Summary

Health Council of the Netherlands. Vaccination of young children against tuberculosis. The Hague: Health Council of the Netherlands, 2011; publication no. 2011/04

Even though the global prevalence of tuberculosis is high, the disease poses no great problem in the Netherlands. Migrants from countries where tuberculosis is endemic constitute a particular risk group. Children under five years of age are more susceptible to the serious complications of tuberculosis infection, with higher risk that infection actually results in disease; consequently, many countries with a high incidence of tuberculosis vaccinate this group. In the Netherlands, children of parents from countries where tuberculosis is endemic are also immunised with the Bacillus Calmette-Guérin (BCG) vaccine. This strategy was initiated in the 1970s, aiming to address the situation of children of Turkish and Moroccan employees in particular who regularly visited relatives in their home country and therefore were at risk of contracting tuberculosis. The risk population has now shifted to the children of refugees. They too are at increased risk of tuberculosis as a result of contacts within their own ethnic group.

Request for Advice

This shift in the paediatric tuberculosis vaccine population raises the question whether the current, specifically risk group-oriented vaccination policy continues to be appropriate, seeing the Netherlands generally has an adequate tuberculosis control programme.

The Minister of Health, Welfare and Sport therefore asked the Health Council of the Netherlands to advise on the question to what extent the current BCG vaccination programme remains feasible. In order to answer this question, a number of experts were added to the Health Council's National Immunisation Programme Committee. Additionally, expertise available in this specific area was extensively consulted, particularly of the Dutch KNCV Tuberculosis Foundation.

The National Immunisation Programme (NIP) does not include BCG vaccination. Children eligible for vaccination receive notice from their local Municipal Health Service (GGD) tuberculosis department at the age of six months. Catch-up vaccinations, e.g. at the time of immigration, are given up to age 12.

The questions to the Health Council are:

1 Evaluation of the national policy to immunise children of immigrants from countries with a high prevalence of tuberculosis with BCG; does this strategy continue to be useful and (cost-)effective?
2 Should continuation of BCG vaccination be appropriate, would inclusion in the NIP be advisable, both in terms of organisation and reach? How can BCG vaccination be included in the NIP?

The Committee tested the current BCG vaccination strategy of risk-group children against the seven criteria for inclusion of vaccinations in a public programme. The Committee compared two options: continuing vaccination or discontinuing vaccination and having risk-group children come under the general tuberculosis control strategy.

Disease burden

There are currently about 1,000 cases of tuberculosis in the Netherlands each year. Some 65 percent involve individuals not born in the Netherlands. Additionally, as a result of source and contact research initiated once a tuberculosis patient is reported, some 2,000 people are identified annually with latent tuberculosis infection (LTBI). They are offered preventive treatment.

Infection with the tuberculosis bacteria may have severe consequences. However, infection does not automatically develop into serious disease symptoms. This risk is generally increased in the first two years after the infection, in children younger than five years, in immunocompromised individuals, e.g. as a result of HIV infection, in certain diseases and in iatrogenic immunosuppression.

In the current situation, with BCG vaccination in risk groups and contact research after the infection in the remainder of the population, tuberculosis is identified in some 50 children each year in the age bracket up to 15 years. This diagnosis is often made during contact research after tuberculosis is reported in an adult. The diagnostic process in children is more difficult. The borderline between latent and active tuberculosis is less pronounced in children, and the clinical picture is more difficult to recognise. Bacteriological diagnosis is also complicated, whereas children develop disease symptoms and serious complications such as meningitis and miliary tuberculosis more rapidly and frequently. It is difficult to estimate the number of children that would develop tuberculosis or severe complications if BCG vaccinations were to be discontinued, among other things due to difficult recognition and diagnostics, whereby cases could be missed.

Even though the number of children with tuberculosis in the Netherlands is low, targeted vaccination continues to be a serious option in view of:

1 The severity of potential symptoms and the rapid course of disease,
2 Multi-drug treatment required for six months or more,
3 Increased risk within migrant groups,
4 The higher vulnerability of children under five years of age,
5 The risk that tuberculosis in children with severe complications is not identified by contact research but as a result of presenting complaints and
6 The difficulty of diagnosis in children.

The Committee therefore regards tuberculosis in risk-group children as a significant public health concern.

Effectiviness and Safety of Vaccination

The protection afforded by the BCG vaccine against paediatric tuberculous meningitis and miliary tuberculosis is high. A protection rate of about 75 per cent against tuberculous meningitis and miliary tuberculosis may be assumed on the basis of effectivity studies of the number of disease cases after immunisation. Protection against other forms of tuberculosis is less clear.

Although immunisation may theoretically interfere with the Mantoux test, which identifies infection, this drawback is much reduced with vaccination during the first year. In this case, potential infection may be also observed after immunisation. The BCG vaccine is the most effective means to prevent severe

forms of tuberculosis in children, and it offers a significant protection rate. Better alternatives are currently unavailable.

The vaccine may be termed safe: adverse events after correct administration are limited. This nevertheless implies that administration requires a strict protocol.

Acceptability of Vaccination

Testing against the vaccination feasibility criteria poses no impediments to continuation of the current BCG vaccination strategy. The groups with highest risk are the groups that benefit most from vaccination. The ratio between protection and burden is favourable at an individual level also. Immunisation is given at a time that no other vaccinations are administered.

Cost-effectiveness of Vaccination

It is currently not possible to compare costs and benefits of vaccination and contact research. Vaccination costs are not high. Cost-efficacy is commonly expressed in *Disability-adjusted life-years* (DALY) – a measure that correlates life years lost, mortality and years with serious disease. The cost-efficacy ratio of the current BCG vaccination strategy is about € 4,500/DALY, which brings it well within the generally accepted limits for preventive interventions.

Note that calculations involve a significant margin of uncertainty. The cost estimate seems low, but benefit estimates are also conservative. The Committee therefore feels that BCG vaccination of risk-group children continues to be cost-effective, even in the event of a higher cost calculation.

Priority

The Committee therefore considers the BCG vaccination of risk-group children urgent. This is a severe, often acute and at times fatal infectious disease against which parents cannot adequately protect their children.

Considering the fact that the incidence of tuberculosis in children is very low, timely identification is not easy. Furthermore, the severe complications of tuberculosis may have a very rapid course in very young children in particular. The clinical utility of prevention by source and contact research would seem limited in this group. Vaccination may largely prevent the serious consequences of tuberculosis in young children, still with very acceptable costs.

Resistance against the current drug arsenal is increasing. This too argues in favour of continuing the current strategy. Indeed the treatment of an infection detected on time not only becomes more difficult with increasing resistance, but also much more prolonged and costly.

Implementation

It is advisable to include BCG vaccination in the NIP. As a result, the target group will be reached more effectively and the immunisation rate registered more reliably. Registration is currently suboptimal in some Municipal Health Services; consequently, the immunisation rate must be estimated. This means that the target group may not have been adequately reached over the past years. Another benefit of NIP inclusion is that general practitioners, youth health care physicians and paediatricians will become more familiar with the vaccine and the disease.

Administering the BCG vaccination requires specific expertise and, for quality reasons, performance should be concentrated. Municipal Health Service tuberculosis control units are well equipped to this end.

If BCG vaccination of risk-group children is included in the NIP, all parties concerned will need to work together and make clear consents about performance, registration, follow up and data sharing for immunisation notices.

Adequate education is required to maintain BCG vaccination acceptance at a high level. The necessary information should be readily accessible, both for population groups where BCG vaccination may be required and for health service professionals.

Conclusion and Recommendation

The current BCG vaccination strategy calls for immunisation of children with one or two parents from a country where the incidence of tuberculosis exceeds 50 cases per 100,000 inhabitants. These children receive notice around the age of six months. Children from these groups who were not born in the Netherlands or not immunised may receive catch-up vaccinations up to the age of 12 years.

This policy satisfies all seven criteria for inclusion of vaccination in a public programme. This is an effective and possibly cost-saving intervention. The Committee therefore advises the Minister to continue the current strategy. Continuation of the current policy involves the immunisation of risk-group children where incidence in the land of origin exceeds 50/100,000. This also implies that

children from some EU states and Suriname should be eligible. These children did not always receive notice in the past.

In total, this involves an estimated 24,000 infants each year.

The Committee is of the opinion that from an administrative perspective, BCG vaccination should come under the NIP in order to optimally reach the target group and better document the immunisation rate. We already have efficient collaboration between Regional Coordination Programmes and Child Health Care Centres to reach the target group. This could also be utilised for BCG vaccination. From a care quality perspective, the Committee recommends to concentrate organisation, implementation and execution of BCG vaccination, e.g. at the Municipal Health Service tuberculosis units. The Committee recommends to ask organisations involved with immunisation to draft a joint proposal for practical organisation and collaboration.

In conclusion, the Committee recommends that the Netherlands also contribute to medical research of a novel and improved vaccine. Around the world tuberculosis is a serious, very common infectious disease. The disease is in principle curable but resistance is becoming an increasing problem. High-level vaccination control programmes are currently not feasible, seeing BCG vaccine efficacy is highest in the prevention of severe complications of tuberculosis in children. Even though an alternative to BCG will not become available in the near future, various new vaccine candidates have shown promising results in preclinical studies.