SELECTIVE BCG VACCINATION IN A COUNTRY WITH LOW INCIDENCE OF TUBERCULOSIS

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In 1975 the BCG vaccination policy in Sweden changed from routine vaccination of all newborn infants to selective vaccination of groups at higher risk. This report aims to evaluate the present BCG policy, with focus on the tuberculosis situation in Sweden during the period from 1989 to 2005. The population structure in Sweden has changed, with increasing numbers and proportions of people who were born outside Sweden, especially in countries with high prevalence of tuberculosis. BCG vaccination coverage fell from more than 95% before 1975 to less than 20% in 1976 to 1980, and then again increased to around 16% (corresponding to about 88% of the risk group recommended for vaccination). The increasing proportion of foreign born tuberculosis patients among all tuberculosis cases of illness in Sweden, and the high age-specific incidence of tuberculosis in the childbearing age groups in the foreign-born population, indicate the need to continue selective vaccination of children in families originating from countries with high tuberculosis incidence. The cumulative incidence of tuberculosis in the 30 cohorts born in Sweden after 1974 and which reached the end of 2004 was estimated at 0.5 cases per 100,000 person-years.

Sweden still has one of the lowest incidences of tuberculosis in the world, which means a minimal average risk of infection for the majority of children born to Swedish parents. The observed increase of tuberculosis in 2005, partly attributed to an outbreak at a day nursery, is a reminder of the serious consequences of delayed diagnosis. Intensified active case finding is the most important action to prevent childhood tuberculosis, by means of eliminating the sources of infection to prevent transmission to the child population. Early detection and treatment of infected children is necessary to prevent development of serious disseminated tuberculosis.

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References


After 1975, the risk groups targeted for BCG vaccination in childhood included children and young people fulfilling at least one of the following criteria:

- A family history of tuberculosis (present or previous, even if long time ago) or close contact with other persons with tuberculosis.
- Origin from continents or regions with high prevalence of tuberculosis, including children born in these regions, and children born in Sweden to parents who were born in these regions.
- Planned travel to high prevalence continents or regions involving close contact with the local population.
- Continents or regions with high incidence of tuberculosis or considerable higher incidence than Sweden are defined as follows: Africa, Asia, Latin America, eastern Europe, central Europe, Spain, and Portugal.

Up to 1993 children born to parents from Finland were also offered BCG vaccination. From 1975 to 1993, it was recommended that vaccination be given during the neonatal period. In 1994 the recommended age for vaccination was postponed until 6 months or older. The reason for postponing vaccination to six months was to avoid accidental vaccination of infants suffering from severe combined immunodeficiency syndrome [6].

However, in cases of overwhelming risk of infection, it is still recommended to give vaccination soon after birth. In these cases, vaccination must be preceded by a careful assessment of family history regarding any occurrence of immune deficiencies or infant deaths in any close family members, in cousins or in siblings to the parents.

Methods

The analysis presented in this paper is mainly based on surveillance available data - routine surveillance of BCG-vaccination coverage and TB statutory notifications - and on previous studies on the impact of the BCG vaccination policy change.

Vaccination coverage

The BCG vaccine used in Sweden, from the introduction of vaccination in 1926 until 1978, was based on the Swedish BCG strain, named Gothenburg. Since 1979 the SSI vaccine, based on the Danish BCG strain Copenhagen 1331, and produced at Statens Serum Institut in Copenhagen, has been used in Sweden.

Estimates of the BCG vaccination coverage are based on nationwide annual reports given since 1981 to the Swedish Institute for Infectious Disease Control from all child health centres in Sweden. During the period from 1981 to 1983, vaccination status was reported for all children aged 0-6 years, and for two year old children only from 1984. The reports for the period 1981 to 1997 cover information on BCG vaccination status for at least 92% of preschool children born during the period from 1974 to 1994 (information missing from two of 24 counties) and from 1998 the reports cover 99% of two year old children belonging to cohorts born in 1995 to 2002. For the most recent period, information was obtained regarding vaccination coverage related to the magnitude of the defined risk group to be vaccinated.

Adverse vaccine reactions must be reported to the Medical Product Agency [4, 6].

Target population for BCG vaccination

Among cohorts born in Sweden between 1975 and 1985, about 12% were born to foreign born parents (one or both parents). The risk group targeted for BCG vaccination was calculated to comprise approximately 17 000 children (17%) per birth cohort. (These estimates are based on the annual statistical reports from the child health centres; the reported figures are in agreement with population statistics related to country of birth and parental origin, as reported in 2002 for age group 0-17 years).

TB notification

Tuberculosis is a notifiable disease according to the Communicable Disease Act. Incidence figures related to national origin for the period from 1984 to 1988 were based on the TB patients’ citizenship (previous or current) and therefore approximated (Swedish National Association against Heart- and Lung Diseases). Comparable figures related to country of birth (for population born in Sweden and born abroad, respectively) are available from 1989 onwards [2].

Population statistics

Population figures are based on data from population statistics, Statistics Sweden. The population of Sweden increased from 8.2 million inhabitants in 1975 to 9.0 million in 2004 and the number of foreign born inhabitants almost doubled from 550 000 (6.7%) to 1.1 million (12%). The proportion of immigrants from Africa and Asia increased from 0.3% to 3.7%. The annual number of live born infants varied during the same period between 90 000 and 124 000. For cohorts born in Sweden in 1969 or later, population figures related to country of birth and to national origin of the parents were specifically requested from Statistics Sweden for calculations of the incidence figures during the first study periods from 1969 to 1993.

Results

Vaccination coverage

Among cohorts born during the first five year period (1976 to 1981) following the changed BCG policy, vaccination coverage of newborns fell from at least 95% (before 1975) to below 2%. This level was too low to cover the risk group. Nurses at the child health centres were given more information and education about the reasons for the change to selective vaccination, and in particular, about the case definition for risk groups to be vaccinated. There was a gradual increase of vaccination coverage from 1982 onwards, reaching levels above 15%, among cohorts born in 1998 and later. The BCG coverage of children in the defined risk groups was estimated at about 88% among children born during the period 1998 to 2002. On average, these figures correspond to 15 000 BCG vaccinated children per birth cohort (annual reports on vaccination statistics from child health centres, Swedish Institute for Infectious Disease Control).

Serious vaccine adverse reactions

Three cases of BCG osteitis were reported among 3500 infants born and vaccinated neonatally with the vaccine based on the Gothenburg strain during the period from 1975 to 1978 [1]. After 1979, a few cases of clinically suspected BCG osteitis have been reported, but none have had bacteriologically confirmed diagnosis of BCG infection. During the period from 1979 to 1991, four cases of serious disseminated BCG infection occurred among 101 000 neonatally vaccinated infants [6]. Three of the infants suffered from severe combined immunodeficiency (SCID) and two of them died because of the BCG infection. These incidents were the impetus for the decision to postpone the ‘routine’ vaccination of risk groups to the age of six months or later. By that age, it was considered that any infant with severe combined immune deficiency would have been diagnosed and thus excluded from vaccination [5,6]. No case of fatal neonatal disseminated BCG infection has been reported since 1991.
Epidemiology of tuberculosis

In 1984, Sweden became a low incidence country, with fewer than 10 cases (all forms) of tuberculosis per 100 000 population [7]. During the period from 1989 to 2005, the previous declining trend [FIGURE 1] slowed down and then increased in 2004, and the incidence in 2005 was 6.4 per 100 000 population. The incidence of highly infectious (that is, sputum smear positive) pulmonary tuberculosis varied during the same period between 1.8 and 1.1 per 100 000, with 1.5/100 000 in 2005.

Figure 1
Annual incidence of tuberculosis per 100 000 population in Sweden during the period 1969 to 2005, and related to national origin of the population during the period from 1984 to 2005

Source: [2]

In the Swedish born population, the incidence of tuberculosis per 100 000 declined from 5.1 in 1989 to 1.5 during 2004, but then increased to 2.0 in 2005. In parallel, the proportion of foreign born tuberculosis patients increased from 34% in 1989 to more than 70% during the last four years. The estimated incidence in the foreign born population has remained on an average level of about 30 cases per 100 000 population per year, but increased to 38 in 2005. In different subgroups of the population, such as the African born population, incidence was more than 200 per 100 000 population. The average age specific incidence were highest in age groups 18-44 years in the population has remained on an average level of about 30 cases per 100 000 population per year, but increased to 38 in 2005. In different subgroups of the population, such as the African born population, incidence was more than 200 per 100 000 population. The average age specific incidence were highest in age groups 18-44 years in the foreign born population, at 58 per 100 000 during 2005 compared with 0.6 in the same age group in the Swedish born population.

The proportion of tuberculosis cases in age groups below 15 years of age amounted, on average, to 4% during the period from 1989 to 2004, but increased to 7% in 2005. The majority of children were born abroad (66% of all paediatric cases) or born in Sweden to foreign parents (20%), and were therefore in the risk groups targeted for BCG vaccination. In age group 0-14 years the average annual incidence per 100 000 population during the period 1989 to 2005 varied during different years from 0.5 to 2.6, in children born in Sweden variations from 0.1 to 2.0 and in foreign born children variations from 6.9 to 41.7.

It was expected that the immediate impact of the changed BCG policy in 1975 would be observed mainly in the youngest age group under five years of age, among children born in Sweden who were no longer vaccinated. Despite a temporarily increased level during the period 1979 to 1983 [1], the annual incidence of tuberculosis in children remained low, varying between 0 and 1.9 per 100 000 during the period 1975 to 2004. The corresponding incidence in children born abroad varied between 0 and 90 per 100 000. During 2005 tuberculosis incidence increased dramatically among children born in Sweden, up to 4.6 per 100 000 [FIGURE 2]. This increase was related to an outbreak at a day nursery, where 20 small children were diagnosed with active tuberculosis in connection with contact tracing around a person who had worked several months at the nursery, despite cough and other symptoms of illness, before the diagnosis of infectious tuberculosis [9].

Figure 2
Annual incidence of tuberculosis per 100 000 children aged 0-4 years in Sweden: all children from 1969 to 2005, and Swedish-born children only from 1975 to 2005

Sources: [1,2]


Today thirty birth cohorts have been born in Sweden after the changed BCG policy. The oldest cohort (born in 1975) was observed during 29 years and the observation period for the youngest one (born in 2004) was on average six months. Up to the end of 2004 the cumulative number of reported cases of active tuberculosis in these birth cohorts amounted to 227, which corresponds to 0.5 per 100 000 person years i.e. on average less than one case per birth cohort per year of observation. The cumulative number of children developing tuberculosis before five years of age was 121 corresponding to 0.8 cases per 100 000 person years. Tuberculosis was diagnosed before 12 months of age in 26 infants i.e. 0.9 per 100 000 live born children. Fifty-seven per cent (129/227) of all cases belonged to the main risk group targeted for BCG vaccination, i.e. born in Sweden to foreign parents. A history of previous BCG was reported in 45% of this risk group (58/129) including 27% (7/26) of infants younger than 12 months of age.

According to information in the notifications of sources of infection, most children were infected by their parents or by other household contacts. In several occasions the source of infection was identified after the diagnosis of tuberculosis in the child. In some cases infection might have occurred during travel abroad [8]. Genetic typing of isolated strains of Mycobacterium tuberculosis has also confirmed transmission from occasional contacts in the community.

The main benefits of BCG vaccination is protection against serious disease, meningeal and/or miliary tuberculosis, therefore increased awareness was directed to the occurrence of these manifestations in the cohorts born in Sweden in 1975 or later [1,10,11]. In total seven children developed serious illness, which corresponds to 0.016 per 100 000 person years. Three of them died. Four of the seven children belonged to the risk group in which vaccination is targeted for BCG vaccination. Only two of them have been BCG vaccinated, but as shown later, they had been exposed before the vaccination. One infant was diagnosed with tuberculosis at seven weeks of age and died. His mother developed tuberculous meningitis after delivery. This case of perinatal infection could not have been prevented by BCG vaccination [11].
Discussion

Previous evaluations of the impact of the changed BCG policy in Sweden, during six years and during 14 years, respectively, demonstrated an increased incidence of tuberculosis in the mainly non-BCG vaccinated birth cohorts born in Sweden after 1975 compared to those born during period of general vaccination in 1969 to 1974.

Cumulative incidence rate before 5 years of age increased from 0.8 to 3.9 per 100 00 children born to Swedish parents and from 2.6 to 39.4 per 100 000 children born in Sweden to foreign parents. In the non-BCG vaccinated child population the incidence of tuberculosis was on average ten times higher among children born in Sweden to foreign parents than in those born to parents of Swedish origin. However, in parallel with improved BCG coverage of the risk group population, the incidence of tuberculosis declined in children born in Sweden to foreign parents [8].

The observed increase of tuberculosis in children after 1975 indicated a protective efficacy of about 85% for the vaccine used in 1969 to 1974. The observed decrease of tuberculosis in parallel with increasing BCG coverage of the risk group population indicated an effectiveness of the selective vaccination program at 82%. However, there are several limitations to be considered, especially the small number of cases, the wide confidence intervals and the retrospective analysis of the period from 1969 to 1974, which implies uncertainties in the calculations [8].

The tuberculosis trend during the past fifteen years, with increasing proportion of new cases of tuberculosis in the foreign born population and especially high incidence of tuberculosis in the childbearing age groups of the foreign population, means an increased risk of exposure for children in these families and the continuous need for them to receive BCG vaccination. However, the optimal age for vaccination to be performed is still a matter of discussion. A small number of children in risk group have been exposed to tuberculosis before receiving BCG vaccination at six months of age or later.

Despite the observed increase in 2004 and 2005, Sweden still has one of lowest incidences of tuberculosis in the world and the incidence of sputum smear positive tuberculosis in the population born in Sweden is very low, 0.5 per 100 000 in 2005. This means a minimal risk of infection for the majority of Swedish born children, which still supports the decision to restrict vaccination to high risk groups [8].

One advantage of the restricted BCG policy is that when non-BCG vaccinated children are unexpectedly exposed to tuberculosis, it will be easier to disclose latent tuberculosis infection by means of the tuberculin skin test than it would be among BCG vaccinated children [12]. However, new methodology with in vitro test of specific cell mediated immunity to M. tuberculosis will make it possible to also diagnose latent infection in BCG vaccinated individuals [13].

The recent outbreak in a day nursery shows that the favourable situation reported in Sweden is subject to change, and serves as a reminder of the serious consequences of delayed diagnosis [11]. Intensified active case finding to identify and treat the sources of infection and therefore avoid infecting children is the most important action to prevent childhood tuberculosis. Early diagnosis and treatment of infected children is crucial to prevent development of serious disseminated tuberculosis. The greatest danger in a country with low incidence of tuberculosis is that the diagnosis might be neglected.

References

2. Swedish Institute for Infectious Disease Control and Swedish Heart Lung Foundation. The Swedish Tuberculosis Index. ISSN 1103-4955.