Executive summary

Health Council of the Netherlands. Vaccination of infants against pneumococcal infections (2). The Hague: Health Council of the Netherlands, 2010; publication no. 2010/02

The inclusion of pneumococcal vaccination in the RVP has led to a considerable decline in pneumococcal disease

Pneumococci can cause serious disease, including meningitis, bacteremia and pneumonia; they are also an important cause of otitis media (middle ear infection). Pneumococcal disease is most prevalent in the very young and the elderly. Partly on the advice of the Health Council the Minister of Public Health, Welfare and Sport (VWS) has decided that as of 1 April 2006 infants may be vaccinated via the National Immunisation Programme (*Rijksvaccinatieprogramma*, RVP) against pneumococcal disease. Until recently only one vaccine was available for this purpose: Prevenar® (hereinafter referred to as PCV7), which confers protection against seven common types of pneumococcus bacterium.

Worldwide, about 20 serotypes of pneumococcus (out of a total of 92 known serotypes) account for the overwhelming majority of serious pneumococcal disease. In the Netherlands, about 69% of serious pneumococcal infections in young children are caused by the seven serotypes against which PCV7 is directed. The inclusion of PCV7 in the RVP has led to a steep drop in the incidence of pneumococcal disease caused by vaccine serotypes amongst vaccinated children: from approximately 25 to 5 cases per 100 000 children per year. A lowered incidence can also be observed amongst non-vaccinated elderly people, a so-called ‘indirect effect’ which stems from the reduction in the numbers of circulating

bacteria. So far this indirect effect has been smaller than had originally been expected, and this has made the cost-effectiveness ratio of pneumococcal vaccination higher than predicted.

There have so far been only limited indications of 'serotype replacement' (in which serotypes not covered by the PCV7 vaccine become more frequently responsible for illness). However, the illness burden occasioned by the other pneumococcal serotypes remains considerable.

New pneumococcal vaccines

Two new pneumococcal conjugate vaccines were recently registered and brought onto the market. Both cover a wider range of serotypes than the current vaccine. One (Synflorix®, hereinafter referred to as PCV10) is a 10-valent vaccine covering the same 7 serotypes as the current vaccine plus the serotypes 1, 5, and 7F; the other (Prevenar 13®, hereinafter PCV13) is a 13-valent vaccine covering the same 7 serotypes as the current vaccine plus six others: 1, 3, 5, 6A, 7F, and 19A. The new vaccines differ from the current one not only in the range of cover they confer, but also with regard to the protein used as a carrier for the pneumococcal antigens. PCV10 uses a protein derived from a bacteria that often causes middle ear infections (non-typeable *Haemophilus influenzae*), while PCV13 uses the same protein as does PCV7 (one derived from the diphtheria bacterium). With the arrival of the new vaccines, PCV7 will be withdrawn from the market.

Request for advice

The Minister has asked the Health Council to advise on the criteria on which he can base the choice for a replacement for PCV7 within the RVP. More specifically, he has also asked against which diseases and which pneumococcal serotypes the vaccine should confer protection, and which vaccination schemes are possible and desirable. For questions to do with the content of the RVP the Health Council employs a specific assessment framework which employs seven criteria.

Against which diseases should pneumococcal vaccination offer protection?

The aim of the RVP is to protect the population against serious infectious disease through immunisation. In this respect, an important criterion is the seriousness and scale of the illness burden itself. Pneumococci can cause a variety of diseases

having different degrees of seriousness. The Health Council has defined the objectives of pneumococcal vaccination in the past as ‘to offer protection against invasive pneumococcal disease: meningitis, bacteremia and invasive (bacteremic) pneumonia. Because non-bacteremic pneumonia can also have serious consequences for young children, including frequent hospitalisation, in this new advisory report the Committee has revised these objectives as follows: ‘the prevention of pneumococcal meningitis, bacteremia and pneumonia’. In the Committee’s opinion, protection against middle ear infection does not form a primary indication for a public immunisation programme; although this disease is quite prevalent, it is not generally a serious health risk. Naturally, the health benefits with regard to middle ear infections that are brought about by vaccination do constitute a relevant bonus.

More health benefits can be obtained with the new pneumococcal vaccines

Because effective pneumococcal vaccines are already available and placebo-controlled research with clinical end points is therefore no longer ethically acceptable, assessment of the effectiveness of new pneumococcal vaccines has to be made by reference to immunological end points. This makes it possible to assess whether a new vaccine can be expected to confer as much protection against invasive pneumococcal disease as does the current vaccine.

PCV10 is not registered for protection against pneumonia, but on the basis of an assessment of the immunological end points and the demonstrated protection against otitis media the Committee considers the assumption of such protection to be reasonable.

For neither of the two new vaccines is data available on the degree to which it confers indirect protection amongst the general population or is subject to serotype replacement. Given that PCV13 and PCV7 use the same carrier protein, the Committee considers the assumption of indirect protection for PCV13 to be reasonable.

Extensive research has been carried out into the possible side effects of the new vaccines; on the basis of the results of this research, both vaccines have been deemed to be safe.

Both vaccines effectively counter pneumococcal disease; the Committee has a slight preference for PCV13

Using the data currently available, the Committee has screened both vaccines within the RVP assessment framework and its component criteria. Both vaccines would effectively counter pneumococcal disease via the RVP.

The Committee is of the opinion that too little clinical data on the new vaccines is currently available to be able to accurately assess their relative merits; however, a number of differences between them can be pointed out.

Firstly, with regard to the primary aim – protection against invasive disease and pneumonia – PCV13 may reasonably be expected to yield more health benefits than PCV10. The large-scale cost price of both vaccines is as yet unknown. Based on the importance of protection against invasive disease and pneumonia and the same vaccine price for PCV7, PCV10 and PCV13, therefore, PCV13 would appear to offer the best cost-effectiveness ratio; this may change with a different price setting.

Secondly, the Committee is of the opinion that given its similarities to the current vaccine, PCV13 offers programming advantages with regard to its expected indirect effects as well as with regard to evaluation and monitoring. Their biochemical similarities also mean that the two vaccines are more readily interchangeable, thereby promising a smoother transition to the new vaccine.

On the basis of the currently available data, the Committee has a slight preference for PCV13. The Committee advises that the choice of RVP pneumococcal vaccine be reviewed after about two years, when more data is expected to be available.

The costs are relatively high

New cost-utility calculations have revealed that the cost-effectiveness ratio of vaccination is higher than previous calculations had suggested, principally as a result of more conservative assumptions – compared to previous analyses – on the degree of indirect protection in the population. Longer follow-up studies will be needed in order to give these assumptions a more secure foundation.

Retain the 3+1 scheme for now

The Minister asked the Health Council to assess alternative vaccination schemes. The advantages of a reduced scheme (2 doses at the age of 2 and 4 months, and a

booster dose at 11 months (2+1) rather than the current 3+1 scheme (2, 3, 4 and 11 months) are clear: the injection load is lower for the children, and the costs are lower. However, in 2005 the Health Council judged that there was insufficient evidence to justify moving to a 2+1 scheme.

In the meantime, more data on the efficacy of the 2+1 approach has become available from countries in which a 2+1 scheme has been put into practice. This data shows that a 2+1 scheme can provide good protection (this protection may partly depend on indirect protection as a consequence of reduced bacterial circulation). Because there is still some uncertainty about the degree of indirect protection afforded by the new vaccines, the Committee recommends that these vaccines employ the existing 3+1 scheme for the time being. After another two years, the new vaccine and the 2+1 scheme can both be reassessed; by then the available data will probably be adequate for the analysis of indirect protection.

Monitoring remains important

An ongoing concern with the use of pneumococcal conjugate vaccines is the possibility of serotype replacement. So far there have been limited indications of possible replacement, but data on serotype replacement following the use of either of the two new vaccines is absent because these vaccines have only just been brought to market. For the same reason, there is no data yet available on the degree of indirect protection conferred by the new vaccines.

The continued monitoring of pneumococcal infections is vital to the adequate assessment of possible serotype replacement and indirect vaccination effects in the population.