated antibiotics except tetracyclines. This may indicate that resistant organisms infect patients preferentially during therapy with antibiotics,10 that patients harbouring resistant pneumococci have prolonged illness, which may give rise to one or more repeat cultures, or that resistant pneumococci are selected in individual patients during therapy, as has been shown for azithromycin resistance \textit{in vitro}.11

Recently, we found a great difference in the quinolone resistance rate of \textit{Escherichia coli} of different age categories corresponding to the lower use of quinolones in earlier calendar years and in children, who are less frequently exposed to quinolones owing to the toxicity of these compounds to cartilage formation.6 In the present study, we observed a lower frequency of resistance to tetracycline of pneumococci from children, in whom tetracyclines are contra-indicated.

Table 2. Pattern of co-resistance to penicillin (P), erythromycin (E), co-trimoxazole (S) and tetracycline or doxycycline (T) in 10 489 isolates of \textit{S. pneumoniae}

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The number of strains found was compared with the number expected if resistances were independent.

Denmark is a country similar to The Netherlands with respect to limited use of antibiotics and low resistance. In
Denmark, the percentage resistance to penicillin of pneumococci from blood increased from <1% in 1995 to 4% in 1999. This percentage was significantly higher than the percentage of penicillin resistance in our survey (P < 0.001). The difference may be explained by the different spectrum of antibiotics used in the two countries. In 1998 the consumption in The Netherlands was 3.5 DDD/1000/day penicillins, 1.1 DDD/1000/day macrolides and 2.3 DDD/1000/day tetracyclines. In the same year in Denmark the use of penicillins (7.6 DDD/1000/day) and of macrolides (2.2 DDD/1000/day) was much higher, but the use of tetracyclines (1.0 DDD/1000/day) was two-fold lower than in The Netherlands. In Spain, the percentage of penicillin-resistant pneumococci was 10-fold higher than the percentage in Denmark. In Spain, 11.8 DDD/1000/day penicillins, 1.9 DDD/1000/day cephalosporins and 3.6 DDD/1000/day macrolides were used, whereas the use of 0.8 DDD/1000/day tetracyclines was as low as in Denmark. So the higher rates of penicillin resistance in Denmark and Spain may be related to the higher use of β-lactams and macrolides and the lower use of tetracyclines compared with The Netherlands, though other factors such as patient compliance may have played a role.

The increase in the use of macrolides and the resistance to erythromycin has levelled off in the last 3 years. The resistant species to penicillin seems not to be related to increased use of β-lactam antibiotics. Recently, the epidemiologic spread of a penicillin-resistant strain of S. pneumoniae in a Dutch clinic was described.In conclusion, the resistance of pneumococci to penicillin and erythromycin in The Netherlands is low compared with other European countries. The use of macrolides increased during 1994–1997 and may have enhanced the resistance to erythromycin. Continuous monitoring of antibiotic use and resistance is needed.

References


