

# New Developments<sup>®</sup>

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### The Carrier State of *S. pneumoniae*: Clinical Relevance in Pediatrics

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The nasopharynx, being directly exposed to the external environment, carries resident microbial flora that usually do not harm the child but which, in some cases, constitute the reservoir of pathogens responsible for upper respiratory tract infections. Among these pathogens, *S. pneumoniae* has become increasingly important in the last few years, due to a deeper understanding of its pathogenic role in several pediatric infections and the worldwide emergence of isolates resistant to penicillin and many other antibiotics.

Nasopharyngeal carriage of *S. pneumoniae* is common in infants and children, reaching percentages as high as 40% to 60%.<sup>1</sup> In adults, carriage is much less common, ranging from 2% to 9%.<sup>1</sup> Carriage rates can vary greatly, and several factors which modify the risk of nasopharyngeal colonization have been identified.

Age is one of these variables: in a recent survey of *S. pneumoniae* carriage in 2802 healthy Italian children aged 1 to 7 years, the percentage of carriers was 6.2% among infants <2 years of age and increased to 9.4% in children aged 2 to 5 years and to 8.6% among those >5 years.<sup>2</sup> Geographic location can also influence carriage: in a 20-center survey of French children aged 3 to 6 years, carriage ranged from 0% to 20%.<sup>3</sup> Day-care centers have been shown to be microenvironments with possibly unique characteristics with regard to carriage of *S. pneumoniae* within a small area.<sup>4</sup> Previous antibiotic use can greatly modify carriage, especially of resistant strains. In areas where penicillin resistance of *S. pneumoniae* has arisen, selective pressure of  $\beta$ -lactam antibiotic use has decisively contributed to the emergence of resistance: carriers of penicillin-resistant strains were exposed to  $\beta$ -lactam antibiotics in the preceding months more frequently than those carrying susceptible strains.<sup>5,6</sup> In Italy, where macrolide-resistant *S. pneumoniae* is common, repeated courses of macrolides in the previous three months is significantly associated with carriage of strains resistant to erythromycin.<sup>7</sup>

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Although risk factors associated with carriage have been studied, the significance of nasopharyngeal colonization of *S. pneumoniae* in healthy children has not received much attention. It is believed that the carrier state can progress to disease, but a precise correlation between these two conditions has been demonstrated only for otitis media. Faden and coworkers<sup>8</sup> have shown that children who become nasopharyngeal carriers of bacterial pathogens in the first months of life are more likely to suffer from otitis media than children who acquire their first colonization at several months of age. In addition, children harboring resistant pneumococci are more likely to experience episodes of unresolved acute otitis media.<sup>9</sup>

With regard to serotypes of *S. pneumoniae*, in a healthy pediatric population the most common nasopharyngeal carriage serotypes are the same as those identified from invasive isolates, although the rank order of specific serotypes can differ.<sup>10</sup> Moreover, *S. pneumoniae* carried in the nasopharynx reflects the susceptibility patterns of invasive isolates found during the same period for most antibiotics.<sup>10</sup>

How can this information be helpful in clinical practice? Should we screen for the healthy nasopharyngeal carrier of pneumococci? Even if appealing, such screening would not be rational or feasible for at least two reasons: a) we do not know the exact interval between the time of colonization and development of a disease; and b) nasopharyngeal carriage is a highly dynamic phenomenon. Ekdahl et al<sup>11</sup> have reported that in 678 individuals followed with weekly nasopharyngeal cultures, the median duration of carriage of *S. pneumoniae* is 19 days; in particular, the median duration is 30 days in children <1 year old and decreases to 21 days in children aged 1-4 years and to 13 days in those aged 5-6 years.

Thus, detection of the individual healthy carrier of *S. pneumoniae* would have no clinical value. But it would be useful to perform periodic surveys of nasopharyngeal carriage of *S. pneumoniae* in healthy children in childcare centers in order to rapidly obtain data on the serotypes and resistance patterns of large numbers of isolates. Since it has been suggested that the nasopharyngeal flora of children in daycare centers may represent a global reservoir of drug-resistant *S. pneumoniae* strains,<sup>12</sup> these data could be used to modify empirical treatment guidelines. Moreover, knowledge of circulating serotypes in different age groups allows measurement of the potential coverage of the new pneumococcal vaccine, thereby anticipating its impact in that particular setting. Of the strains isolated in a recent survey in Italy, which included children from birth to 8 years of age, an average of 63.2% were covered by or cross-reactive with the heptavalent pneumococcal vaccine; in children aged <2 years and in those aged 2 to 5 years, the figures were 73.1% and 68.9%, respectively.<sup>13</sup>

During active upper respiratory tract infections, particularly otitis media, children are more likely to carry *S. pneumoniae* than during healthy periods.<sup>14</sup> The usefulness of data on nasopharyngeal

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colonization to predict the causative organism for a given case of acute otitis media, however, is quite limited. In fact, when simultaneous cultures are obtained from the nasopharynx and middle ear fluid in children suffering from acute otitis media, *S. pneumoniae* is more often isolated from the nasopharynx, and thus the positive predictive value is low (22% to 40%).<sup>15</sup> When a semiquantitative culture can be readily obtained, however, the recovery of *S. pneumoniae* heavily growing in the nasopharynx correlates well with the isolate from the middle ear effusion.<sup>16</sup>

Despite their limited value in predicting the etiology of acute otitis media, nasopharyngeal cultures can provide valid information on the antibiotic resistance pattern of the pathogens causing the acute episode. In fact, Gehanno et al<sup>15</sup> have shown that a substantial overlap exists between the resistance pattern of strains of *S. pneumoniae* isolated in the nasopharynx and the susceptibility of those cultured from the middle ear fluid. Thus, in the individual child, nasopharyngeal culture can be extremely useful in deciding the most appropriate antibiotic regimen, avoiding the possible selection of resistant strains. Cohen et al<sup>17</sup> have in fact demonstrated that the more active an antibiotic is against a given bacterial species, the greater is the impact on carriage of the susceptible organisms at the end of the treatment, resulting in a higher percentage of resistant versus susceptible strains. More recently, our group has demonstrated that in children with a history of recurrent acute otitis media and with otitis media with effusion persistent for three months, resistance of nasopharyngeal pathogens is much greater than in patients with acute otitis media and in healthy controls (see Table 1), again providing evidence for the need to obtain nasopharyngeal cultures in children with these types of ear disease before starting antimicrobial treatment.<sup>18</sup>

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**Table 1.** Resistance (%) of *S. pneumoniae* carried in nasopharynx of children affected by ear disease

Ear disease	Macrolides	Penicillin
Acute otitis media	35	9.1
Recurrent acute otitis media	63.3	21.2
Otitis media with effusion	43.6	24.1
Controls	25.0	8.3

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# Unanswered Questions Regarding Pneumococcal Behavior

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*Streptococcus pneumoniae* (pneumococcus) is among the most versatile and complex human pathogens and a major cause of morbidity and mortality in all age groups, particularly in children and elderly persons. *Streptococcus pneumoniae* is the most common etiological agent of community-acquired pneumonia and is responsible for a high proportion of cases of bacterial meningitis and septicemia as well. Pneumococci are isolated from more than half of all otitis media samples from children.<sup>1</sup> A recent report from the World Health Organization concluded that the impact of pneumococcal diseases worldwide is similar to that of tuberculosis.<sup>2</sup> Despite the fact that *S. pneumoniae* has been extensively studied by both clinicians and basic researchers, many questions about its biological behavior remain unanswered.

## Why are some pneumococci more virulent than others?

Although 90 distinct capsular serogroups/serotypes (SGTs) have been described, only a small number account for the great majority of human pneumococcal infections. In Spain for example, only six SGTs are responsible for 61% of all known infections.<sup>3</sup> The SGTs most commonly associated with disease are also the ones that are usually found in the nasopharyngeal tracts of carriers. It is not clear whether these SGTs are more virulent or whether they are simply more often transmitted. Recently, Müller-Graf et al analysed a broad sample of pneumococci isolated from patients with systemic diseases and from asymptomatic carriers. Their molecular studies showed that the clones responsible for invasive diseases are frequently isolated from nasopharyngeal samples as well, suggesting that there are no differences between carried and invasive pneumococci.<sup>4</sup>

Nevertheless, differences in virulence among pneumococci have been well established. Many studies that have examined pneumococcal isolates in animal virulence assays suggest a correlation between serotype and virulence, although these results cannot be directly extrapolated to human disease. The data indicate, further, that within each serotype, virulence is individually related to each strain or clone of strains. The

capacity of 69 pneumococcal isolates, representing eight SGTs, to kill mice and the period of time between inoculation of the strain and death of the animal were strongly associated with the capsular type. All type 4 isolates, 40% of type 3 isolates, and 60% of group 6 isolates were virulent. Type 1 isolates were only marginally virulent, whereas all isolates belonging to SGTs 14, 19, and 23 were avirulent. The interval from inoculation until death was generally longer for mice infected with group 6 or type 1 than for those infected with pneumococci of types 3 or 4.<sup>5</sup>

The pneumococcal capsule is without doubt the principal virulence factor. Kelly et al constructed isogenic strains differing only in the type of capsular polysaccharide expressed and found that an alteration in the capsular type had a major effect on the virulence of some pneumococci.<sup>6</sup> An *in vivo* capsular transformation event, in which the multidrug-resistant type 23F Spanish/USA clone was the recipient of capsular gene type 3, was documented by Nesin et al.<sup>7</sup> When they tested the virulence of both bacteria in a mouse model, the isolate expressing the acquired capsular type 3 possessed a tremendously increased virulence over that of the same pneumococcus expressing the original 23F capsular type. These results provide genetic evidence that the capsular type influences the virulence of pneumococcus.

The polysaccharide capsule protects pneumococci circulating in the bloodstream by hindering phagocytosis. In this way, pneumococci reach the sites where they multiply, causing inflammation and disease. At this point, the influence of the genetic background probably gains in importance, and other components apart from the capsule, such as pneumolysin, autolysin, and PspA or PsaA,<sup>8</sup> may be required for maximum virulence.

If use of a conjugated pneumococcal vaccine were to reduce the number of carriers in the population, as has happened with the *Haemophilus influenzae* vaccine, then circulation of more virulent pneumococcal serotypes might also be reduced. In such a scenario, the impact of a possible nasopharyngeal replacement of the SGTs included in the vaccine by other serotypes depends on whether or not we accept the existence of

vaccine serotypes that have a higher level of intrinsic virulence than others.<sup>9</sup>

### The prevalence of serotypes depends on time, geographic distribution, and the age of the infected persons

With time, important changes in the prevalence of some serotypes have taken place. Pneumococci belonging to type 2, for example, which were responsible for many severe infections at the beginning of this century, are only rarely isolated from clinical samples today. In 1979, 7% of pneumococci isolated from cases presenting with invasive disease in our country belonged to type 2, whereas in 1999 only 1 of 3000 studied strains belonged to that type. Figure 1 shows examples of the differences we found in the evolution of several SGTs. The prevalence of pneumococci of type 1 has diminished from 10% to 3%. The prevalence of type 3 has remained constant during the last 20 years, whereas the prevalence of serogroup 19 has increased significantly.<sup>3,10</sup>

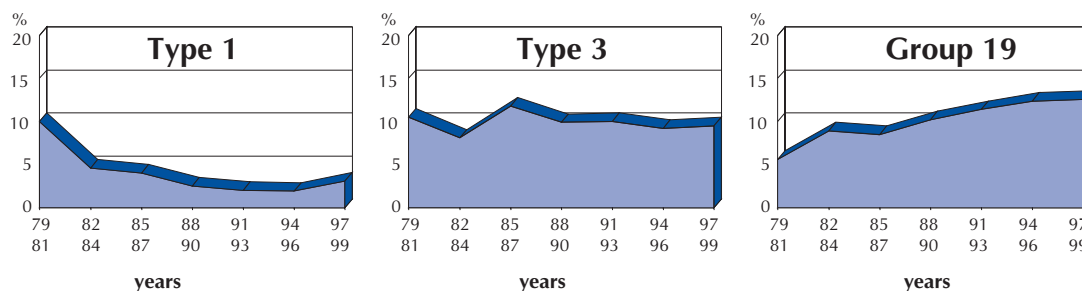
Furthermore, significant differences exist among the serotypes which most frequently cause disease in different parts of the world. Serotypes 1 and 5 are very frequently isolated from patients in South America, whereas they are scarcely present among strains

isolated in the United States and Canada. In European countries, a relatively high proportion of invasive serotype 1 strains has been isolated from children.<sup>9</sup> In Spain, type 3 ranks first among isolates from patients with systemic disease; however, type 3 is not even among the most common types in the other European countries.<sup>3,9,11</sup>

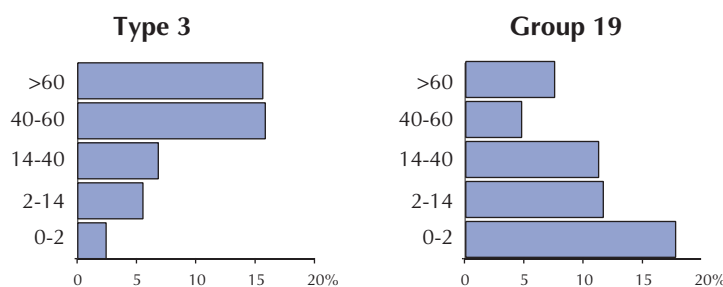
Hausdorff et al<sup>11</sup> have suggested that some of the apparent differences in serotype distribution could be caused by regional variations in diagnostic procedures and in selection of patients from whom blood cultures are taken. The reported incidence of total invasive pneumococcal disease in children is much higher in the United States than in Europe, but no such regional differences are apparent in the incidence of pneumococcal meningitis, a condition for which all patients are hospitalised. This observation suggests that in the U.S., outpatients, such as young children with fevers of unknown origin, are more likely to undergo blood cultures than their counterparts in European countries.

Serotype distribution also varies depending on the age of the patient. In Spain, the SGTs 6, 14, 19, and 23 are more frequently associated with disease in children, whereas SGTs 3, 8, and 9 have an obvious predilection for adults.<sup>3</sup> Figure 2 shows the prevalence of SGTs 3 and 19 among different age groups.

**Figure 1.** Evolution of SGTs 1, 3, and 19



**Figure 2.** Distribution of SGTs 3 and 19 according to age of the patient (years)



**Why do some serotypes cause certain clinical patterns more frequently than others?**

Figure 3 shows the distribution of the SGTs 3, 6, 8, and 18 according to the age of the patient and the source of the clinical sample. In adults, type 3 causes both invasive and non-invasive disease, and is one of the most frequently isolated types from all sources. In contrast, type 3 is only rarely recovered from children presenting with invasive disease, although this type is an important cause of otitis media and is frequently present in the nasopharynx of children. Serogroup 6 is a typical pediatric serogroup — its prevalence in children is much higher than in adults, independent of the source of the sample. The SGTs 8 and 18 are more frequently isolated from blood and cerebrospinal fluid (CSF) than from other sources. Type 8 strains seem to have a marked preference for adult persons, whereas the strains of type 18 are responsible for a huge proportion of the pneumococcal meningitis and sepsis cases diagnosed in children.

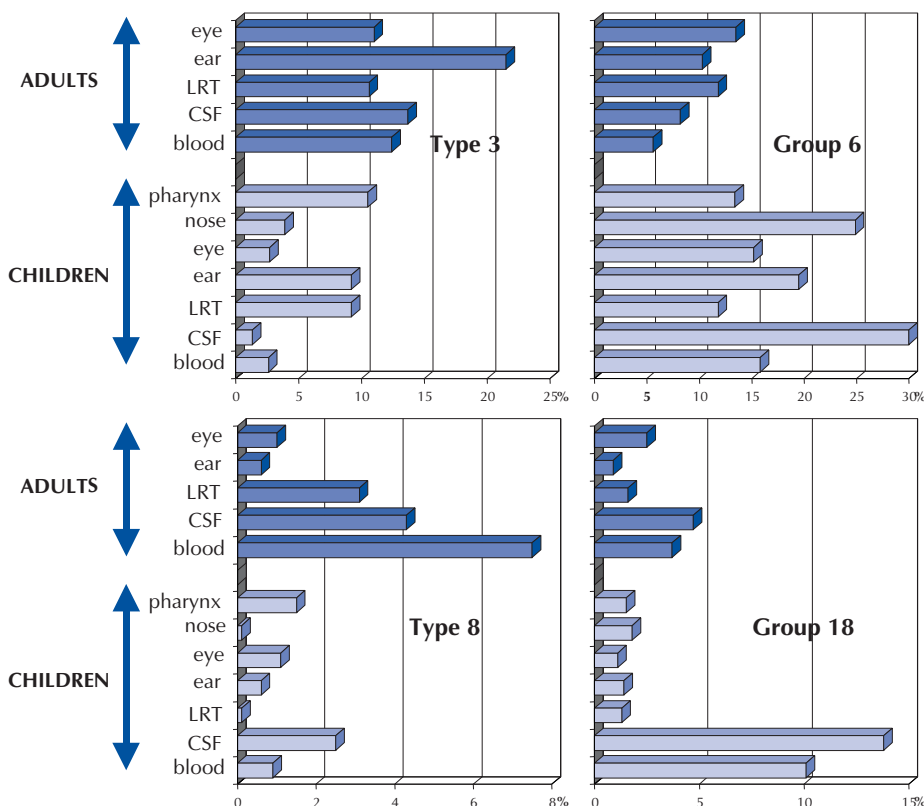
**Why did penicillin resistance in Spain increase during the 1980s and remain stable during the 1990s?**

Surveillance carried out in our lab over the past 20 years has demonstrated that about 80% of resistant pneumococci were confined to some of the clones of SGTs 6, 9, 14, 19, and 23 (Figure 4). The impressive increase in the number of resistant strains that occurred in Spain during the 1980s was caused by an increase in the number of pneumococcal isolates belonging to these SGTs. At first, SGTs 6 and 23 predominated; then the other SGTs appeared to gain importance over time. During the 1990s, the prevalence of these SGTs remained stable, showing

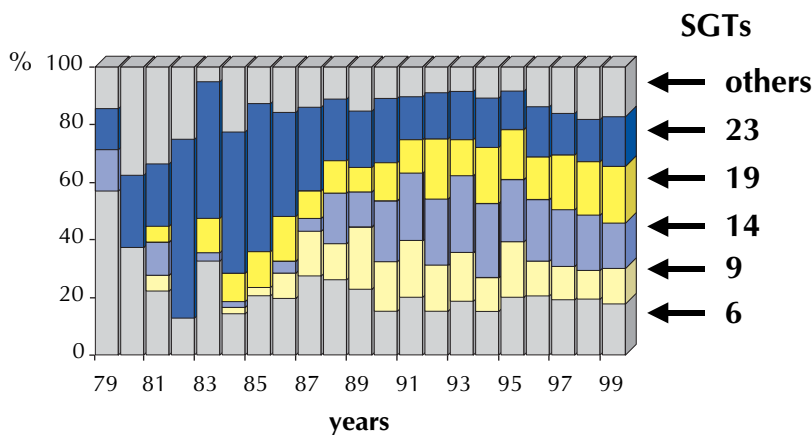
little to no variation. From the outset, we found a small proportion of penicillin-resistant pneumococci belonged to other SGTs. The number of these strains has remained insignificant throughout the 20 years — for reasons unknown, none of these SGTs has become established in our country (Figure 4).

Among possible explanations for the increase in the number of resistant pneumococci are the incorrect

**Figure 3.** Distribution of SGTs 3, 6, 8, and 18 isolated from various sources from Spanish children and adults



**Figure 4.** Relative frequency of SGTs 6, 9, 14, 19, and 23 among the penicillin-resistant pneumococcal population in Spain



application and abuse of antibiotic drugs, especially in children. The selective pressure exerted could have encouraged the survival of resistant strains. These surviving strains could then have spread to other countries, causing the rapid worldwide increase in the prevalence of resistant strains. These factors could explain why resistance levels in the United States, which were low only a few years ago, are now relatively high.

It is surprising that the extremely virulent serotype 3, the most important causative agent of invasive infections in adults and frequently present in the nasopharynx of many carriers, is still susceptible to penicillin. The observation that some SGTs seem not to acquire resistance could be related to the particular structure of their capsular polysaccharide and their union to the cell wall peptidoglycan.<sup>12,13</sup>

## Conclusion

Pneumococcus is a very complex species which consists of many serotypes with particular characteristics that are responsible for a variety of clinical patterns. The differences among serotypes are so important that some authors question whether all pneumococcal infections should be regarded as a single disease entity.<sup>14</sup>

It is not surprising that many open questions remain, related to the description of new antigens and their connection to virulence and protection, to the understanding of the human immune response and the detection of functional antibodies, and to intra- and inter-species gene exchange and pathogenicity studies. Imminent technological advances will allow us to answer many of these questions, but these efforts should be accompanied by epidemiological studies, permitting a new multidisciplinary synthesis which will help bring about a profound understanding of the complex relationship between bacteria and human beings.

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# The Portuguese National Program of Vaccination: Impact and Challenges

Mário Cordeiro, MD, PhD

In 1965, Portugal established a National Program of Vaccinations (NPV) and was, in fact, one of the first countries to adopt an organized vaccination schedule with rapid and universal implementation at a time when the nation was still underdeveloped. The success of this program was due to the efforts and tenacity of the professionals — mainly nurses — of the Maternal Institute and later of the General Directorate for Primary Care.

The vaccination campaigns that were then undertaken, and the initiatives that followed, extended the Program to the national network of health centers and to other health systems including the private one. The consequent rise in the number of children immunised has resulted in a dramatic decrease in the number of cases of the infectious diseases covered by the Program, compared to the entire country, in terms of both mortality and morbidity.

The NPV is periodically reviewed to examine the vaccines that are included in the Program and their characteristics and to consider other matters such as contraindications, vaccine associations, techniques of administration, improvements in the components of the cold chain process (namely the delivery time and maintenance of the recommended temperatures in all health centers including the very small and distant ones), vaccine storage, monitoring of side effects, etc. Furthermore, the NPV is increasing its attention to the follow-up of diseases that are about to be controlled or eradicated in order to improve clinical and laboratory diagnosis in each case. The vaccines of the NPV are given free of charge in the NHS health centers or in the “subsystems” of health, which are formed by the big firms or equivalent agencies (the private pediatric offices administer less than 0.5% of the total amount of vaccines given), and the acquisition of the vaccines is state-oriented through an international public bidding process.

After 35 years it is pertinent to ask: what is the impact of this Program? We present some data that may give a clue to this question.

## Mortality data

The number of deaths in the population aged 0-19 years by all causes and by diseases avoidable by vaccination (DAV) are shown in Figures 1 and 2.

The dramatic decrease in fatal cases caused by DAV after the introduction of the NPV in 1965 is clear, especially when compared with the more gradual decrease in the overall mortality figures for children and adolescents, as shown above. The mass vaccination campaigns that took place, especially in rural and suburban areas, led to this very good result.

Table 1 shows a detailed evolution for all age groups of deaths from diseases that were recently controlled and some that still cause deaths: tuberculosis, tetanus (not neonatal), and measles. All other diseases whose vaccines are included in the NPV have not caused any deaths since 1985.

Figure 1. Number of deaths in the population by all causes\*

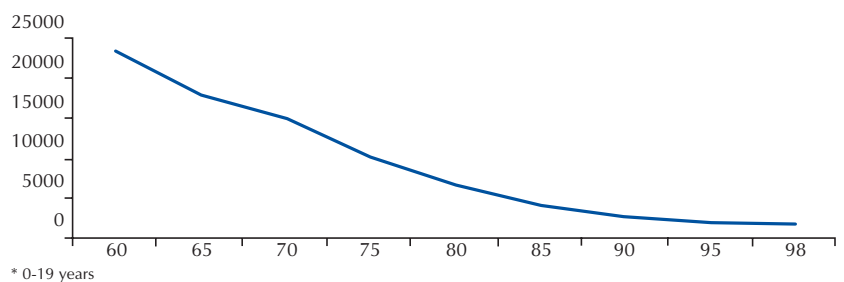
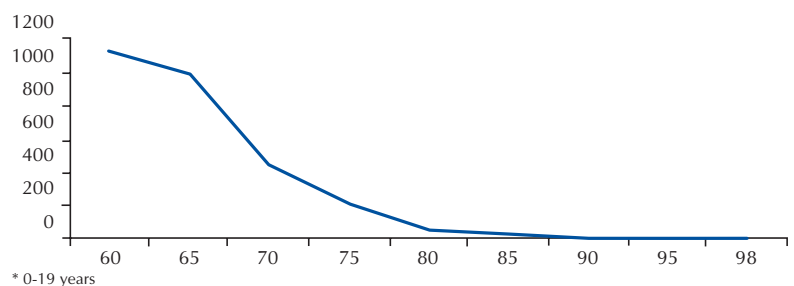


Figure 2. Number of deaths by DAV\* (see text for details)



**Table 1.** Deaths by diseases avoidable by vaccination (in all age groups)

Year	Tuberculosis	Polio	Diphtheria	Tetanus	Pertussis	Measles	TOTAL
1930*	13.013	NA	1.017	NA	995	1.151	NA
1950*	12.069	NA	232	NA	474	269	NA
1960*	4.274	31	150	264	62	120	<b>4.901</b>
1965*	3.687	25	123	212	56	118	<b>4.221</b>
1970*	1.463	2	16	108	13	254	<b>1.712</b>
1975	910	6	25	84	9	105	<b>1.139</b>
1980	577	1	1	38	5	31	<b>653</b>
1985	377	–	1	28	–	32	<b>438</b>
1990	274	–	–	15	1	–	<b>290</b>
1994	242	–	–	9	–	–	<b>251</b>
1995	313	–	–	16	–	32	<b>361</b>
1996	295	–	–	12	–	7	<b>314</b>
1997	321	–	–	10	–	2	<b>333</b>
1998	345	–	–	15	–	3	<b>363</b>
1999	281	–	–	7	–	3	<b>291</b>

\* Before ICD9

NA = not available

Source: National Institute of Statistics

**Table 2.** Deaths by disease in pediatric age groups (0-19 years)

Year	Tuberculosis	Polio	Diphtheria	Tetanus	Pertussis	Measles
1960*	535	30	149	193	60	119
1965*						
1970*	83	–	16	88	13	252
1975	38	6	24	41	9	103
1980	14	1	1	7	5	31
1985	3	–	1	–	–	30
1990	3	–	–	–	–	4
1994	3	–	–	–	–	–
1995	5	–	–	–	–	–
1996	2	–	–	–	–	–
1997	5	–	–	–	–	–
1998	2	–	–	–	–	–
1999	1	–	–	0	–	3

\* Before ICD9

Source: National Institute of Statistics

The results are striking: since 1994, only tuberculosis continues to cause deaths in the population aged less than 19 years (Table 2).

### Hospital admissions data

Table 3 shows the annual hospital admissions and Table 4 the annual number of hospital days for these diseases over a seven-year period as reported by all hospitals in the country from 1993 (the first year of functioning of the National Admissions Database) to

1999. The pediatric age groups are reported up to age 14.

Clearly, tuberculosis is still the largest cause for admission. Tetanus in the elderly is also an important cause of admission and hospital days. There was an outbreak of measles in 1994, and children during the first year of life (as well as adolescence) were a target group for the infection, which is a consequence of the high (but yet not ideal) rates of vaccination in children above fifteen months of age. The adolescent vaccina-

**Table 3.** Hospital admissions – total number of cases accumulated in the last seven years (1993-99)

	Age (Years)				TOTAL
	<1	1-4	5-14	≥15	
<b>Tuberculosis</b>	1,043	3,654	5,565	173,131	<b>183,393</b>
<b>Late effects of tuberculosis</b>	–	4	–	804	<b>808</b>
<b>Diphtheria</b>	–	3	4	3	<b>10</b>
<b>Pertussis</b>	629				<b>629</b>
<b>Tetanus</b>	1	–	–	315	<b>316</b>
<b>Polio (imported)</b>	–	–	–	8	<b>8</b>
<b>Measles</b>	204	374	135	124	<b>837</b>
<b>Rubella</b>	5	6	3	13	<b>27</b>

Source: National Observatory for Health

**Table 4.** Hospital days – total number of days, accumulated over seven years (1993-99)

	Age (Years)				TOTAL
	<1	1-4	5-14	≥15	
<b>Tuberculosis</b>	4,355	9,213	12,274	567,707	<b>593,549</b>
<b>Late effects of tuberculosis</b>	–	67	–	9,424	<b>9,491</b>
<b>Diphtheria</b>	–	71	23	53	<b>147</b>
<b>Pertussis</b>	737				
<b>Tetanus</b>	61	–	–	14,025	<b>14,086</b>
<b>Polio (imported)</b>	–	–	–	46	<b>46</b>
<b>Measles</b>	1,534	2,695	1,207	768	<b>6,204</b>
<b>Rubella</b>	36	26	41	81	<b>184</b>

Source: National Observatory for Health

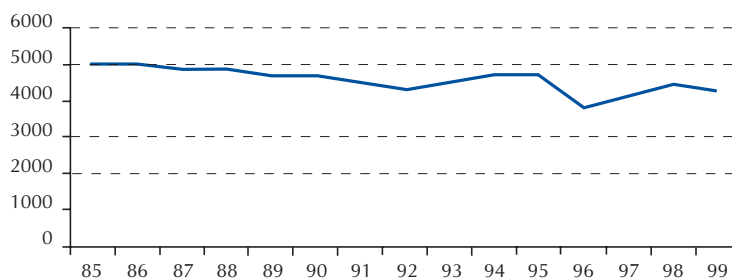
tion coverage rate is not so high, and given that this is a “difficult” age group for healthcare delivery, the Vaccination Committee decided in 1999 to move the MMR second shot from 11-13 years to 5 years of age.

### Notification data

The notification system started in 1950 and has been updated regularly, not only in terms of the diseases that are notifiable but also as far as the details to be reported are concerned. The present system comprises 44

diseases, including all that constitute the NPV. It is well known, as in other countries in the Western World, that diseases are sub-notified and sub-declared. Nevertheless, given the fact that the reasons for sub-notification or notification errors are considered to be more or less the same over the years, the notification curves may be interpreted as trends. Figures 3-11 display the trend curves for notifications (reported cases by physicians, both in public and private sectors) of the individual diseases.

**Figure 3.** Evolution of notifications for tuberculosis (number of reported cases)



Source: General Directorate of Health

BCG vaccine was part of the first NPV and has always been included, although at its last review, in 1999, BCG immunization was limited to one shot, and very rarely, two. Tuberculin testing has also been abandoned as a screening tool. The verification of the vaccine scar at six months is used to determine if a positive reaction to vaccination has occurred, although we are fully aware of the number of false positives and negatives associated with this method of screening.

### Diphtheria, tetanus, and pertussis

The vaccine against diphtheria, tetanus, and pertussis was introduced in 1965. In the 1999 NPV review, two major decisions were taken: to maintain the whole-cell pertussis vaccine and to add the adult diphtheria vaccine to the tetanus schedule at 11-13 years of age. Acellular pertussis vaccine must be prescribed by a physi-

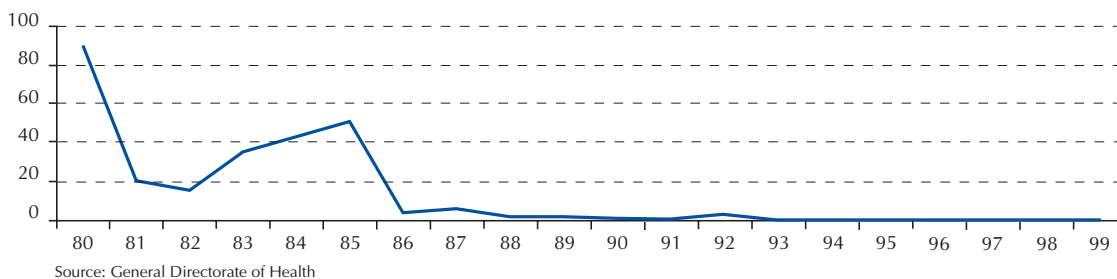
cian and paid for by the parents. Therefore, its use is not practical in children. (*Editor's note: In January, 2001, Wyeth-Lederle International announced that it would no longer manufacture and distribute pertussis vaccines.*)

Figure 4 illustrates the enormous decrease in the number of reported cases of diphtheria. The last case of poliomyelitis (Figure 7) was reported in 1993. A surveillance program currently monitors all cases of flaccid palsy, Guillan-Barré syndrome, etc., and performs regular analyses.

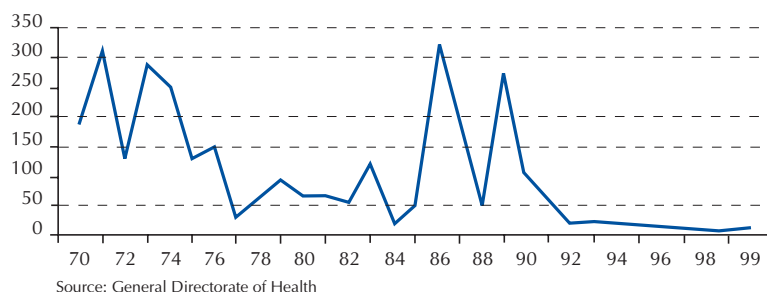
### Measles, Mumps, and Rubella

The MMR vaccine was introduced in 1982 and the reporting system in 1987. The vaccine has undergone changes based on the products available on the market.

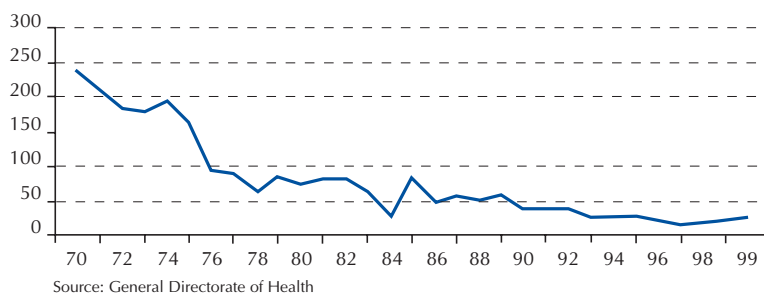
**Figure 4.** Evolution of notifications for diphtheria (number of reported cases)

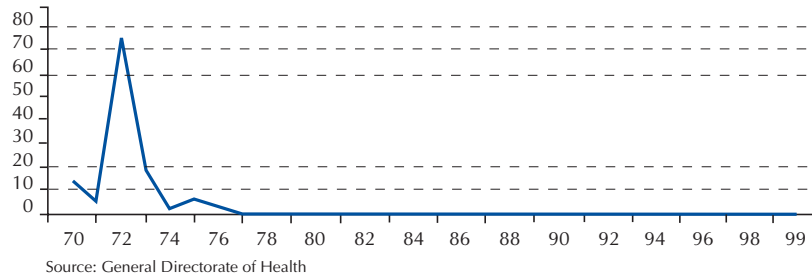
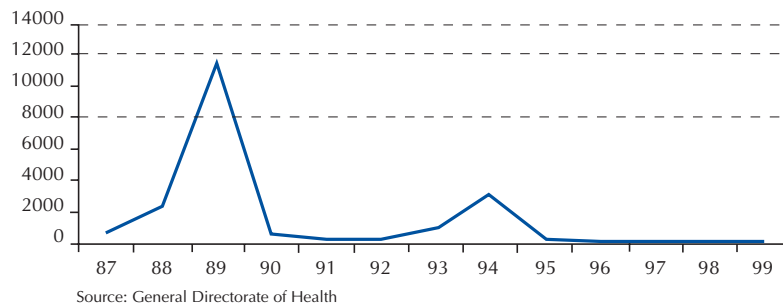
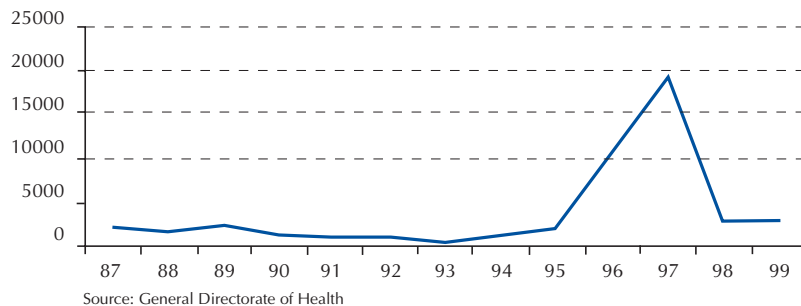


**Figure 5.** Evolution of notifications for pertussis (number of reported cases)



**Figure 6.** Evolution of notifications for tetanus (number of reported cases)



**Figure 7.** Evolution of notifications for indigenous poliomyelitis (number of reported cases)**Figure 8.** Evolution of notifications for measles (number of reported cases)**Figure 9.** Evolution of notifications for mumps (number of reported cases)

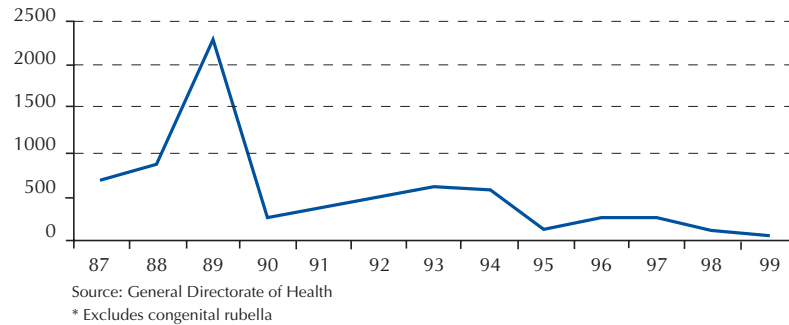
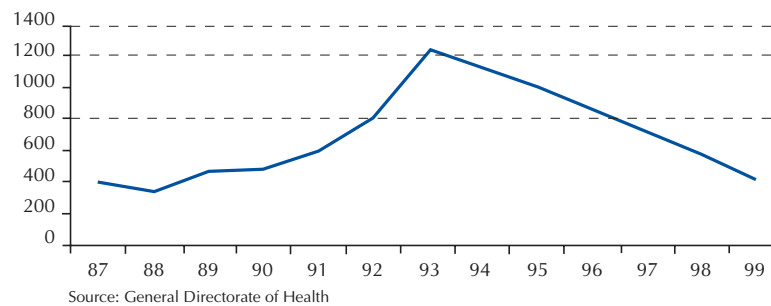
Administration of MMR vaccine at 15 months of age was started in 1987. In 1990, Portugal introduced the booster shot at 11-13 years and was the second European country to do so after Denmark. In the 1999 review, this MMR booster was shifted to an earlier age: 5 years.

The first mumps vaccine to be used was the SKF strain, which has been very effective. When the drug company withdrew this vaccine from the market after a British report of cases of meningitis associated with the vaccine, and given the non-immediate availability of the Jerryl-Lynn strain, Portugal opted for the Rubini strain (Berna vaccine). However, in 1997 and 1998 we noted (Figure 9) a nationwide outbreak like those observed in other countries (Spain, Switzerland, etc.) which used the same strain. The identification of the source of the problem, in association with the British

laboratory surveillance system, prompted us to change the vaccine given to children. The adoption of the Jerryl-Lynn strain was followed by a decrease in the number of reported cases, demonstrating the efficacy of this vaccine.

### Hepatitis B

Hepatitis B notification started in 1987. It has been assumed that the number of cases reported is far from the actual number of patients diagnosed. The hepatitis B vaccine was included in 1990 in the NPV, although in a non-universal approach: most at-risk groups were defined and the vaccine offered free of charge to the population of these groups. Adolescents aged 11-13 years were included soon after. In the 1999 review, the vaccine was extended to newborn children and kept as well in the above-mentioned adolescent age group. No

**Figure 10.** Evolution of notifications for rubella (number of reported cases)\***Figure 11.** Evolution of notifications for hepatitis B (number of reported cases)

serologic determinations are requested, either before or after administration of the vaccine.

A full representative serological study is underway to determine the immunological status of the various age groups in the several Health Regions in order to identify the real impact of the NPV. In addition, this study will attempt to determine the prevalence of natural “wild” infections and assess the age/antibody profile of other diseases, such as hepatitis A and varicella, for which vaccines are now available.

### Vaccination uptake rates

Vaccination uptake rates in Portugal are quite good for virtually every vaccine. Estimates for the first decades of the program are subject to error, however, because the numerator was the number of administered doses and the denominator the number of children born in the area. An improved knowledge of the population (including those children not attending NHS services either because they are seen in private offices or because they simply do not attend any services) by health center personnel along with an understanding by nurses that registration is fundamental to the decision-making process has led to better assessment of vaccination uptake rates. The vaccination uptake rates for all vaccines are above 95%, although inequalities

still warrant an innovative approach. Deprived children and children of special communities (ethnic groups, gypsies, and immigrants, for example) need a new strategy most urgently.

### New and old challenges

The NPV faces several challenges:

- the maintenance of awareness about infectious diseases and the benefits of vaccines, both in the population at large and among professionals. The virtual absence of certain diseases, news articles about side effects or complications, debates about ecological problems, and the popularity of “alternative medicine” may all contribute to an inappropriately casual attitude toward this subject;
- an increase in vaccination uptake rates to 100%, an aim that, given our actual high uptake rates and the concentration of non-vaccinees in deprived socio-economic groups with special accessibility characteristics, will require innovative approaches and strategies, increased commitment by medical professionals, and concerted actions on the part of communities, government agencies, etc.
- a decrease in the number of children and adolescents who are not vaccinated because of *false contraindications*: having the flu, receiving antibiotic

therapy, having asthma, cerebral palsy, or congenital heart disease, or the fact that it is summer and the weather is hot. Many parents simply do not bring their children back to the health center after being sent away by health care professionals.

- a decrease in “missed opportunities for vaccination,” which warrants, among other measures, the articulation of several actions and activities, like child health clinics and immunization sessions, the use of “opportunistic” visits to the E&A departments, organized sessions in the community especially in deprived areas or regular non-attendant groups, school environment, etc. Efforts to consider daily life events and rhythms will avoid difficulties: for instance, getting time off to take children several times to the health centers. Missed opportunities for vaccination are a problem to which services, professionals, and parents should give increasing attention in order to find out what the difficulties and obstacles are and which strategies should therefore be implemented.
- an approach for special cases such as HIV-positive citizens, other immunodeficient persons, and other similar situations;
- a study of the unwanted effects and secondary reactions of vaccines;
- a full study and laboratory investigation of rare disease cases such as polio, measles, and diphtheria, to establish whether the clinical diagnosis is correct, not only to trigger immediate measures but also for the purposes of epidemiological surveillance;
- a coordination of the administration of vaccines, in order to avoid multiple punctures and repeated visits to health centers;
- a cost/benefit study of the introduction of new vaccines in the NPV, in light of the limits of the Health Ministry budget, given the fact these vaccines will be available on the market very soon if not already, either for new agents not yet covered (eg, anti-meningococcal C vaccine) or as new formulas for “old” agents (eg, acellular pertussis vaccine);
- some new vaccines will soon be introduced and their inclusion in the NPV will have to be considered. The vaccines that can be anticipated are anti-varicella vaccine (available in pharmacies in early 2001), anti-meningococcal C vaccine (which has been approved and will be available in late 2001), and 7-valent anti-pneumococcal vaccine. Both professionals and parents will find all of these vaccines

very desirable. Their high price, however, may be an obstacle. Generally, the government pays 40% of any prescription for vaccines that are not included in the NPV, and the other 60% is paid for by the citizen or by his/her insurance. If significant amounts of non-NPV vaccines are prescribed, the total amount paid by the government might be greater than the cost of full inclusion in the NPV, in which case the vaccines would be bought wholesale in an international bidding process and prices would come down as a consequence.

## Conclusion

The Portuguese NPV has been among the most effective and efficient institutions of preventive medicine, and many thousands of persons are alive and well thanks to vaccines and to vaccinators.

Economically, the advantages are also prominent: if we consider that a single year of life lost corresponds to around 26,000 Euro plus hospital admissions, costs for diagnosis and therapies, absenteeism, handicap services, etc, we see that the benefits of the NPV go even further.

But, as in many other areas, we cannot rest under the “conquered laurel.” On the contrary, we have to increase our effort and commitment, because both the population and the professionals are losing contact with infectious diseases avoidable by vaccination. This unfamiliarity can lead to misdiagnosis and to an incorrect conclusion that the NPV is no longer important. The experience of countries where the vaccination effort has diminished shows how infectious diseases can break out in a dramatic way. In Portugal, the example of the mumps vaccine is, as described above, paradigmatic, showing that the NPV has to be continuously updated according to evidence-based strategies.

Infectious diseases will perhaps never be dominated. They pose both old and new problems. They are a challenge and a source of worry but also an opportunity for human creativity and ingenuity to demonstrate what a good, sound, efficient Public Health program can be.

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# Perspectives in Pertussis Vaccination Strategies

*Alberto E. Tozzi, MD*

Pertussis remains a major cause of morbidity worldwide, with an estimated 20-40 million new cases and 200,000-400,000 deaths every year. Deaths caused by this disease occur mostly in children in developing countries where the case-fatality ratio can reach 15%. In developed countries pertussis causes death much less frequently. In some areas of Europe the incidence of pertussis remained high until the early 1990s due to low vaccination coverage, but with the introduction of acellular vaccines and an increase in vaccination coverage, the incidence of pertussis in Sweden, Italy, and Germany has decreased rapidly.

Other developed countries which had successfully controlled pertussis previously with whole-cell vaccines have also shifted to acellular vaccines. In the United States, where vaccination coverage has been high for a long time, the incidence of pertussis is nearly 2 per 100,000, the disease sometimes reemerges in young adults, and may be underdiagnosed in older age groups. In the U.S., adolescents and young adults represent the most important reservoir for the infection and may transmit pertussis to newborns and infants before they are fully immunized, with the risk of severe complications including death.

Outbreaks of pertussis have also been observed in groups with high vaccination coverage rates. A recent pertussis outbreak in the Netherlands in a population of children with high vaccination coverage with whole-cell vaccines suggested that vaccine selective pressure favored the emergence of genetically diverse *B. pertussis* strains resistant to vaccines. In the U.S., however, where whole-cell vaccines have been used for many years and outbreaks of pertussis have occurred in highly vaccinated populations, no evidence of genetic diversity in *B. pertussis* has been found, and an increase in the proportion of susceptible hosts may account for the outbreaks.

## **Safety of acellular pertussis vaccines**

Whole-cell vaccines remain the necessary choice for developing countries where the cost of acellular vaccines is unaffordable. Although the feared association between whole-cell vaccines and encephalopathy has never been definitely proven, the lower reactogenicity

of acellular vaccines favored their use in areas in which the safety of the old vaccines was a matter of concern. Because of their low reactogenicity, and given the fact that some adverse events increase with age, acellular vaccines represent the preferred choice for adults.

Now that the first cohorts of children primed with acellular vaccines have reached preschool age, more data are available on reactogenicity of booster doses in children primed with these acellular vaccines. Although severe adverse events are observed very rarely with acellular vaccines, local reactogenicity increases with age and number of doses. As many as 50% of vaccinees experience a local reaction following preschool booster doses, and 1% suffer extensive local reactions at the injection site with swelling of the entire limb. These reactions, however, are rarely associated with tenderness and infrequently limit the usual activities of vaccine recipients, although they may be worrying for vaccinees' parents. In fact, the shift from whole-cell to acellular pertussis vaccines has resulted in a marked reduction in adverse events in Canada and the U.S. where a significant decrease has been observed in the frequency of febrile seizures and hypotonic-hyporesponsive episodes following pertussis immunization.

## **Duration of protection induced by acellular vaccines**

The efficacy of acellular pertussis vaccines has been demonstrated in the short term by several trials. Numerous studies performed in the last decade demonstrated that some whole-cell vaccines are less than optimally effective, while others are better than the most efficacious acellular vaccine, underlining the difficulties in standardization of whole-cell preparations. Efficacy of acellular vaccines is related to the number of components: five- and three-component vaccines perform better than two- and one-component vaccines.

Long-term efficacy of acellular vaccines has also been demonstrated. Data from the Italian trial on acellular pertussis vaccines demonstrate that three doses of a three-component acellular vaccine administered at 2, 4, and 6 months of age protect at least until preschool age with an efficacy of nearly 85%. Moreover, the

sharp decrease in pertussis incidence observed in Sweden after the introduction of several acellular vaccines suggested that acellular pertussis vaccines are able to induce herd immunity in the population. It is difficult to say whether these results depend on the circulation of *B. pertussis*, which might work as a natural booster in populations with a previous low vaccination coverage. In this respect it would be important to understand if these outstanding long-term results are applicable also to populations in which vaccination coverage has been high and circulation of *B. pertussis* has been low. Data on the long-term efficacy of booster doses are also not yet available, but the Italian pertussis trial showed that immune response to the preschool booster is excellent. Because immunogenicity results in this study are better than those observed after primary immunization, it can be speculated that a booster dose at preschool age confers protection for a long period.

### Correlates of protection for pertussis

No definite correlates of protection have yet been found for pertussis. The lack of such correlates implies that seroprevalence studies aimed at identifying unprotected groups are still difficult to perform. Some recent studies suggest, however, that antibodies against pertactin, fimbriae 2/3, and pertussis toxin might be reasonable candidates for correlates of protection. These findings also encourage speculation that pertactin and fimbriae enhance the efficacy of acellular pertussis vaccines and could explain the superiority of three- and five-component vaccines. Nevertheless, these data are not sufficient to explain the mechanism of protection elicited by acellular vaccines, considering that cell-mediated immunity plays a major role in protection from the disease.

### Diagnosis of pertussis

From the clinical viewpoint, pertussis is generally suspected in a patient with paroxysmal cough, but the clinical presentation in adolescents and adults may be very different from the typical severe picture observed in infants. Mild chronic cough is occasionally diagnosed as pertussis in these age groups. Furthermore, vaccinated persons may have pertussis disease with a mild presentation. For laboratory confirmation, new diagnostic tools have been developed in the last few years. Commercial and in-house ELISA tests have started to be widely used for serologic diagnosis, along

with culture of the nasopharyngeal aspirate. In fact, classical culture methods greatly benefit from the addition of serology which contributes to improved test results. Furthermore, culture of nasopharyngeal aspirates alone has a low sensitivity in adolescents and adults. Finally, PCR techniques are rapidly replacing culture. All these methods, however, still need to be carefully examined for their specificity and sensitivity in the light of the changing epidemiology of pertussis.

### Vaccination schedule

Although a vaccination schedule is not universally agreed upon, there are now new elements to take into consideration. Three doses of a three-component acellular vaccine administered in the first year of life seem to be sufficient to guarantee long-term protection, maybe even beyond preschool age. The use of a booster dose in the second year of life remains in the U.S. schedule and in those of other countries as well. If evidence can be gathered that three doses in the first year of life confer a long duration of protection even in countries with low pertussis circulation, the booster dose in the second year of age might be delayed. Many countries have adopted a schedule in which a booster dose is administered at preschool age. Considering that local reactogenicity increases with age and number of doses, and that the immunogenicity of acellular vaccines in preschool-aged children is excellent, it might be adequate to administer a booster dose later and with a reduced amount of pertussis antigens. This approach has recently been adopted in Germany, where a DT dose only is given at 4-5 years of age, and a dTap dose is administered at 10-16 years of age. Finally, in countries where a high vaccination coverage in pediatric age groups has been achieved for many years, vaccination might possibly be targeted to adults. The optimal timing of booster doses remains to be thoroughly investigated, but it seems natural to employ the same time intervals used for dT boosters.

### Conclusion

Many questions regarding pertussis prevention remain unresolved. The burden of disease as well as the impact of different vaccination strategies still need to be accurately measured. With the introduction of acellular pertussis vaccines, we might have the appropriate tool to achieve a better control of the disease. Acellular vaccines are, however, still a privilege for the developed countries, and their use should be extended to

developing countries as well. The priority in all countries remains to achieve the best vaccination coverage possible with routine programs and with the implementation of catch-up strategies. Recent studies suggest that the current schedule of pertussis vaccination in many countries could be reviewed. Considering that both whole-cell and acellular vaccines induce a protection which wanes over time, a vaccination strategy expanded to adolescents and adults, who sustain the circulation of infection, will be needed at least in countries where the incidence of infection starts to increase in these age groups. In particular, the use of acellular vaccines containing reduced amounts of pertussis antigens seems feasible in adolescents and adults. Also,

more data should be gathered on the validity of proposed serologic correlates of protection of pertussis, which would greatly facilitate the identification of susceptible individuals. Finally, the use of PCR on nasopharyngeal aspirates might rapidly replace culture for pertussis diagnosis even in adolescents and adults. Great progress has been achieved over the last few years, but the path to eradication of pertussis remains long.

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