Evaluation of the Norwegian Adolescent BCG Vaccination Programme in a Nordic Perspective

Arne Broch Brantsæter

Master of Public Health

MPH 2008:20

Nordic School of Public Health

Evaluation of the Norwegian Adolescent BCG Vaccination Programme in a Nordic Perspective

ISSN 1104-5701
ISBN 978-91-85721-59-7

NHV – Nordiska högskolan
för folkhälsovetenskap

MPH 2008:20
Dnr U12/04:161

Master of Public Health
– Examensarbete –

Examensarbetets titel och undertitel
Evaluering av det norske BCG – vaksinasjonsprogrammet for ungdommer i et nordisk perspektiv

Författare
Arne Broch Brantsæter

Författarens befattning och adress
Overlege
Sykehuset Asker and Bærum HF, Medisinsk avdeling, Postboks 83, N-1309 Rud, Norway

Datum då examensarbetet godkändes	Handledare NHV/extern
2008-01-25	Einar Heldal, MD, PhD

Antal sidor	Språk – examensarbete	Språk – sammanfattning	ISSN-nummer	ISBN-nummer
46	engelsk	norsk/engelsk	1104-5701	978-91-85721-59-7

Sammanfattning
Mål: Å vurdere effekten av det norske BCG-vaksinasjonsprogrammet blant ungdommer ved (1) å vurdere om forskjeller i tuberkuloseepidemiologi i fire nordiske land er assosiert med forskjeller i bruk av BCG og (2) å estimere betydningen av BCG vaksinasjon blant ungdommer i Norge.
Metode: Studieperioden var 1975-2005, med hovedvekt på 1996-2005. Artikler, overvåkingsrapporter, EuroTB-databasen og nasjonale tuberkuloseregistre var datakilder. Data fra EuroTB ble brukt til å beregne insidensrater for tilfeller rapportert som "born in country/national" i Norge, Sverige, Finland og Danmark. Data fra de norske og svenske tuberkuloseregistrene ble brukt til å beregne insidensrater for tilfeller som var født i de respektive land og som hadde foreldre som begge var født i et land med lav insidens av tuberkulose. Insidensrater for aldersgruppene 0-14 and 15-29 år ble sammenlignet
Hovedresultater: Fra 1975 til 2005 var det et fall i insidensrate i alle landene, mest uttalt i Finland. I 1996-2005 hadde Finland lavest insidensrate i aldergruppen 0-14 år, og Norge hadde lavest insidensrate i gruppen 15-29 år. Dette er forenlig med beskyttende effekt som følge av BCG-vaksinasjon av nyfødte i Finland og av 12-14-åringer i Norge. Vi estimerer at det norske BCG vaksinasjonsprogrammet blant ungdommer gir 61-64% beskyttelse i aldersgruppen 15-29 år. Om man forutsetter 50-80% beskyttelse, er det nødvendig med 14918 - 51409 vaksinasjoner for å forebygge ett tilfelle av tuberkulose. I 1996-2005 kan tidligere BCG-vaksinasjon blant ungdommer ha forebygget 1,2 – 3,9% av tilfeller av tuberkulose blant norskfødte, og 0,4 – 1,2% av totalt antall tilfeller.
Konklusjoner: BCG-vaksinasjon av norske ungdommer med lav risiko for tuberkulose kan ha bidratt til redusert risiko for tuberkulose i en periode på 15 år etter vaksinering. Men et stort antall vaksinasjoner er nødvendig for å forebygge ett tilfelle.

Nyckelord
tuberkulose, BCG, overvåking, nordiske land

NHV – Nordic School of Public Health

MPH 2008:20
Dnr U12/04:161

Master of Public Health
– Thesis –

Title and subtitle of the thesis
Evaluation of the Norwegian Adolescent BCG Vaccination Programme in a Nordic Perspective

Author
Arne Broch Brantsæter

Author's position and address
Consultant
Asker and Bærum Hospital, Dept. of Internal Medicine, POB 83, NO-1309 Rud, Norway

Date of approval	Supervisor NHV/External
January 25, 2008	Einar Heldal, MD, PhD

No of pages	Language – thesis	Language – abstract	ISSN-no	ISBN-no
46	English	Norwegian/English	1104-5701	978-91-85721-59-7

Sammanfattning

Purpose: to assess the effectiveness of the Norwegian adolescent BCG vaccination programme by (1)examining if differences in tuberculosis epidemiology in four Nordic countries is associated with different use of BCG and (2) using evidence from this and past studies on BCG efficacy to estimate the impact of vaccination in the present epidemiological situation.

Method: The study period was 1975-2005, with main focus on 1996-2005. Data sources were articles, surveillance reports, the EuroTB database, and national tuberculosis registers. EuroTB data were used to calculate incidence rates for cases reported as "born in country/national" in Norway, Sweden, Finland and Denmark. Data from the Norwegian and Swedish tuberculosis registers were used to calculate incidence rates for cases that were born in the respective countries and that had parents who were both born in countries with low incidence of tuberculosis. Incidence rates in the age groups 0-14 and 15-29 years were compared.

Main results: From 1975 to 2005 all countries experienced a reduction in incidence rates, most pronounced in Finland. During 1996-2005 Finland had the lowest incidence rate in the 0-14 year age group, and Norway had the lowest incidence rate in the 15-29 year group. This is consistent with protection by BCG vaccination of newborns in Finland and of 12-14 year olds in Norway. We estimated that the Norwegian adolescents BCG vaccination programme confers 61-64% protection in the age group 15-29 years. Assuming 50-80% protection, 14 918 - 51 409 vaccinations are needed to prevent one case of tuberculosis. During 1996-2005, prior BCG vaccination of Norwegian teenagers may have prevented 1.2 - 3.9% of cases of tuberculosis among Norwegian-born and 0.4 - 1.2% of total cases.

Conclusions: BCG vaccination of low-risk Norwegian adolescents may have contributed to reduced risk of tuberculosis for a period of 15 years after vaccination. However, a large number of vaccinations must be given in order to prevent one case of tuberculosis.

Nyckelord
tuberculosis, BCG, surveillance, Nordic countries

Table of contents

Introduction/Background

Tuberculosis

Tuberculosis is one of the oldest diseases known to mankind and is caused by the bacteriae *Mycobacterium tuberculosis*, *M africanum* and *M bovis*. *M tuberculosis* was first identified by Robert Koch in 1882, a discovery for which he was later awarded the Nobel Prize in 1905. Infection usually requires close and prolonged contact with a person with infectious lung tuberculosis. Only 5-10% of people infected will develop disease, often many years after infection. Globally, tuberculosis is one of the major causes of infection related morbidity. One third of the world's population is infected with tuberculosis and has latent disease. Globally there are almost 9 million cases and 2 million deaths annually, but incidence and notification rates vary greatly (1).

In our neighbouring Baltic countries and Russia there has been a sharp increase in tuberculosis since 1990. Furthermore, in these countries 10-15% of cases are caused by multi-drug resistant tuberculosis (MDRTB). There has been concern that increased contact and travel between these countries might be a source of infection in people living in Norway.

Tuberculosis is a disease that is closely linked to poverty, aggravated internationally by the HIV epidemic. The incidence of tuberculosis among persons born in Norway has been steadily decreasing over several decades (2) (Figure 1). However, this trend has been counteracted by a gradual increase in tuberculosis among immigrants from high-prevalence countries. The end result is a fairly stable incidence of tuberculosis in Norway in recent years, with 230-300 cases being reported annually.

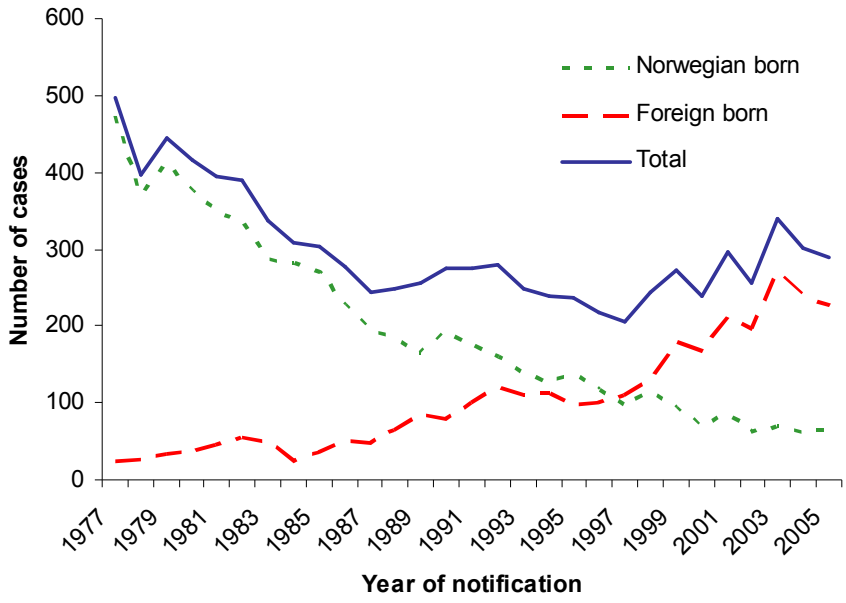

Figure 1 Number of notified cases among Norwegian and foreign born in Norway, 1977-2005

"Finger print" analysis of tuberculosis isolates has shown that there is little transmission of disease between immigrants and Norwegian-born (3,4).

The BCG vaccine - indications and protective effect

Bacillus Calmette-Guérin (BCG) is a live attenuated vaccine first derived from a virulent strain of *M bovis* by Edmond Nocard in 1902. After 230 serial passages of *M bovis* over 13 years in special media, Calmette and Guérin derived a stable attenuated bacillus named after them. It was initially given by the oral route, for the first time in 1921. This form of administration was later replaced by intracutaneous injection.

The WHO recommendations for the use of BCG vaccination are shown in the text box below (5).

BCG vaccination is indicated

- for all infants living in areas where TB is highly endemic
- for infants and children at particular risk of TB exposure in otherwise low-endemic areas
- for persons exposed to multidrug-resistant Mtb (impact not established)

BCG vaccination is contraindicated

- for persons with impaired immunity (symptomatic HIV infection, known or suspected congenital immunodeficiency, leukaemia, lymphoma or generalized malignant disease)
- for patients under immunosuppressive treatment (corticosteroids, alkylating agents, antimetabolites, radiation)
- in pregnancy

Studies on the protective effect of BCG vaccination have shown great variation, and several meta-analyses have been conducted (6). The protection offered by BCG vaccination is best documented for newborns (7). Against tuberculous meningitis and meningeal disease, most common in small children, the efficacy was 81% (8). The protective effect against tuberculosis was 63-74% and against death 65-71% (7,9). BCG vaccination of newborns and infants significantly reduces the risk of tuberculosis - by over 50%, on average (9) . Rates of protection against cases that were confirmed by laboratory tests, reflecting reduced error in disease classification and consequently more accurate estimates of BCG efficacy, were 83% (7).

However, there is also evidence of vaccine protection when administered after the neonatal period. In Norway a non-randomised study of 12-14 year old school children vaccinated during the period 1956-1973 showed a protective effect of 81% during a follow-up period of 10 years (10). For the first five years the protective effect was 90%

and for the next five years was 56%. Protection against infectious tuberculosis (cases with number of bacilli sufficiently great to be detected by microscopy) was 59% for the entire 10 year period. Randomised studies from Britain on vaccination of 15 year olds with follow-up from the 1950s to the 1970s showed a protective effect of 77% during the first 20 years (11). During the last 5 years of follow up there were too few cases to make a reliable assessment of vaccine efficacy.

In the late 1920s BCG vaccination of tuberculin-negative Norwegian nursing students before entering TB wards reduced the development of tuberculous disease by > 80% during a 3-year observation period (12). Similar results were found in medical students (13). Although, these studies have been criticised for not having been randomised, the results were the basis for the implementation of BCG vaccination in Norway after the Second World War.

In Sweden the efficacy of BCG vaccination of military recruits in the 1940s was 69% during the follow-up period of 6 months to 5 years; 20% from 5 to 15 years, and 54% for the whole period from 6 months to 15 years (14).

A comparison of tuberculosis age specific incidence trends in Norway, Sweden, Denmark and two states in the USA during the period 1948-61 demonstrated that trends were more favourable among age groups in the respective countries in the immediate years following vaccination compared to countries given vaccine at another age or no vaccine at all (15).

The protective effect of BCG against MDRTB seems to be within the same range of protection and was shown to be 69% in one study (16).

Based on these studies, there has been widespread agreement that the efficacy of BCG at best is around 80%. Until recently there was no evidence that the effect of BCG vaccination lasted for more than 15 years (17). The preventive effect of childhood vaccination on tuberculosis in adults has been variable (9). However, a recent meta-analysis from USA showed a protective efficacy of BCG of 52% lasting 50-60 years after vaccination (18). A study from Brazil also found protection lasting for up to 20 years (19).

BCG has generally been regarding as protective against tuberculous disease, not against infection. A recent study using novel interferon gamma assays, however, found that BCG also provided some protection against TBC infection (20).

The following factors are possible explanations for observed differences in the protection against tuberculosis offered by BCG vaccination (17,21-24).

- age at administration
- prior exposure to environmental non-tuberculous mycobacteria
- the BCG strain
- study design
- route of administration
- genetic differences in immune response

- risk of infection in the study population
- time since vaccination
- nutrition effect of immune response
- immune response due to helminth infection

Global use of BCG vaccination

Globally, BCG is one of the most commonly administered vaccines and the vaccination coverage at birth is high in most countries. WHO/UNICEF estimate for the period 1980-2006 estimate a coverage of over 90% in 110 countries (57%), 80-89% in 28 countries (14%), 50-79% in 20 countries (12%) <50% in 2 countries (2%), and was not applicable due to low incidence in 33 countries (25).

BCG vaccination in Europe

In 2005 a survey of BCG vaccination in all 25 EU countries and 5 other European countries, including Norway, demonstrated wide differences in vaccination policies (26). BCG was recommended nationally for all children under 12 months in 12 countries, in all older children in five countries, and only in children at risk (from origin, contact or travel) in 10 countries. Seven countries did not use BCG systematically. Since then, Britain has stopped routine vaccination of 10-14 year old school children (2005) and Finland has stopped routine vaccination of newborns (2006). In both countries children at high risk are selectively vaccinated.

BCG vaccination practice in Norway, Sweden, Denmark and Finland

In the Nordic countries, mass BCG vaccination was introduced during the 1940s but was never used in Iceland (27). The age and risk groups targeted for vaccination have varied over the years and continue to differ in these countries (Table 1).

Norway
In Norway BCG vaccination came into general use in 1947 (28). All Norwegian 12-14 year olds have been offered vaccination, except those already infected (tuberculin positive) and persons already vaccinated because of high risk of tuberculosis in earlier life. BCG vaccination was compulsory during the first decades after its introduction, but has been voluntary (recommended) since 1 January 1995. Although vaccination coverage is probably very high, exact data are lacking. Prior to 1996 coverage was estimated to be 97- 98%. After this time, the Norwegian childhood vaccination register (SYSVAK) has registered BCG coverage among 16 year olds. Between 1996-1999 statistics are not available. During the period 2000-2005 the registered BCG vaccination coverage was around 91% among persons targeted for adolescent BCG vaccination, but this is probably an underestimate of the actual coverage, as registration has been incomplete. Reasons for incomplete registration include lack of data entry by health personnel in the municipalities and technical problems in communication between electronic patient records and the SYSVAK database (personal communication, Synne Sandbu).

The vaccination of adolescents at low risk of tuberculosis is not in agreement with current WHO recommendations on the use of BCG vaccination (5).

Sweden
Sweden started universal vaccination of newborns in the 1940s, but this programme was stopped in 1975. At that time, the incidence of tuberculosis in the total population was 18 per 100 000. After 1975, tuberculosis increased slightly and transiently among non-BCG vaccinated cohorts, but the incidence in Swedish children remained low (29,30). Among cohorts born in Sweden from1975 to 2003 observed to the end of 2003 there were five cases of miliary or meningeal tuberculosis in non-vaccinated children, one of which died of congenital tuberculosis (Victoria Romanus, personal communication). Another two children developed serious TB one or two months after vaccination, although infected before the vaccination, and one of these died. Another case of military tuberculosis occurred in a 7 year old non-vaccinated girl in 2005.

In Sweden selective vaccination is offered to children at increased risk of tuberculosis exposure (31)

- previous or current tuberculosis in a close relative or household contact
- family origin in a country with high incidence of tuberculosis
- planned visit to a country with high incidence of tuberculosis if the child will have close contact with the local population.

Serious disseminated BCG infections developed in four infants vaccinated neonatally in Sweden during the period 1979-1991 (32). Three of the infants suffered from severe, combined, immunodeficiency syndrome, undiagnosed at the time of vaccination. Currently, children at high risk are offered vaccination at the age of 6 months, in order to prevent serious complications in patients with undiagnosed congenital immunodefiency. According to Swedish vaccination statistics, around 15% of children born each year are given BCG vaccination because they belong to a high-risk group (33).

Denmark
Denmark started routine vaccination of 7 year olds in 1949, but this programme was stopped in 1985 after a gradual decrease in coverage during the early 1980s. BCG vaccination has since almost stopped, but is still recommended for children travelling for long periods to high-prevalence countries (34).

Finland
Finland introduced mass vaccination of newborns in 1941, but this programme was stopped in September 2006, and has later been replaced by a programme that targets risk groups (35). Tuberculin testing and revaccination of tuberculin-negative school children was practised until 1990.

Presently children with at least one of the following risk factors for tuberculosis are targeted for BCG vaccination in Finland (36):

- one or both parents, siblings or other household members born in a country with high incidence of tuberculosis or have had tuberculosis
- planned move to a country with high incidence of tuberculosis

In addition, if the child has regular and close contact with persons with high risk of tuberculosis, or who have tuberculosis, vaccine may be offered on recommendation from a physician.

Table 1 Persons targeted for BCG vaccination in Norway, Sweden, Denmark and Finland, 2007

Country	All 12-14 year olds	All children with origin* in high-incidence countries	Family history of TB/contact with TB case	Travel to high-incidence country	Health personnel at high risk of TB exposure
Norway	X	X	X	X	X
Sweden		X	X	X	(X)
Finland		X		X	
Denmark				X	(X)

*having been born in or having parents from high-incidence countries

Consequences of discontinuing BCG vaccination — previous experiences

Several studies have demonstrated a transient increase in incidence of tuberculosis after stopping universal BCG vaccination. In Sweden the cumulative incidence of tuberculosis per 100 000 children before the age of 5 years born in Sweden of Swedish parents increased from 0.8 (during 1969-75) before discontinuation in 1975 to 3.9 during 1975-79, but then decreased to 2.9 as expected from mathematical models (30). This increase was even higher in children born of immigrant parents before being brought down by increased selective vaccine coverage.

Similarly, increased rates of infection were observed after stopping vaccination in Germany in 1975 (37). By comparing the increase in tuberculosis incidence after BCG discontinuation in one group with the incidence in a reference group continuing vaccination in the Czech Republic (1986), it was estimated that BCG vaccination conferred a protection of about 80% in newborns followed for up to 6 years (38).

BCG side effects

BCG is generally considered a safe vaccine, but minor adverse effects are common, and serious side effects are occasionally seen. Osteitis and disseminated BCG infection are severe but uncommon adverse reactions. The incidence of BCG associated adverse reactions correlate with the strain used in the vaccine (39). The risk of severe adverse reactions is particularly high in children with immunodeficiency. In Sweden BCG osteitis (29 per 100 000) was the main reason for discontinuing universal BCG vaccination (30). A rise in side effects in the form of adenitis and osteitis after changing BCG strain was also contributory to the recent Finnish decision to stop BCG vaccination (35).

Potential rationale for continued BCG vaccination of 12-14 year olds in Norway

Until recently, only Britain and Norway practised routine vaccination of older children and adolescents (aged 10-14 in Britain and 12-14 in Norway). When Britain replaced universal vaccination with a selective programme in September 2005 (40), impetus was added to the more than decade long debate in Norway over the need for continued universal vaccination of low-risk adolescents (41). In Norway there has been no systematic evaluation of the adolescent BCG vaccination programme, but in 1998 a report commissioned by the Norwegian Ministry of Health recommended continuing the existing programme, but that the use of BCG vaccination should be continuously assessed (28). Reasons provided for continuing universal vaccination of adolescents included

- No decrease in transmission pressure in recent years
- Increasing proportion of drug resistant strains of *M tuberculosis*
- Likely infection of adolescents travelling to high-prevalence countries
- BCG as travel vaccine likely to achieve low coverage due to long preparation time.
- Vaccination at the end of compulsory schooling last opportunity for reaching out to all. Most new infections in the following years.
- BCG vaccination is one of several measures that ensure a well functioning school health service

Potential rationale for discontinuing BCG vaccination of 12-14 year olds in Norway

In the above mentioned report, reasons provided for discontinuing universal vaccination of adolescents included (28)

- Low incidence of new infections makes it unreasonable to vaccinate all
- Complications of vaccinations
- Cost of vaccination

It was argued that following factors would be in favour of stopping BCG vaccination if observed in the future:

- Reduced inland transmission of tuberculosis
- Reduced risk of infection from abroad: a fall in incidence of tuberculosis and proportion of resistant isolates
- Reduced travel to countries with high incidence of tuberculosis
- Increasing number of adverse reactions
- No increase in incidence of tuberculosis among Norwegian-born adults

Tuberculosis in children mainly causes non-infectious tuberculosis which cannot easily be transmitted to others, whereas tuberculosis in adolescents and adults is more likely to cause infectious tuberculosis. Since protection after BCG probably wanes with time, this might offer a rationale for vaccinating adolescents rather than children.

Interpretation of tuberculin tests is made more difficult by prior BCG vaccination, and this is an additional argument for discontinuation of routine vaccination. Resources spent on BCG vaccination may be put to better use in other disease preventing and health promoting activities.

International criteria for discontinuation of BCG vaccination

In 1994 the International Union Against Tuberculosis and Lung Disease (IUATLD) published criteria for discontinuing BCG vaccination programmes in countries with low prevalence of tuberculosis (42). General requirements for a country considering discontinuation were

1. a well functioning tuberculosis control programme
2. a reliable reporting system over the previous 5 or more years, enabling estimation of the annual incidence of active tuberculosis by age and risk groups, with particular emphasis on tuberculous meningitis and sputum smear-positive pulmonary tuberculosis
3. due consideration given to the possibility of an increase in incidence of tuberculosis resulting from infection with the human immunodeficiency virus

Prior to discontinuing a BCG vaccination programme in a country with low prevalence of tuberculosis the following criteria should be met (text box):

- The average annual notification rate of sputum smear-positive pulmonary tuberculosis should be 5 cases per 100 000 population or less during the previous 3 years or
- The average annual notification rate of tuberculous meningitis in children under 5 years of age should be less than one case per 10 million general population over the previous 5 years
- The average annual risk of tuberculosis infection should be 0.1 % or less.

Norway clearly meets the two first criteria for discontinuing BCG vaccination programmes in countries with low prevalence of tuberculosis (42). The incidence of smear-positive pulmonary tuberculosis was approximately 3 cases per 100 000 population during the period 2003-2005, and no cases of tuberculous meningitis in children under 5 years of age were reported. It is difficult to assess the annual risk of infection because of the limitations of the tuberculin skin test with many false positive tests, but unpublished data indicate that among 14 year olds the annual risk of infection is below this threshold (Brita Winje, personal communication).

According to IUATLD, additional factors that need to be considered before stopping a BCG vaccination programme are costs (by calculating the number of cases that would be prevented by continuing BCG vaccination), adverse reactions, and the need for continued vaccination of risk groups (selective vaccination).

Purpose/Objective

The purpose of this study was to assess the effectiveness of the Norwegian adolescent BCG vaccination programme by

- examining if differences in tuberculosis epidemiology in four Nordic countries is associated with different use of BCG
- using evidence from this and past studies on BCG efficacy to estimate the impact of vaccination in the present epidemiological situation.

Methods

The study covers the period 1975-2005, with main focus on the period 1996-2005. Data sources included published articles, national surveillance reports, the EuroTB database (allowing password-protected on-line data query at www.eurotb.org, and other Internet resources. Additional information was obtained directly from the national tuberculosis registers in Sweden (Victoria Romanus) and Denmark (Peter Andersen). The MPH student (Arne Broch Brantsæter) and his supervisor (Einar Heldal) had direct access to data in the Norwegian tuberculosis register at the Norwegian Institute of Public Health.

Population data necessary for calculation of incidence rates were obtained from Statistics Norway, Statistics Sweden, Statistics Denmark and Statistics Finland, as required. The population data included total population, population born in the country, and population born in the country with two parents from countries with low incidence of tuberculosis. Population data for immigrants from countries with high incidence of tuberculosis were also obtained. Where insufficient data was available from the online population statistics databases, supplementary data were requested from the respective institutions.

In part one of our paper (Appendix), the number of cases of tuberculosis in persons classified as "born in country/national" was obtained from the EuroTB database. The category "born in country/national" generally represents a group at low risk of tuberculosis and include low-risk groups given BCG vaccination in Norway and Finland. Incidence rates in Norway, Sweden, Denmark and Finland were compared in order to assess possible impact of BCG vaccination of newborns in Finland and of Norwegian adolescents. However, persons classified as "born in country/national" include second generation immigrants from countries with high incidence of tuberculosis, and this may affect the incidence rates to different degrees depending on the size and origin of the second generation immigrants in the respective countries.

In part two of our paper (Appendix), we compare incidence rates among persons born in Norway or Sweden, respectively, of parents who were both born in a country with low incidence of tuberculosis. In Norway this low-risk group is offered BCG vaccination at the age of 12-14 years. Ideally, one would have liked to compare incidence rates of tuberculosis in corresponding low-risk groups in all four countries. However, it was only possible to obtain these data from the tuberculosis registers in Norway and Sweden, and only for the period 1996-2005.

Low-incidence countries, as presently defined in Norway, were all the countries of Western- Europe plus Poland, Hungary, the Czech Republic, Slovakia, Slovenia, USA, Canada, Japan, Australia and New Zealand. Portugal, Spain, Poland, Hungary, the Czech Republic, Slovakia and Slovenia were not considered low-incidence countries in Sweden. However, for comparison of incidence rates in part two, the Norwegian definition was used.

In order to assess the effectiveness of the BCG vaccination programmes targeting either Finnish newborns or Norwegian adolescents, three measures were used for comparison:

(1) incidence rates for the age group 0-14 and 15-29 years

(2) incidence rate ratios between the age group 15-29 and 0-14 *within* the countries (WCIRR), where

$$\text{WCIRR} = \frac{\text{incidence rate age } 15 - 29 \text{ years}}{\text{incidence rate age } 0 - 14 \text{ years}}$$

(3) (part two only): incidence rate ratios *between* Norway and Sweden (BCIRR), where

$$\text{BCIRR} = \frac{\text{incidence rate in Norway}}{\text{incidence rate in Sweden}}$$

for the age groups 0-14 years and 15-29 years.

Results

General tuberculosis epidemiology

Trends 1975-2005

From 1975 to 2005 all Nordic countries experienced a reduction in the total annual rate of notified cases of tuberculosis (Figure 2): Finland from 74.2-6.9 per 100 000, Sweden from 17.6-6.3 per 100 000, Norway from 12.5-6.3 per 100 000, and Denmark from 12.2 to 7.8 per 100 000 (1,27,43). Finland had the most impressive reduction in incidence rate during the period.

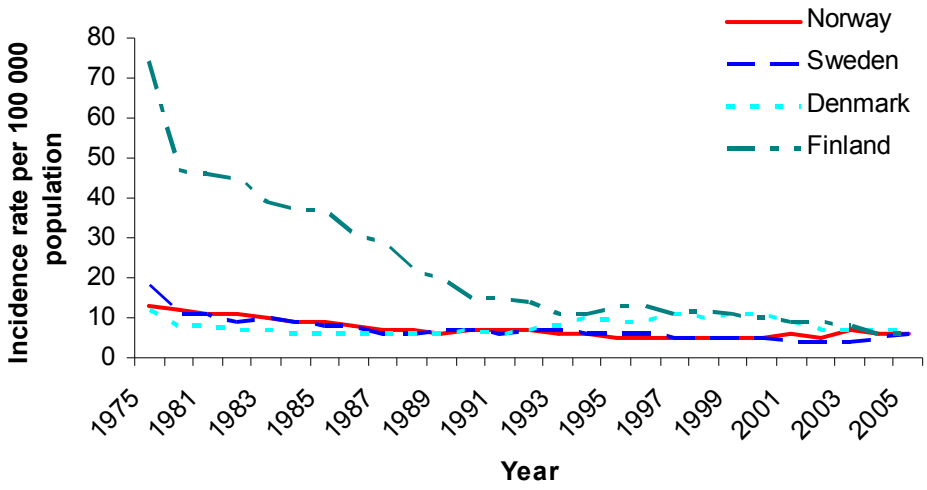

Figure 2 Crude incidence rate of tuberculosis in Norway, Sweden, Finland and Denmark, all ages, 1975-2005. Based on data in references (1,27)

From 1975 to 2005, the total incidence of tuberculosis for all age groups in non-immigrants in Norway (based on name from 1975-1995 and on country of birth from 1996) decreased from 12.3 to 1.5 per 100 000 person-years (Figure 3).

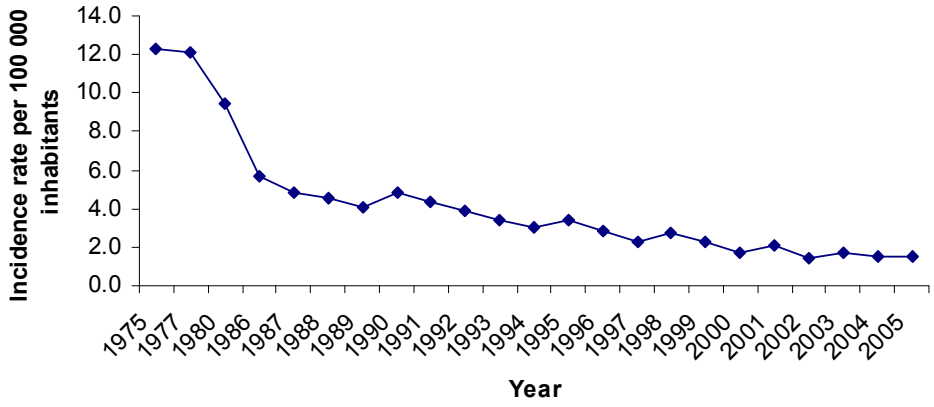

Figure 3 Total incidence rates of tuberculosis in non-immigrants in Norway, all ages, 1975 – 2005

Trends 1996-2005

During the period 1996-2005, the crude incidence rate was falling or stable in all four countries (Figure 4). Finland had the greatest drop in incidence rate during this 10-year period.

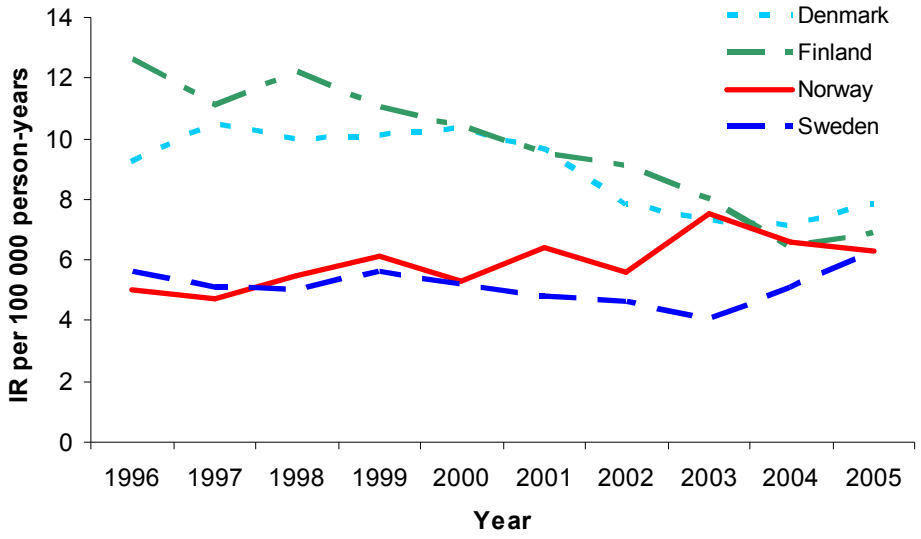

Figure 4 Crude incidence rates (IRs) of tuberculosis in Norway, Sweden, Denmark and Finland reported to EuroTB, 1996-2005

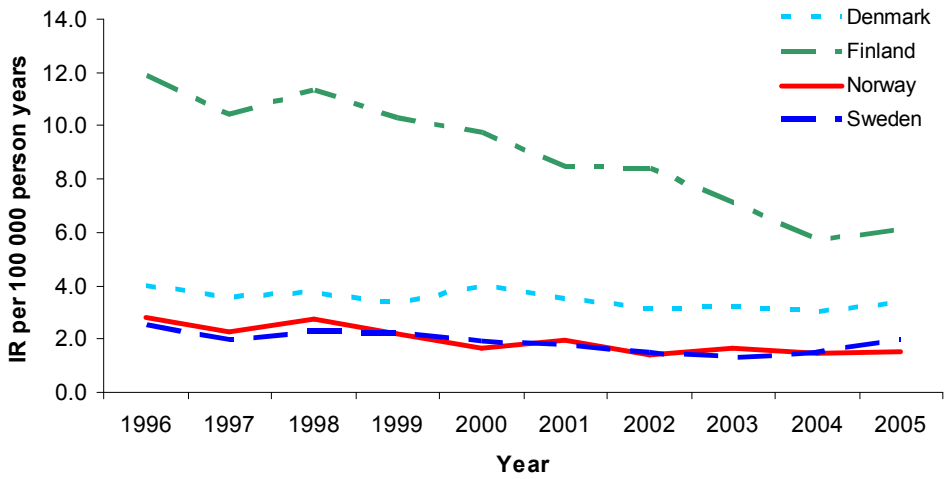

Figure 5 Incidence rate (IR) of tuberculosis in persons "born in country/national" in Norway, Sweden, Denmark and Finland reported to EuroTB, 1996-2005

Similar crude incidence rates in the four Nordic countries hide larger differences in incidence rates among persons of "born in country/national", due to differences in proportion of immigrants from countries with high incidence of tuberculosis (Figure 5). From1996 to 2005, among persons categorised as "born in country/national" in the EuroTB database, the decline in the respective incidence rates per 100 000 was highest in Finland (11.9-6.1), followed by Norway (2.8-1.5), Sweden (2.5 - 1.9) and Denmark (3.9-3.3). The incidence rates in Finland and Norway were approximately halved during the period, whereas the reduction was less pronounced in Sweden and in Denmark

In all countries except Finland, less than half of the cases with tuberculosis were in patients "born in country/national" (Figure 6).

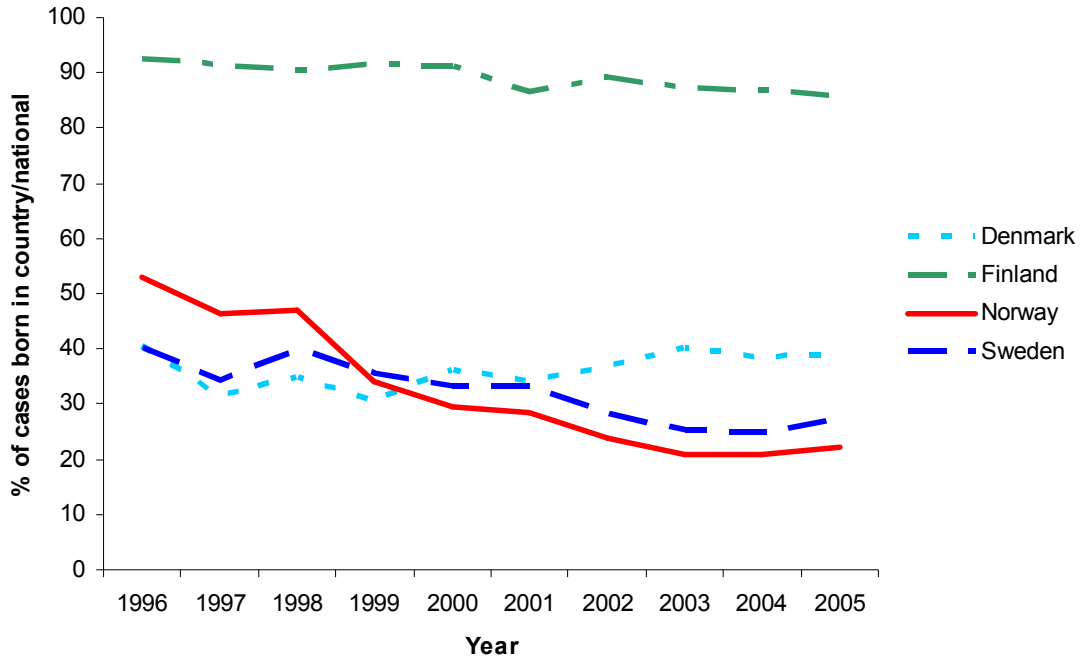

Figure 6 Percentage of cases with tuberculosis in Norway, Sweden, Denmark and Finland reported to EuroTB as "born in country/national", 1996-2005

Finland was the country with the lowest percentage of the population coming from countries with high incidence of tuberculosis, at least partially explaining the high percentage of tuberculosis cases among persons born in Finland as shown in Table 2.

Table 2 Average percentage of the population born in countries with high incidence of tuberculosis

Period	Proportion of population from high-incidence countries*			
	Norway	Sweden	Denmark	Finland
1996-1999	3.6	NA	3.7	1.5
2000-2005	4.8	6.6	4.6	2.0
1996-2005	4.3	NA	4.3	1.8

* High indicidence countries are defined as all countries other than countries of western- Europe plus Poland, Hungary, the Czech Republic, Slovakia, Slovenia, USA, Canada, Japan, Australia and New Zealand.

NA:not available

Source: Statistics Norway, Statistics Sweden, Statistics Denmark and Statitsics Sweden

Average total incidence rates and average incidence rates of tuberculosis in persons born in the respective countries during the period 1996-2005 are shown in Table 3. Finland had the highest incidence rate both in the total population and in persons classified as "born in country/national".

Table 3 Average incidence rates of tuberculosis in four Nordic countries in the total population and in persons categorised as "born in country/national", 1996-2005

	Norway	Sweden	Denmark	Finland
IR entire population	5.9	5.1	9.0	9.7
IR born in country	2.0	1.9	3.5	8.9

IR: Incidence rate per 100 000 person-years

In Norway the total incidence of tuberculosis was fairly constant during the period and was 6.3 per 100 000 inhabitants in 2005 (Figure 4). In 2005 the median age in Norwegian-born cases of tuberculosis was > 64 years, as compared to 25-34 years in immigrants. From 1996 to 2005, the incidence rate per 100 000 inhabitants among Norwegian-born dropped from 2.8 to 1.5 (Figure 5).The proportion of cases in persons born in Norway decreased from 53 to 22% during the period (Figure 6).

In Sweden, the total incidence of tuberculosis did not change much during the period, and was 6.3 per 100 000 inhabitants in 2005 (Figure 4). From 1996 to 2005, the incidence rate per 100 000 inhabitants among Swedish-born dropped from 2.5 to 1.9 (Figure 5). In 2005 the median age was > 64 years in Swedish nationals and 35-44 years in non-nationals. The proportion of cases in persons born in Sweden decreased from 44.1 to 27.1% during the period (Figure 6).

In Denmark there was a clear drop in incidence rate of tuberculosis during the last half of the period, and in 2005 the total incidence rate was 7.8 per 100 000 inhabitants (Figure 4). From 1996 to 2005, the incidence rate per 100 000 inhabitants among Danish born only dropped from 3.9 to 3.3 (Figure 5). In 2005 median age was 45-54

years in Danish nationals, which is also lower than in Norway and Sweden, and was 25-34 years in immigrants. Among the four nations, Denmark was the country with the smallest decrease in percentage of cases among persons classified as "born in country/national". The proportion of cases in Danish nationals was fairly constant during the period and was 39.2% in 2005, which is considerably higher than in Norway and Sweden (Figure 6).

Finland had a steady drop in incidence of tuberculosis during the period and was 6.9 per 100 000 inhabitants in 2005 (Figure 4). In 2005 Finland had by far the highest average incidence of tuberculosis among persons classified as "born in country/national" of the respective countries, 6.1 per 100 000, but having dropped from 11.9 in 1996 (Figure 5). In 2005, 85.3% of cases were Finish-born (Figure 6), and their median age was > 64 years. The median age in immigrants diagnosed in 2005 was 25-34 years.

Tuberculosis among persons below 30 years of age in Norway, Sweden, Finland and Denmark reported to EuroTB as "born in country/national", 1996-2005

In part one of our paper (Appendix, Table 1), we found that the incidence rate of tuberculosis in Finnish 0-14 year olds classified as "born in country/national" was significantly lower than in the other three countries, even though this country had the highest incidence rate for tuberculosis among non-immigrants. We also found that the incidence rate among Norwegian 15-29 year olds was significantly lower than in all other three countries, both in absolute terms and relative to the 0-14 year old group (WCIRR).

The annual incidence rates of tuberculosis in persons categorised as "born in country/national" in the age group 0-14 and 15-29 in the four countries for the period 1996-2005 are shown in Figure 7 and Figure 8.

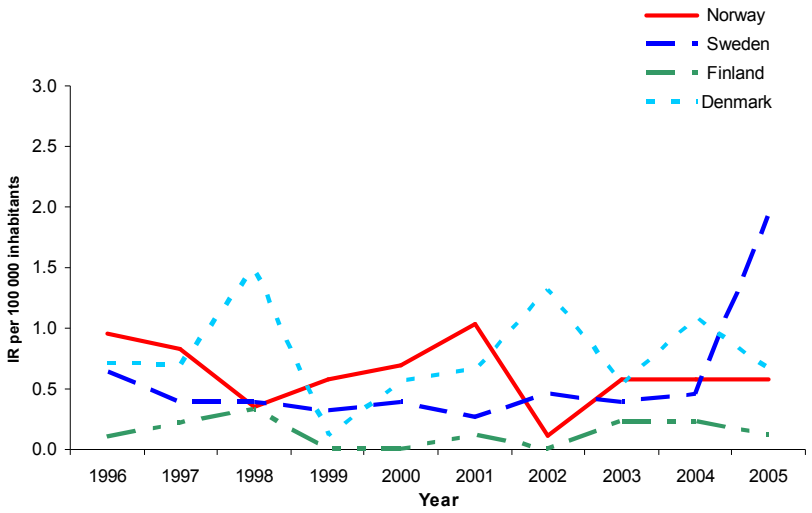

Figure 7 Incidence rate of tuberculosis among 0-14 year old cases "born in country/national" in Norway, Sweden, Finland and Denmark, 1996-2005

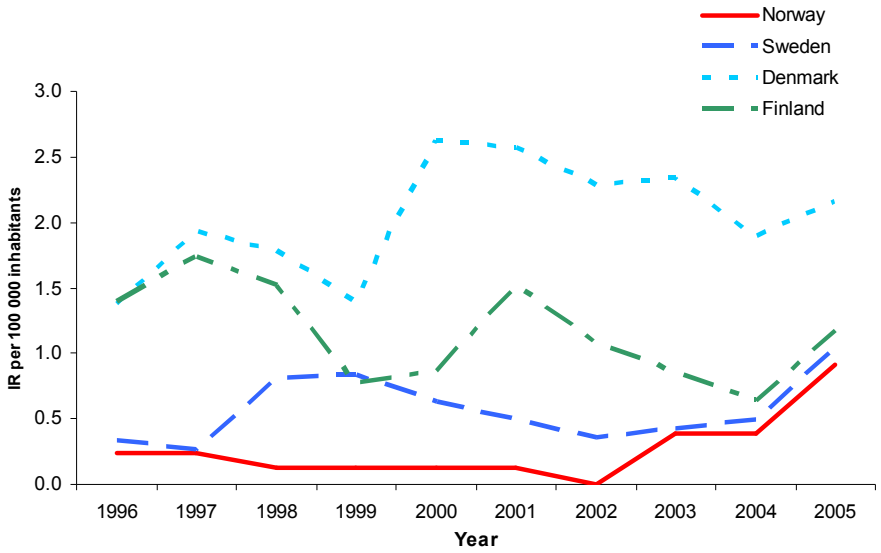

Figure 8 Incidence rate of tuberculosis among 15-29 year old cases "born in country/national" of Norway, Sweden, Finland and Denmark, 1996-2005

In Norway the incidence rate of tuberculosis in the 0-14 year age group was stable during the period, but in the 15-29 year age group there was an increasing incidence rate after 2002. The incidence rate of tuberculosis for persons born in Sweden below the age of 30 years was stable until 2005, when there was an outbreak of tuberculosis in a Swedish day-care centre which affected 18 children and which explains most of the increased incidence rate among 0-14 year olds in that year. In Denmark and Finland there was little change in incidence rate during the period.

Potential influence of previous and present vaccination programmes on the incidence of tuberculosis during 1996-2005 in the age groups 0-14 and 15-29 years

Persons in the 0-14 year age group were born from 1981-2005 and persons in the 15-29 year age group were born from 1967-1990. During this period there was no change in BCG vaccination policy in Norway that could affect the temporal change in the incidence of tuberculosis in these age groups. Persons born in Norway at low risk of tuberculosis were vaccinated at the age of 12-14 years, and high-risk children were vaccinated as newborn.

Finland practised universal newborn vaccination during the entire period. Revaccination of tuberculin-negative 11-13 year olds was stopped in 1990, but a later study showed that this did not affect the incidence of tuberculosis among adolescents (44).

In Sweden vaccination of neonates was stopped in 1975, which means that 0-14 year olds diagnosed during the study period not belonging to defined risk groups, would not have been vaccinated as a result of the previous universal neonatal vaccination programme. However, second generation immigrants from high-incidence countries continued to be offered BCG vaccination after 1975, and one would expect the group

classified as “born in country/national” to include some vaccinated second generation immigrants. In the age group 15-29 years, all persons born 1967-1974 were eligible for BCG vaccination under the previous programme, but if one assumes that BCG protection lasts for 15 years, previous BCG vaccination in this age group would not result in reduced incidence during 1996-2005.

In Denmark universal BCG vaccination was stopped in 1985, after some years of falling coverage. However, as the oldest birth cohort, vaccinated at the age of 7 according to the national programme, was born in 1977, no 0-14 year olds diagnosed during 1996-2005 would have been vaccinated. In the 15-29 year age group, some children (born 1967-1977) could have been vaccinated. If one assumes that the protective effect of BCG vaccination lasts from age 7 to 22 years (15 years), only persons born from 1974 - 1977 would have some protection. As the proportion of total life years contributed by these one year age cohorts is small (4 of 24 one year birth cohorts), the potential reduction in incidence as a result of BCG vaccination among 15-29 year olds would be expected to be small.

Tuberculosis in Norway and Sweden in persons below the age of 30 years with two parents from low-incidence countries, 1996-2005

In part two of our paper (Appendix, Table 2) we found that the incidence of tuberculosis in Norwegian 15-29 year olds with two parents from countries with low incidence of tuberculosis was significantly lower than in the corresponding Swedish age group.

In Norwegian-born children whose parents were born in low-incidence countries, 32 cases of tuberculosis were notified in the age group below 30 years during the period 1996-2005 (Figure 9). Of these, two children had one parent from Poland, and one child had a parent from Denmark (the latter with foreign name), all in the age group 0-14 years. All the other children had parents who were both born in Norway.

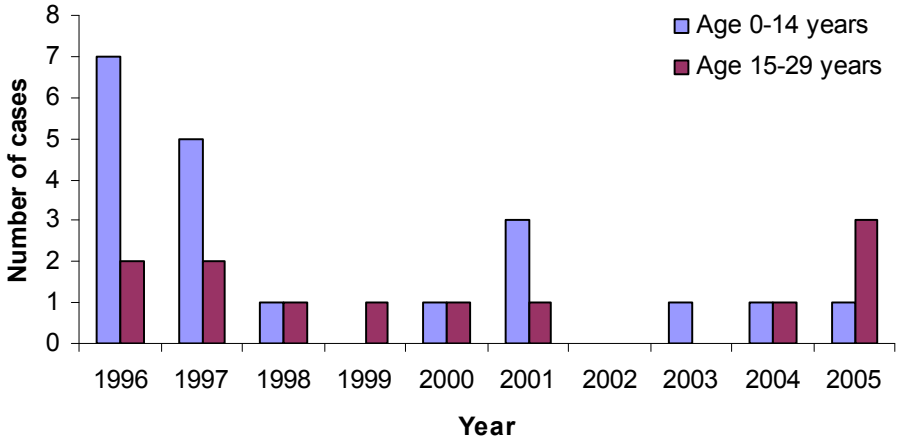

Figure 9 Number of cases notified with tuberculosis in Norway 1996-2005 in persons born in Norway and with both parents born in a low-incidence country

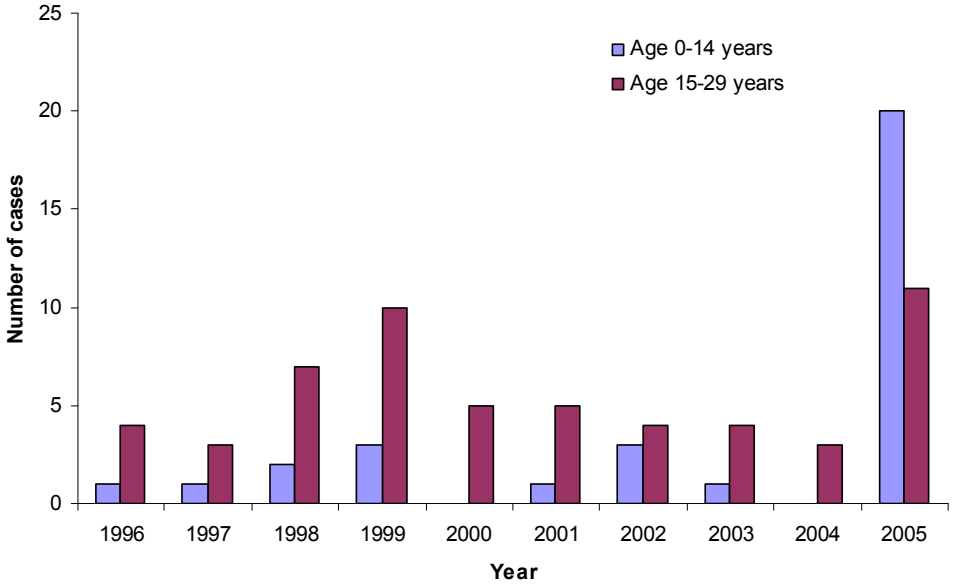

Figure 10 Number of cases notified with tuberculosis in Sweden 1996-2005 in persons born in Sweden and with both parents born in a low-incidence country

In Swedish-born children whose parents were born in low-incidence countries, 88 cases of tuberculosis were notified in the age group below 30 years during the period 1996-2005 (Figure 10).

For the total 0-29 year age group, total incidence rate was somewhat higher in Sweden than in Norway, mainly due to the high number of cases reported in Sweden in 2005. If the year 2005 is excluded and incidence rates are calculated for 1996-2004, the incidence rates for the 0-29 year group in Sweden and Norway become very similar, 0.23 and 0.21 per 100 000 life years, respectively. However, the incidence rate in the 15-29 year age group remains significantly lower in the Norwegian group (0.18 and 0.37 per 100 000 in Norway and Sweden, respectively). There was no significant difference in incidence rate in the 0-14 year group.

Estimation of the effectiveness of the Norwegian adolescent BCG vaccination programme

Results from part two of our paper (Appendix) indicate that the Norwegian adolescent vaccination programme may have conferred 61-64% protection against tuberculosis for the 15-29 year olds during the study period. If one uses a low end estimate of 50% protection and a high end estimate of 80% protection, it is estimated that between 1 and 3.2 cases are prevented annually in the age group 15-29 years. The number of adolescent vaccinations needed to prevent one case of tuberculosis in the age group 15-29 years is between 14 918 and 51 409. During the study period, the average total (all ages) annual number of tuberculosis cases reported in Norwegian-born was 83, and the average total number of cases was 264. In other words, BCG vaccination of Norwegian adolescents may have prevented 1.2 - 3.9% of cases of tuberculosis in Norwegian-born and 0.4 - 1.2% of total cases during the period 1996-2005.

Discussion

Incidence rates of tuberculosis among persons under 30 years of age – observed differences

When originally designing this study, we intended to compare incidence rates of tuberculosis in persons below the age of 30 born in Norway, Sweden, Finland or Denmark who had parents who were both born in countries with low incidence of tuberculosis. In this way we planned to ensure that cases come from a comparable low-risk background. However, it was only possible for us to obtain these data from Norway and Sweden. Therefore, as an alternative data source for all four countries, we analysed incidence of tuberculosis among cases reported to EuroTB as "born in country/national" (Appendix, part one).

Finland had the lowest incidence rate, both for total number of cases ("definite" and "other than definite") and culture verified ("definite") cases in the age group 0-14 years. Norwegian-born 15-29 year olds had the lowest incidence rate of tuberculosis both in the EuroTB category "born in country/national" (Appendix, part one) and in the comparison with Swedish cases born of parents that both were born in low-incidence countries (Appendix, part two).

However, when using data sources from different countries there are many possible sources of bias that may affect international and domestic comparison of incidence rates between age groups.

Differences in incidence rates of tuberculosis in persons born in the four countries – possible explanations

Possible explanations for observed differences in incidence rates include varying

1. application of the case definition
2. completeness of case detection and notification
3. risk of infection - in second generation immigrants and from immigrants originating in high-incidence countries, infection control measures and travel
4. risk of developing disease (effect of preventive therapy for latent infection and BCG vaccination)

From the above list it is clear that BCG vaccination, our focus of interest, is but one possible explanation for observed differences in incidence rates.

Application of the case definition

Norway, Sweden and Denmark report clinical cases without laboratory confirmation as other-than-definite cases, whereas Finland requires laboratory confirmation before reporting a case to EuroTB (Appendix, methods section). However, the same criteria for definite (culture verified) tuberculosis were adopted by all four countries. Therefore, the incidence rates of culture verified tuberculosis was considered most appropriate for comparative purposes in part one of our paper (Appendix).

In Denmark, persons reported as "born in country/national" do not include persons up to the age of 25 who are born in the country, but who have parents of foreign origin, i.e. second generation immigrants. Therefore, by definition, Danish incidence rates for cases classified as "born in country/national" are less influenced by second generation immigrants from high-incidence countries than in Norway and Sweden. Despite this, Denmark had the highest incidence rate of tuberculosis in the 0-14 year age group.

Completeness of case detection and notification

All four countries have well developed systems for diagnosis and reporting of cases of tuberculosis. Therefore, we have no reason to believe that differences in completeness of case detection and notification contribute to the observed difference, but this cannot be excluded. In Norway surveillance of tuberculosis is based both on mandatory reports from clinicians and from laboratories of clinical microbiology, and from pharmacy registers of anti-tuberculous drugs. In Finland the notification system, which is based on reports from clinicians and laboratories, was found to be highly sensitive for culture confirmed cases.(45). In both Sweden and Denmark there is also notification of cases both from clinicians and laboratories.

Risk of infection and second generation immigrants

Second generation immigrants with parents from high-incidence countries have increased risk of infection due to close contact with people from these countries, both in the Nordic countries and during visits to their countries of origin. In part one of our paper (Appendix), differences between the Nordic countries in the proportion of persons reported as "born in country/national" that are second generation immigrants, are likely to influence incidence rates. We did not have access to statistics regarding the number of cases accounted for by second generation immigrants from high incidence countries, and was therefore unable to adjust for this in our analysis. However, Norway and Sweden have a higher percentage of the population originating in high-incidence countries than Finland (Table 2), and it is likely that among persons reported as "born in country/national", the proportion of second generation cases is lowest in Finland.

In both Norway and Sweden, newborns with parents from high-incidence countries are offered BCG vaccination. The vaccination coverage is probably high, but exact figures are not available. BCG vaccination in this group would be expected to attenuate differences in incidence rates in the 0-14 year age group that might be attributed to different proportion of second generation immigrants with origin in high-incidence countries. Because vaccination is unlikely to provide more than 80% protection, and because vaccination coverage is not 100%, the size of the second generation immigrant population will, therefore, affect the incidence rate of tuberculosis in persons reported to EuroTB as "born in country/national".

In part two of our paper, second generation immigrants with origin in high-incidence countries are not included, avoiding this source of bias in the comparison between the two nations. The overall incidence rates of tuberculosis in Norway and Sweden are very

similar, but there may be differences in the risk of infection of the low-risk group population resulting from differences in behaviour.

For example, different degree of integration of immigrants from countries with high incidence of tuberculosis may result in different risk of transmission to the low-risk native population. However, molecular biological studies from both Norway and Denmark have shown that there is little transmission of tuberculosis from immigrants to persons born in the respective countries (4,46,47). Transmission from foreign-born tuberculosis patients is occasionally observed both in Sweden and in Norway, but we do not have data that allow us to analyse potential differences in magnitude of this problem between the countries. Also, different travel behaviour may result in different risk of infection. However, the travel habits of Norwegians and Swedes are probably quite similar and represent an unlikely explanation for differences in tuberculosis incidence in the low-risk native born population.

Differences in screening programmes and contact tracing may also influence risk of transmission to low-risk groups. In Norway, Sweden and Finland there is active screening for tuberculosis in immigrants, but only passive screening in Denmark (48). It is possible that this may contribute to the relatively high incidence of tuberculosis in Denmark, as opportunities for prevention may be lost. We have no data to indicate that other aspects of infection control programmes influence incidence rates to different degrees in the four countries, but this may not be excluded.

Risk of developing disease

In persons infected with *M tuberculosis,* immunodeficiency is a strong risk factor for the development of tuberculosis. Internationally, HIV has been a driving force for the tuberculosis epidemic in resource poor settings. In Norway we have poor data, but HIV infection probably plays a minor role in the epidemiology. We are aware of no data from the other four countries to indicate that the situation is different there.

The two possible interventions that that may influence the risk of disease after infection are preventive therapy and BCG vaccination. Although, it is internationally acknowledged that preventive therapy may be indicated for cases with latent infection, we have not been able find studies or other comparative information about the extent of use in the four countries. In Norway, there has been increasing use of preventive therapy during the last years.

Use of incidence rates to estimate BCG protection

In order to avoid bias, a double-blind randomised controlled trial is the ideal design for studying vaccine efficacy. However, BCG vaccination was introduced in an area before this became standard practise, and few randomised controlled trials have been conducted.

We compare incidence rates in four Nordic countries in an attempt to assess the effectiveness of BCG vaccination. To our knowledge, few other studies have used

incidence rates in different countries to estimate vaccine efficacy. In a study from 1950-1960 comparing Norway, Sweden, Denmark and two states in the US (upstate New York and Ohio), it was observed that incidence trends were more favourable in the age groups following first inoculation compared to other age groups in the same country or compared to the same age group in the other countries where a different BCG programme was applied (15).

In our study, the incidence rates for persons below the age of 30 born in the countries were low and stable in all four countries during the period 1996-2005. However, we did find that Norway and Finland had the greatest drop in incidence rates for non-immigrants during this period. These are also the two countries that practised BCG vaccination of low-risk groups until 2005. However, from this crude comparison, it cannot be concluded that this was an effect of BCG vaccination.

During the period 1996-2005, Finland was the only country with a universal neonatal BCG vaccination programme, and this may be one explanation for the low incidence rate of tuberculosis in 0-14 year olds in the EuroTB category "born in county/national". In Norway, adolescents born in the country and not belonging to a high-risk group are offered vaccination at the age of 12-14, and this may be one explanation for the low incidence rate of tuberculosis in the15-29 year group.

In both Norway and Sweden, newborns at increased risk of tuberculosis, mainly second generation immigrants, are offered BCG vaccination. In Denmark BCG vaccination is generally not used, except for in children moving for long periods to a high-incidence country. This may be one possible explanation why Denmark had the highest incidence of tuberculosis in the age group 0-14 years.

Above we have discussed factors that may bias our analysis of BCG protection. These are most relevant to part one of our paper (Appendix), where EuroTB data for the category "born in country/national" are analysed. In an attempt to correct for inter-country variation in these factors, we also compared the incidence rate in the 15-29 year age group with the incidence rate in the 0-14 year age group within the same country, and expressed this as a "within-country incidence rate"(WCIRR). Finland had the highest and Norway the lowest WCIRR. Again, this is consistent with a protective effect of BCG vaccination lasting 15 years after neonatal vaccination in Finland, and 15 years after vaccination of 12-14 year olds in Norway. In our paper we also describe limitations in the use of WCIRR to estimate vaccine protection related to different rates of decline in tuberculosis infection since 1967 when the oldest participants were born.

In conclusion, cases reported to EuroTB as "born in country/national" are not directly comparable, and differences in incidence rates may have several explanations other than different BCG vaccination policy. For this reason we did not attempt to quantify vaccine protection based on these data. However, differences in incidence rates were observed in Norway, Sweden, Finland and Denmark which are consistent with different use of BCG vaccination.

In part two of our paper (Appendix), bias resulting from inclusion of second generation immigrants from high incidence countries and use of different case definitions is avoided. Based on different incidence rates between Norway and Sweden in the 0-14 and 15-29 year age group we estimate the effectiveness of the Norwegian BCG vaccination programme to be in the range of 61-64%. BCG protection in persons vaccinated was estimated to be in the range 67-71%, using WCIRRs and BCIRRs. This level of protection is well within the range of previously estimates of BCG protection (7-11).

During the period 1996-2005 the incidence of tuberculosis in this age group has been fairly constant, indicating no great change in risk of infection during the last decades. In such a situation, we estimate that the Norwegian BCG vaccination programme of Norwegian adolescents prevents between 1 and 3 cases annually, i.e. less than 4% of cases among Norwegian-born. Between 14 918 - 51 409 vaccines are needed to prevent one case of tuberculosis.

Conclusions and future perspectives

Our study suggests that BCG vaccination of low-risk Norwegian adolescents may have contributed to reduced risk of tuberculosis for a period of 15 years after vaccination. However, a large number of vaccinations must be given in order to prevent one case of tuberculosis.

Many European countries are in the process of reviewing their BCG vaccination programmes. Both Finland and Britain have recently stopped BCG vaccination of low-risk inhabitants, and both have higher incidence of tuberculosis than Norway. Norway clearly meets the two first IUATLD criteria for discontinuing BCG vaccination programmes in countries with low prevalence of tuberculosis. Also, the vaccination of adolescents at low risk of tuberculosis is not in agreement with current WHO recommendations for the use of BCG vaccination.

In Norway, BCG vaccination policy is now being re-examined by a committee with mandate from the Norwegian Institute of Public Health. In this evaluation, direct and indirect costs of the adolescent BCG vaccination programme need to be calculated and traded off against the small, but probably real, reduction in number of tuberculosis cases.

Acknowledgements

First, I would like to thank my tutor Einar Heldal for his help, guidance and encouragement in the preparation of this thesis. His experience and knowledge of tuberculosis epidemiology has been invaluable. My gratitude is also extended to Victoria Romanus for providing Swedish surveillance data, and for her many constructive comments and suggestions. Thanks also to Peter Andersen for Danish data, and to Brita Winje and Vigdis Dahl for help with extracting data from the Norwegian tuberculosis register. Finally, I would like to thank my wife Anne Lise for practical help and support during my years as an MPH student.

References

1. World Health Organization (WHO). WHO report 2007. Global tuberculosis control: surveillance, planning, financing. 2007.

2. Winje B, Mannsåker T, Heldal E et al. Tuberkulose i Norge i 2005. MSIS-rapport 2006; 34.

3. Dahle UR, Sandven P, Heldal E et al. Continued Low Rates of Transmission of Mycobacterium tuberculosis in Norway. J Clin Microbiol 2003; 41: 2968-73.

4. Dahle UR, Eldholm V, Winje BA et al. Impact of Immigration on the Molecular Epidemiology of M. tuberculosis in a Low-incidence Country. Am J Respir Crit Care Med 2007.

5. BCG vaccine. WHO position paper. Wkly Epidemiol Rec 2004; 79: 27-38.

6. Spruyt LL, Siegfried N , Matchaba PT et al. Bacillus Calmette-Guerin (BCG) vaccine for preventing tuberculosis (Protocol for a Cochrane review). The Cochrane Library 2004.

7. Colditz GA, Berkey CS, Mosteller F et al. The Efficacy of Bacillus-Calmette-Guerin Vaccination of Newborns and Infants in the Prevention of Tuberculosis - Metaanalyses of the Published Literature. Pediatrics 1995; 96: 29-35.

8. Rodrigues LC, Diwan VK, Wheeler JG. Protective Effect of Bcg Against Tuberculous Meningitis and Miliary Tuberculosis-A Metaanalysis. International Journal of Epidemiology 1993; 22: 1154-8.

9. Colditz GA, Brewer TF, Berkey CS et al. Efficacy of Bcg Vaccine in the Prevention of Tuberculosis - Metaanalysis of the Published Literature. Jama-Journal of the American Medical Association 1994; 271: 698-702.

10. Tverdal A, Funnemark E. Protective Effect of Bcg-Vaccination in Norway 1956-73. Tubercle 1988; 69: 119-23.

11. Hart PD, Sutherland I. BCG and vole bacillus vaccines in the prevention of tuberculosis in adolescence and early adult life. Br Med J 1977; 2: 293-5.

12. Heimbeck J. BCG Vaccination of nurses. Tubercle 1948; 29: 84-8.

13. Scheel O. Tuberkuløse sykdommer og vaksinasjon mot tuberkulose hos medisinske studenter. Nord Med 1941; 11: 2540-4.

14. Sjogren I. Tuberculosis in BCG-vaccinated and unvaccinated young Swedish Men. A comparative study. Scand J Respir Dis 1976; 57: 208-22.

15. Bjartveit K, Waaler H. Some evidence of the efficacy of mass BCG vaccination. Bull World Health Organ 1965; 33: 289-319.

16. Kritski AL, Marques MJ, Rabahi MF et al. Transmission of tuberculosis to close contacts of patients with multidrug-resistant tuberculosis. Am J Respir Crit Care Med 1996; 153: 331-5.

17. Sterne JA, Rodrigues LC, Guedes IN. Does the efficacy of BCG decline with time since vaccination? Int J Tuberc Lung Dis 1998; 2: 200-7.

18. Aronson NE, Santosham M, Comstock GW et al. Long-term efficacy of BCG vaccine in American Indians and Alaska Natives: A 60-year follow-up study. JAMA 2004; 291: 2086-91.

19. Barreto ML, Cunha SS, Pereira SM et al. Neonatal BCG protection against tuberculosis lasts for 20 years in Brazil. Int J Tuberc Lung Dis 2005; 9: 1171-3.

20. Soysal A, Millington KA, Bakir M et al. Effect of BCG vaccination on risk of Mycobacterium tuberculosis infection in children with household tuberculosis contact: a prospective community-based study. The Lancet 2005; 366: 1443-51.

21. Clemens JD, Chuong JJ, Feinstein AR. The BCG controversy. A methodological and statistical reappraisal. JAMA 1983; 249: 2362-9.

22. Fine PE. Variation in protection by BCG: implications of and for heterologous immunity. Lancet 1995; 346: 1339-45.

23. Springett VH, Sutherland I. A re-examination of the variations in the efficacy of BCG vaccination against tuberculosis in clinical trials. Tuber Lung Dis 1994; 75: 227-33.

24. Fine PEM. BCG: the challenge continues. Scandinavian Journal of Infectious Diseases 2001; 33: 243-5.

25. Word Health Organization. Immunization coverage with BCG at birth, 2006 http://www.who.int/immunization_monitoring/diseases/BCG_coverage_map.JPG. [updated 23-8-2006]

26. Infuso A, Falzon D. European survey of BCG vaccination policies and surveillance in children, 2005. Euro Surveill 2006; 11: 6-11.

27. Romanus V, Tala E, Blondal T et al. [Tuberculosis control in Scandinavia]. Nord Med 1995; 110: 45-7.

28. Norges offentlige utredninger. Utryddelse av tuberkulose? - Strategi for fremtidig tuberkulosekontroll. 3. 1998.

29. Romanus V. First experience with BCG discontinuation in Europe. Experience in Sweden 15 years after stopping general BCG vaccination at birth. Bull Int Union Tuberc Lung Dis 1990; 65: 32-5.

30. Romanus V, Svensson A, Hallander HO. The Impact of Changing Bcg Coverage on Tuberculosis Incidence in Swedish-Born Children Between 1969 and 1989. Tubercle and Lung Disease 1992; 73: 150-61.

31. Socialstyrelsen. Rekommendationer för preventiva insatser mot tuberkulos. Hälsokontroll, smittspårning och vaccination. 2007.

32. Romanus V, Fasth A, Tordai P et al. Adverse reactions in healthy and immunocompromised children under six years of age vaccinated with the Danish BCG vaccine, strain Copenhagen 1331: implications for the vaccination policy in Sweden. Acta Paediatr 1993; 82: 1043-52.

33. Romanus V. Tuberkulos hos förskolebarn. EPI-aktuellt 2005; 4.

34. BCG-vaccine Statens Serum Institut. [updated 24-4-2007]. Available from: http://www.ssi.dk/sw1351.asp.

35. Salo EP. BCG in Finland: changing from a universal to a selected programme. Euro Surveill 2006; 11: 18-20.

36. Nationellt tuberkulosprogram 2006. Helsinki, Finland, 2006.

37. Genz H. [Incidence of infant tuberculosis in Germany during the first year after cessation of unselected BCG vaccination (author's transl)]. Dtsch Med Wochenschr 1977; 102: 1271-3.

38. Trnka L, Dankova D, Svandova E. Six years' experience with the discontinuation of BCG vaccination. 2. Cost and benefit of mass BCG vaccination. Tuber Lung Dis 1993; 74: 288-92.

39. Milstien JB, Gibson JJ. Quality control of BCG vaccine by WHO: a review of factors that may influence vaccine effectiveness and safety. Bull World Health Organ 1990; 68: 93-108.

40. Hagan P. Routine vaccination for tuberculosis ends in UK. BMJ 2005; 331: 128.

41. Eskild A. [Mass vaccination against tuberculosis--is it necessary in Norway?]. Tidsskr Nor Laegeforen 1994; 114: 1840-4.

42. Criteria for discontinuation of vaccination programmes using Bacille Calmette-Guerin (BCG) in countries with a low prevalence of tuberculosis. A statement of the International Union Against Tuberculosis and Lung Disease. Tuber Lung Dis 1994; 75: 179-80.

43. EuroTB and the national coordinators for tuberculosis surveillance in the WHO European Region. Surveillance of tuberculosis in Europe. Report on tuberculosis cases notified in 2005, Institut de veille sanitaire, Saint-Maurice, France. 2007.

44. Tala-Heikkila MM, Tuominen JE, Tala EO. Bacillus Calmette-Guerin revaccination questionable with low tuberculosis incidence. Am J Respir Crit Care Med 1998; 157: 1324-7.

45. Kokki M, Holmstrom P, Ruutu P. High sensitivity for tuberculosis in a national integrated surveillance system in Finland. Euro Surveill 2005; 10: 90-3.

46. Dragsted UB, Bauer J, Poulsen S et al. Epidemiology of tuberculosis in HIV-infected patients in Denmark. Scand J Infect Dis 1999; 31: 57-61.

47. Lillebaek T, Andersen AB, Bauer J et al. Risk of Mycobacterium tuberculosis transmission in a low-incidence country due to immigration from high-incidence areas. J Clin Microbiol 2001; 39: 855-61.

48. Rieder HL, Zellweger JP, Raviglione MC et al. Tuberculosis control in Europe and international migration. Eur Respir J 1994; 7: 1545-53.

Appendix

Draft article: A revised version of this paper has been accepted for publication in the International Journal of Tuberculosis and Lung Disease and is scheduled to be published in April 2009.

Epidemiological evidence of protective effect of BCG vaccination in persons at low risk of tuberculosis - a comparative study from four Nordic countries

Arne Broch Brantsæter[1, 2]

Einar Heldal[1]

Victoria Romanus[3]

[1]Norwegian Institute of Public Health, Division of Infectious Disease Control, Department of Infectious Disease Epidemiology, POB 4404 Nydalen, NO-0403 Oslo, Norway

[2]Asker and Bærum Hospital, Department of Internal Medicine, POB 83, NO-1309 Rud, Norway

[3]Swedish Institute for Infectious Disease Control, SE-17182 Solna, Sweden

Running title: BCG vaccination in four Nordic countries

Key words: tuberculosis, BCG, surveillance, Nordic countries

Summary

Setting: BCG vaccination policies in the Nordic countries of Norway, Sweden, Denmark and Finland have varied between and within the nations over time. At the end of 2005 all newborns were vaccinated in Finland, and all 12-14 year olds not previously vaccinated and at low risk of tuberculosis, were vaccinated in Norway. Denmark and Sweden no longer recommended use of BCG vaccination except among groups at high risk of tuberculosis.
Objective: The purpose of this study was (1) to assess if different incidence rates of tuberculosis among persons at low risk in the four countries could be related to different use of BCG vaccination, and (2) to estimate the number of adolescent BCG vaccinations needed to prevent one case of tuberculosis in Norway in the present epidemiological situation.
Design: The study period was 1996-2005. In part one of the study, where incidence rate in all four countries were compared, the EuroTB database was used to obtain the number of cases classified as "born in country/national" in Norway, Sweden, Denmark and Finland. In part two, the number of cases among persons born in Norway and Sweden and having two parents from low-incidence countries were obtained from the tuberculosis registers of Norway and Sweden. Population statistics were obtained from the official statistics agencies in the four countries. In both parts of the study incidence rates and incidence rate ratios among 0-14 year olds and 15-29 year olds were compared and related to different BCG vaccination policies.
Result and conclusions: EuroTB data (part one) are consistent with a protective effect of BCG vaccination against tuberculosis in 0-14 year olds born in Finland, and in 15-29 year olds born in Norway. Data obtained directly from the tuberculosis registers in Norway and Sweden (part two) suggest that the Norwegian adolescents BCG vaccination programme confers 61-64% protection against tuberculosis in the age group 15-29 years among persons who are born in the country and have two parents from Norway or another country with low incidence of tuberculosis. We estimate that between one and three cases of tuberculosis are prevented annually in the age group 15-29 years as a result of vaccination of Norwegian 12-14 year olds, and that 14 918 - 51 409 vaccinations are needed to prevent one case, assuming vaccine protection ranging from 50-80%.

Introduction

The Nordic countries of Norway, Sweden, Finland and Denmark are geographically and culturally similar, have well developed health care and tuberculosis surveillance systems, and today all have low incidence rates of tuberculosis. BCG vaccination came into general use in the late 1940s, but the targeted age groups and the national BCG vaccination programmes have differed greatly over time.

In Norway BCG vaccination is offered to Norwegian tuberculin negative 12-14 year old adolescents at low risk of tuberculosis (1). High-risk groups, e.g. immigrants from high-incidence countries and their children, are selectively vaccinated at the earliest possible age (2). In Sweden, the programme of universal vaccination of newborns was stopped in 1975, after incidence rates had fallen to low levels (3), but selective vaccination continues among high-risk children. In Denmark routine vaccination of 7 year olds was stopped in 1985, after a gradual decrease in vaccination coverage during the early 1980s. Since then, BCG vaccination has almost ceased in Denmark, and is currently only recommended for children travelling for long periods to countries with high incidence of tuberculosis (4). In Finland all newborns were BCG vaccinated until September 2006, but this programme was then stopped, and presently only high-risk children are vaccinated (5).

The Word Health Organization recommends BCG vaccination of all infants living in areas where tuberculosis is highly endemic, of infants and children at particular risk of tuberculosis exposure in otherwise low-endemic areas, and of persons exposed to multidrug-resistant *Mycobacterium tuberculosis* (6). The protection offered by BCG vaccination is best documented for newborns (7). Meta-analyses have demonstrated 63-74% protective effect against tuberculosis disease and 65-71% against death from tuberculosis (7,8). Against tuberculous meningitis and meningeal disease, most common in small children, the efficacy has been estimated to be 81% (9).

There is also some evidence of BCG protection following vaccination of adolescents, which has only been the policy in the United Kingdom and Norway. A British randomised BCG study from the early 1950s showed a protective effect of 84% for the first five years after vaccination of 14-15 year olds, thereafter decreasing, and averaging 77% during the follow-up period of 20 years (10). During the last 5 years of follow up there were too few cases to make a reliable assessment of vaccine efficacy. In Norway, a non-randomised study of 12-14 year old school children vaccinated during the period 1956-1973 demonstrated a protective effect of 81% during a follow-up period of 10 years (11). The protective effect was 90% for the first five years and 56% for the next five years.

Based on previous studies, there has been widespread agreement that the efficacy of BCG at best is around 80%. Generally, there has been little evidence that the effect of BCG vaccination lasts for more than 10-20 years (12,13). However, one study from the USA demonstrated protection lasting for 50-60 years (14).

From the 1975 to 2005 all Nordic countries have experienced a reduction in the total annual rate of notified cases of tuberculosis: Finland from 74.2-6.9 per 100 000, Sweden from 17.6-6.3 per 100 000, Norway from 12.5-6.3 per 100 000, and Denmark from 12.2 to 7.8 per 100 000 (15,16). However, the similar crude incidence rates hide larger differences in incidence rates among persons born in the country, due to differences in immigrant populations. From beginning to the end of the period, i.e. from 1996-2005, the decline in respective incidence rate per 100 000 among persons of national origin was highest in Finland (11.9-6.1), followed by Norway (2.8-1.5), Sweden (2.5 - 1.9) and Denmark (3.9-3.3).

In 1998 a report commissioned by the Norwegian Ministry of Health recommended to maintain the existing BCG vaccination programme, but proposed that the programme be continually assessed (1). The purpose of our study was to:
(1) assess if different incidence rates of tuberculosis among persons at low risk in the four countries could be related to different use of BCG vaccination, and
(2) estimate the number of adolescent BCG vaccinations needed to prevent one case of tuberculosis in the Norwegian population in the present epidemiological situation.

Study population and methods

The study population comprised notified cases of tuberculosis in non-immigrants under the age of 30 years in Norway, Sweden, Denmark and Finland during the period 1996-2005. The study has two parts.

In part one the annual number of new cases reported to Surveillance of tuberculosis in Europe (EuroTB) as “born in country/national” was obtained by accessing the database at www.eurotb.org. In this databases Norway and Finland permit query on individual data, allowing data analysis of number of cases in defined age groups. As Sweden and Denmark only permit aggregate data analysis, additional data were requested from the Swedish and the Danish tuberculosis registers. In Norway, Sweden and Finland, all persons born in the respective countries are reported to EuroTB as “born in country/national”, i.e. second generation immigrants are included. However, in Denmark second generation immigrants, including persons with one foreign-born parent, are reported as “born abroad/foreign origin” up to the age of 25 years.

In part two the annual number of new cases of tuberculosis among persons who were born in Norway and Sweden, respectively, and who had parents who were both born these or in other low-incidence countries, were obtained directly from the Norwegian and the Swedish tuberculosis registers. We used the present Norwegian definition of low-incidence countries, developed for infection control purposes: all the countries of Western-Europe plus Poland, Hungary, the Czech Republic, Slovakia, Slovenia, USA, Canada, Japan, Australia and New Zealand.

The EuroTB case definition for tuberculosis was used in both parts of the study (16).

> **Definite TB:** a patient with culture-confirmed disease due to *M.tuberculosis*, *M. africanum* or *M. bovis* (excluding *M. bovis* BCG).
> **Other-than-definite TB:** A patient meeting the two following conditions:
> 1. a clinician's judgement that the patient's clinical and/or radiological signs and/or symptoms are compatible with tuberculosis **and**
> 2**.** a clinician's decision to treat the patient with a full course of anti-tuberculosis treatment.

However, with regards to other-than-definite cases, Finland only reported cases that had laboratory support for the diagnosis by either microscopy or histological findings.

Population data were obtained from Statistics Norway, Statistics Sweden, Statistics Denmark and Statistics Finland. Where insufficient data were available at the respective on-line population statistics databases, supplementary data were obtained directly from these agencies. The number of persons in the age groups 0-14 and 15-29, at the end of the calendar years 1996-2005 were added to calculate the number of person-years.
In part one, person-years were calculated from the number of persons who were born in the country, except for Denmark. Danish person-years were calculated from the number of persons of Danish origin, as this was the classification used by statistics Denmark, Danish origin being defined as having either a mother or father born in Denmark and holding Danish citizenship. In part two, Statistics Sweden was unable to provide exact population data for the period 1996-2000 regarding 0-14 and 15-29 years olds who were born in Sweden and had parents who were both born in low-incidence countries. Therefore, an estimate was made by multiplying the total population born in the country in the age group 0-14 years by 85.8% and 15-29 years by 94.6%, the average percentage of persons born in the country that had two parents from low-incidence countries during the period 2001-2005.

In order to assess the effectiveness of the BCG vaccination programmes targeting either Finnish newborns or Norwegian adolescents, three measures were used for comparison:

(1) incidence rates for the age group 0-14 and 15-29 years

(2) incidence rate ratios between the age group 15-29 and 0-14 *within* each country (WCIRR), where

$$\text{WCIRR} = \frac{\text{incidence rate age 15-29 years}}{\text{incidence rate age 0-14 years}}$$

(3) (part two only): incidence rate ratios *between* Norway and Sweden (BCIRR), where

$$\text{BCIRR} = \frac{\text{incidence rate in Norway}}{\text{incidence rate in Sweden}}$$

for the age groups 0-14 years and 15-29 years, respectively.

Information about BCG status of cases was available only for cases included in part two of the study. Norwegian adolescent BCG vaccination coverage data were obtained from the Norwegian childhood vaccination register (SYSVAK), and was used to estimate BCG protection from the above mentioned incidence rate ratios.

The number of prevented cases of tuberculosis in Norway in the 15-29 year age group was calculated by the formula

Tbprev = Tbnot x (1/(1- EffBCG x CovBCG)-1),

where Tbprev = cases of tuberculosis prevented by BCG vaccination, Tbnot = annual number of notified cases of tuberculosis, EffBCG = efficacy of BCG, and CovBCG = BCG vaccination coverage (17). The number of BCG vaccinations needed to prevent one case of tuberculosis was made using estimates of vaccine efficacy from this and previously published studies.

All statistical analyses were performed using ‘‘Episheet’’© 2002, 2004, version November 10, 2005, by Ken Rothman. This is a spreadsheet based analytical package for statistical analyses in epidemiology which can be downloaded for free at http://members.aol.com/krothman/modepi.htm. 95% confidence intervals not overlapping, or rate ratios not covering 1 were considered statistically significant.

Results

Part one –
Tuberculosis among persons below 30 years of age in Norway, Sweden, Denmark and Finland reported to EuroTB as “born in country/national”.

The incidence rate of tuberculosis in persons less than 30 years of age categorised as “born in county/national” are shown in Table 1.

The incidence rate in the 15-29 year age group was significantly lower in Norway, than in the other three countries both for total and culture verified cases. The incidence rate for culture verified tuberculosis among 15-29 year olds was 56% lower than Sweden ((0.45-0.20)/0.45 x 100), 88% lower than Denmark ((1.70-0.20)/1.70 x100) and 79% lower than Finland ((0.96-0.20)/0.96 x 100). Norway was the only country with a lower average incidence rate of tuberculosis in the 15-29 year age group than among the 0-14 year olds (WCIRR<1). The WCIRR in Norway was significantly lower than in the other three countries both for total and culture verified cases.

Table 1 Incidence rates and rate ratios for cases of tuberculosis among persons "born in country/national" below 30 years of age in Norway, Sweden, Denmark and Finland, 1996-2005

Country	Total cases		Culture verified		
	IR (95% CI)	N	IR (95% CI)	N	Person-years†
Norway					
0-29 years	0.45 (0.36-0.57)	75	0.25 (0.18-0.34)	42	16 567 951
0-14 years	0.63 (0.47-0.82)	54	0.30 (0.20-0.44)	26	8 601 941
15-29 years	0.26 (0.16-0.40)	21	0.20 (0.11-0.33)	16	7 966 010
WCIRR	0.41 (0.25-0.70)		0.66 (0.36-1.23)		
Sweden					
0-29 years	0.56 (0.48-0.65)	168	0.33 (0.27-0.40)	99	29 851 794
0-14 years	0.56 (0.45-0.69)	86	0.22 (0.15-0.31)	34	15 442 649
15-29 years	0.57 (0.45-0.71)	82	0.45 (0.35-0.58)	65	14 409 145
WCIRR	1.02 (0.75-1.38)		2.05 (1.35-3.10)		
Denmark					
0-29 years	1.41 (1.24-1.59)	254	1.03 (0.88-1.18)	185	18 042 696
0-14 years	0.78 (0.61-0.99)	70	0.34 (0.23-0.48)	30	8 934 686
15-29 years	2.02 (1.74-2.33)	184	1.70 (1.44-1.99)	155	9 108 010
WCIRR	2.58 (1.96-3.40)		5.07 (3.43-7.49)		
Finland					
0-29 years	0.65 (0.54-0.78)	119	0.53 (0.43-0.65)	98	18 353 224
0-14 years	0.12 (0.06-0.22)	11	0.10 (0.05-0.19)	9	9 096 294
15-29 years	1.16 (0.95-1.40)	107	0.96 (0.77-1.18)	89	9 256 930
WCIRR	8.76 (4.82-15.91)		9.72 (4.90-19.29)		

IR = incidence rate per 100 000 person-years
CI = confidence interval
N = number of cases
† Sweden, Denmark and Norway: based on persons born in the country, Denmark: persons of Danish origin (see methods section for details)
WCIRR = Within-country IR ratio, IR 15-29 year olds/incidence rate 0-14 year olds

In Finland, the total incidence rate in the 0-14 year age group was significantly lower than in the other countries. Although confidence intervals for culture verified tuberculosis in the age group 0-14 year overlapped with the corresponding age group in Sweden, the incidence rate ratio was significant, 0.45 (95% CI 0.22-0.94). Culture verified tuberculosis in Finland in this age group was 67% lower than in Norway ((0.30-0.10)/0.30 x100), 56% lower than in Sweden ((0.22-0.10)/0.22 x 100) and 71% lower than in Denmark ((0.34-0.10)/0.34 x 100). The WCIRR was also significantly higher in Finland than in the other countries.

Among the two countries that had abandoned non-selective BCG vaccination, Sweden and Denmark, the former had significantly lower incidence rates for both age groups, and also lower WCIRR, than did Denmark

Part two-
Tuberculosis in Norway and Sweden in persons below the age of 30 years with two parents from low-incidence countries

The incidence rates and rate ratios of tuberculosis (definite plus other-than definite) in persons under the age of 30 years who were born in Norway and Sweden and who had two parents who were both born in low-incidence countries, are shown in Table 2.

In the 15-29 year age group, the incidence rate and BCIRR was significantly lower in Norway.

In addition to these cases, there were nine cases born in Norway with distinctly foreign (non-West European) names with no information about parents' place of birth (6 in the age group 0-14 and 3 in the age group 15-29). These cases were assumed to have parents from high-incidence countries, and were not included in the data shown in table 2. Two Swedish cases had parents whose country of birth was unknown (both in the age group 15-29 years), and these cases were not included in table 2. However, inclusion of these subjects did not alter the significant differences in rates and rate ratios in the 15-29 year age group (data not shown).

Table 2 Incidence rates and rate ratios for cases of tuberculosis in persons below 30 years of age born in Norway and Sweden with two parents from low-incidence countries, 1996-2005

Age group	Norway			Sweden			
	IR (95% CI)	N	Person-years	IR (95 % CI)	N	Person-years†	BCIRR (95% CI)
Total 0-29 years	0.21 (0.15-0.30)	32	15 086 121	0.32 (0.26-0.40)	88	26 879 334	0.65 (0.43-0.97)
0-14 years	0.26 (0.16-0.41)	20	7 579 055	0.24 (0.17-0.34)	32	13 248 464	1.09 (0.62-1.91)
15-29 years	0.16 (0.08-0.28)	12	7 507 066	0.41 (0.31-0.53)	56	13 630 870	0.39 (0.21-0.73)
WCIRR	0.61 (0.30-1.24)			1.70 (1.10-2.63)			

IR = incidence rate per 100 000 person-years
CI = confidence interval
N = number of cases
WCIRR = within country incidence rate ratio, incidence rate (IR) 15-29 year olds/IR 0-14 year olds
BCIRR = between country incidence rate ratio, IR Norwegian age group/IR Swedish age group
† For the period 2001-2005 Statistics Sweden provided exact population data.
For the period 1996-2000 an estimate was made (se method section for details).

Among the 20 Norwegian born cases in the 0-14 age group, two cases were known to have received BCG vaccination. In one case this was probably because parents originated in a high-incidence country, as indicated by the by their names (but were born in Norway/Denmark). The other case was BCG vaccinated before moving to the Philippines. Fifteen cases were known not to have been vaccinated, and three had unknown vaccination status. Among the twelve Norwegian 15-29 year old cases, nine were known to have been BCG vaccinated, one was known not to have been vaccinated, and vaccination status was unknown for two.

Among the 32 Swedish 0-14 year olds, one was known to have been BCG vaccinated, 22 were unvaccinated and 9 had unknown vaccination status. Of 56 cases in the 15-29 year age group 23 were vaccinated, mostly because they were born before universal BCG vaccination was stopped (born 1967-1975) or because one of the parents was born in Finland, previously considered a high-risk country. Twenty-two cases were unvaccinated and 11 had unknown vaccination status.

Estimation of the effectiveness of the Norwegian adolescent BCG vaccination programme

In part one it was shown that Norway had the lowest incidence rate of tuberculosis among 15-29 olds, and Finland the lowest incidence rate among the 0-14 year olds. Also, the WICRR was significantly higher in Finland and lower in Norway than the other countries. This is consistent with a protective effect of BCG vaccination of adolescents in Norway and of newborns in Finland.

However, in our quantitative assessment of the protective effect of the Norwegian adolescent vaccination programme, we used data from part two of our study. The WCIRR was 64% lower (non-significant) in Norway than in Sweden ((1.70-0.61)/1.70 x 100). In the 15-29 year age group, the BCIRR in the 15-29 year age group in the two countries was 61% lower (significant) in Norway ((0.41-0.16)/0.41 x 100). There was no significant difference in the BCIRR for 0-14 year olds. In other words, given a number of assumptions discussed later, our data indicate that the Norwegian adolescent vaccination programme may have conferred 61-64% protection against tuberculosis for the 15-29 year olds during the study period.

According to the Norwegian childhood vaccination register (SYSVAK), BCG coverage among 16 year olds was 91% during the period 2000-2005. Coverage data were not available for the period 1996-1999. Using available vaccine coverage data, we also estimated BCG efficacy in Norwegian adolescents, using the following assumptions:

1. There was no change in BCG coverage during the study period.
2. BCG protection last for 15 years
3. The differences in the WCIRRs and the BCIRRs in Norwegian and Swedish incidence rates are entirely due to differences in BCG vaccination programmes in the two populations.

After adjustment for vaccination coverage, the protective effect of BCG vaccination was 71% using the WCIRR method (0.64/0.91 x 100) and 67% using the BCIRR method (0.61/0.91 x 100%).

During 1996-2005, 12 cases in the 15-29 year age group were notified in Norway, or on average 1.2 cases per year. With 67-71% protection from BCG vaccination in the 15-29 year group, as suggested by our study, and 91% vaccination coverage, the average annual number of prevented cases during the study period was 1.9-2.2 using the formula presented in the methods section. Assuming 80% protection (high end estimate based on previous studies, 3.2 cases are prevented annually, and with 50% protection (low end

estimate based on previous studies), 1.0 cases are prevented annually. It is likely that the SYSVAK data underestimate the true vaccination coverage, but if one assumes a vaccination coverage of 98%, these estimates are only slightly altered (data not shown).

The 15-29 year olds were born 1967-1991 and were vaccinated 12-14 years after birth. Taking age 13 as average, they were vaccinated during the years 1980-2004.The average size of the 13 year old cohorts in 1980-2004 born in Norway and having parents from Norway or another low-endemic country during the period 1980-2004 was 52 458.

Assuming vaccine coverage between 91 and 98%, between 47 737 and 51 409 persons were vaccinated. With estimates of protection between 50 and 80%, the number of vaccinations needed to prevent one case of tuberculosis in the age group 15-29 years is between 14 918 and (47 737/3.2) 51 409 (51 309/1.0).

During the study period, the average annual number of tuberculosis cases reported in Norwegian-born was 83, and the average total number of cases was 264. In other words, BCG vaccination of Norwegian teenagers may have prevented 1.2 - 3.9% of cases of tuberculosis in Norwegian-born and 0.4 - 1.2% of total cases.

Discussion

Results of our epidemiological study from four Nordic countries are consistent with a protective effect of BCG in persons at low risk of tuberculosis. Because Finland had a more restrictive practise than the other nations in reporting other-than-definite-cases, our comparison of incidence rates in part one is probably most valid for culture verified cases. Finland, the only country that practised universal neonatal BCG vaccination during the study period, had the lowest incidence rate among the 0-14 year olds and the highest WCIRR. Norwegian 15-29 year olds, vaccinated at the age of 12-14, had the lowest incidence rate and lowest WCIRR of the four countries. Denmark, the country with the most restrictive use of BCG vaccination, was the country with the highest incidence rate of tuberculosis.

However, there are caveats in use of EuroTB data for the purpose of assessing the effectiveness of BCG vaccination programmes in the Nordic countries. Of particular concern is the fact that the proportion of cases among second generation immigrants from high incidence countries included in the category “born in country/national” may have differed among the four countries. To illustrate this, in 2005 the proportion the population comprising immigrants from high-incidence countries, was highest in Sweden (7.2%), followed by Norway (5.4%), Denmark (4.9%) and Finland (2.3%). (Source: Statistics Norway, Statistics Sweden, Statistics Denmark and Statistics Finland). Unfortunately, population data for second generation immigrants from these countries was not available to us, but the above differences probably reflect corresponding differences in proportions of second generation immigrants. Therefore, the low proportion of the population from countries with high incidence of tuberculosis in Finland also indicates a low proportion of second generation immigrants from these countries, and this may have contributed to the low incidence of tuberculosis in the 0-14

year age group. Furthermore, it is possible that completeness of case detection and notification may have varied among the countries. Differences in infection control measures, use of preventive therapy and prevalence of infectious tuberculosis in the population are factors that may also influence the risk of infection and subsequent disease.

WCIRRs were used for country comparison in an attempt to reduce the impact of country specific factors that may have influenced incidence rates. However, comparison of WCIRRs for the purpose of estimating BCG efficacy may be confounded by different rates of decline in tuberculosis. Generally, WCIRR will increase when the risk of infection and subsequent disease decreases over a time period. Persons in the age group 0-14 were generally born later (1982-2005) than persons in the age group 15-29 (1967-1990). Finland had the greatest decline in total tuberculosis incidence rate during the years of birth of cases (1967-2005) and this may have contributed to the relatively high WICRR in Finland. However, we observed no clear drop in incidence rates in the age groups 0-14 and 15-29 from 1996-2005 in Finnish cases reported as “born in country/national”, indicating that this is unlikely to be the sole explanation for the high WCIRR. Also, the low WCIRR in Norway may not easily be explained by changes in risk of infection.

Therefore, although results from part one are consistent with an effect of non-selective BCG vaccination programmes in Norway and Finland, other factors may have confounded our findings. For this reason we did not attempt to make a quantitative estimate of protection offered by the vaccination programmes based on these data.

In part two of our study, we attempted to eliminate confounding of incidence rates by second generation immigrants, by including only cases born in Norway and Sweden, and having parents who were both born in low-incidence countries. Because Norway and Sweden use identical case definitions, we chose to compare the total number of cases (definite plus other-than-definite cases). Our results indicate that the Norwegian adolescent BCG vaccination programme confers 61-64% protection against tuberculosis for a period of 15 years after vaccination. Norway and Sweden have experienced very similar declines in total incidence rates of tuberculosis, and had identical total incidence rates in 2005. Therefore, differences in risk of infection over time are unlikely to have confounded our analysis. An estimate of population data was required for the period 1996-2000. However, the observed statistical differences in tuberculosis incidence rates among 15-29 year olds is robust to large errors in this estimate.

By using BCG vaccination coverage data, we estimate that the efficacy of BCG vaccination is 67-71%, which is well within the range of other epidemiological studies that have assessed BCG vaccine efficacy (7,8). Detailed knowledge about BCG vaccination status of cases and vaccine coverage should ideally be known in order to calculate vaccine efficacy. Cases with unknown vaccination status and cases that were not vaccinated according to the current guidelines during the study period introduce a possible source of error in the calculation of vaccine efficacy, but not in our estimate of the overall effectiveness of the vaccination programme.

The duration of protection after vaccination is a source of contention (12-14). We based our estimates on previous studies of vaccination of adolescents, that have demonstrated protection lasting for at least 15 years, but with waning of protection during the last years (10,11). Although longer protection have been demonstrated in Native Americans (14), it is by no means clear that these data can be extrapolated to the Nordic countries. However, even if BCG were to confer life long protection, several thousand vaccines would be needed to prevent one single case of tuberculosis among low-risk individuals in the present epidemiological situation in Norway and the other Nordic countries.

During the period 1996-2005, the incidence of tuberculosis in Norwegian 15-29 year olds with low risk of tuberculosis has been fairly constant, indicating no great change in the risk of infection during the last decades. In this situation, we estimate that the Norwegian adolescent BCG vaccination programme prevents between 1.0 and 3.2 cases annually, and less than 4% of cases among Norwegian-born. At least 14 918 vaccinations are necessary to prevent one case of tuberculosis during the subsequent 15 years. This does not take into account possible protective effect or BCG vaccination more than 15 years after vaccination or the prevention of secondary cases, which would increase the favourable effects of vaccination.

In conclusion, our study suggests that BCG vaccination of low-risk newborns in Finland and of Norwegian low-risk adolescents may have contributed to reduced risk of tuberculosis for a period of 15 years after vaccination. However, a large number of persons at low risk of tuberculosis must be vaccinated in order to prevent a single case.

Many European countries with low incidence of tuberculosis, including Norway, are in the process of reassessing their BCG vaccination programmes. In this evaluation, direct and indirect costs of the programmes need to be traded off against the small number of cases prevented by BCG vaccination in the low-risk population.

Acknowledgements*:* We are grateful for helpful suggestions in the preparation of this study from Petri Ruuti at the Finnish National Public Health Institute. We also thank Peter Andersen at the Danish Serum Institute for having provided individual data sets needed for our analysis.

References

1. Norges offentlige utredninger. Utryddelse av tuberkulose? - Strategi for fremtidig tuberkulosekontroll. 3. 1998.

2. Norwegian Institute of Public Health. Forebygging og kontroll av tuberkulose. 2002.

3. Romanus V, Svensson A, Hallander HO. The Impact of Changing Bcg Coverage on Tuberculosis Incidence in Swedish-Born Children Between 1969 and 1989. Tubercle and Lung Disease 1992; 73: 150-61.

4. BCG-vaccine Statens Serum Institut. [updated 24-4-2007]. Available from: http://www.ssi.dk/sw1351.asp.

5. Salo EP. BCG in Finland: changing from a universal to a selected programme. Euro Surveill 2006; 11: 18-20.

6. BCG vaccine. WHO position paper. Wkly Epidemiol Rec 2004; 79: 27-38.

7. Colditz GA, Berkey CS, Mosteller F et al. The Efficacy of Bacillus-Calmette-Guerin Vaccination of Newborns and Infants in the Prevention of Tuberculosis - Metaanalyses of the Published Literature. Pediatrics 1995; 96: 29-35.

8. Colditz GA, Brewer TF, Berkey CS et al. Efficacy of Bcg Vaccine in the Prevention of Tuberculosis - Metaanalysis of the Published Literature. Jama-Journal of the American Medical Association 1994; 271: 698-702.

9. Rodrigues LC, Diwan VK, Wheeler JG. Protective Effect of Bcg Against Tuberculous Meningitis and Miliary Tuberculosis-A Metaanalysis. International Journal of Epidemiology 1993; 22: 1154-8.

10. Hart PD, Sutherland I. BCG and vole bacillus vaccines in the prevention of tuberculosis in adolescence and early adult life. Br Med J 1977; 2: 293-5.

11. Tverdal A, Funnemark E. Protective Effect of Bcg-Vaccination in Norway 1956-73. Tubercle 1988; 69: 119-23.

12. Sterne JA, Rodrigues LC, Guedes IN. Does the efficacy of BCG decline with time since vaccination? Int J Tuberc Lung Dis 1998; 2: 200-7.

13. Barreto ML, Cunha SS, Pereira SM et al. Neonatal BCG protection against tuberculosis lasts for 20 years in Brazil. Int J Tuberc Lung Dis 2005; 9: 1171-3.

14. Aronson NE, Santosham M, Comstock GW et al. Long-term efficacy of BCG vaccine in American Indians and Alaska Natives: A 60-year follow-up study. JAMA 2004; 291: 2086-91.

15. Romanus V, Tala E, Blondal T et al. [Tuberculosis control in Scandinavia]. Nord Med 1995; 110: 45-7.

16. EuroTB and the national coordinators for tuberculosis surveillance in the WHO European Region. Surveillance of tuberculosis in Europe. Report on tuberculosis cases notified in 2005, Institut de veille sanitaire, Saint-Maurice, France. 2007.

17. Barrault Y, Decludt B, Lévy-Bruhl D, Schwoebel V. Impact épidémiologique d'une modification de la politique de vaccination par le BCG en France.Revue de la littératur et analyse des données disponibles. 2007.

Förteckning över NHV-avhandlingar och MPH-uppsatser

Se vår hemsida www.nhv.se

Nordic School of Public Health • Box 12133 • SE-402 42 Göteborg
Visiting address: Nya Varvet • Building 25 • Phone: +46 (0)31 69 39 00 • Fax: +46 (0)31 69 17 77
E-mail: administration@nhv.se • www.nhv.se