Vaccine (2008) **26**, 2253–2259

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/vaccine

Assessing the impact of different BCG vaccination strategies on severe childhood TB in low-intermediate prevalence settings

Davide Manissero[a,*], Pier Luigi Lopalco[a,1], Daniel Levy-Bruhl[b,2], Marta Luisa Ciofi degli Atti[c,3], Johan Giesecke[a,4]

[a] *Scientific Advice Unit, European Centre for Disease Prevention and Control, 171 83 Stockholm Sweden*
[b] *Department of Infectious Diseases, National Institute for Public Health Surveillance, 12 rue du val d'Osne, 94415 Saint Maurice Cedex, France*
[c] *National Centre of Epidemiology, Surveillance and Health Promotion, Istituto Superiore di Sanita', Via Giano della Bella 34 00162 Roma, Italy*

Received 6 August 2007; received in revised form 22 January 2008; accepted 13 February 2008
Available online 11 March 2008

KEYWORDS
BCG;
Selective vaccination;
Tuberculosis

Summary The decrease in overall incidence of TB in industrialised countries, together with the increasing concern for adverse events following BCG immunization, has led to important modifications of BCG policies in the last decades. This article adapts and validates — with surveillance data — a theoretical model estimating the impact of different national BCG vaccination policies on severe childhood TB in low to intermediate TB prevalent countries. The model shows that a universal BCG programme could be beneficial in settings with prevalence levels around 30 sputum smear positive per 100,000. In settings with prevalence levels below 15 per 100,000 the benefit of universal BCG vaccination should be carefully assessed, particularly where prevalence is below 5 per 100,000 and universal vaccination might lead to an excess of adverse events per case prevented. To this purpose the model also provides a tool to assess the theoretical impact of a policy change towards selective 'high-risk groups' vaccination.

Introduction

The Bacillus Calmette-Guérin (BCG) vaccine is one of the most widely used of all current vaccines [1].

Whilst BCG efficacy against pulmonary TB — particularly in adults — is highly variable, more consistent results are available on BCG efficacy against tuberculous meningitis and miliary tuberculosis (severe forms of TB) [2,3].

BCG vaccination often results in local adverse effects, but serious complications are rare. Globally, incidence of

* Corresponding author. Tel.: +46 8 58601218; fax: +46 8 58601001.
E-mail addresses: davide.manissero@ecdc.europa.eu (D. Manissero), pierluigi.lopalco@ecdc.europa.eu (P.L. Lopalco), d.levybruhl@invs.sante.fr (D. Levy-Bruhl), ciofi@iss.it (M.L. Ciofi degli Atti), johan.giesecke@ecdc.europa.eu (J. Giesecke).
[1] Tel.: +46 8 58601212; fax: +46 8 58601001.
[2] Tel.: +33 1 41 79 68 74, fax: +33 1 41 79 68 72.
[3] Tel.: +39 06 4990 1, fax: +39 06 49 90 41 10.
[4] Tel.: +46 8 58601210, fax: +46 8 58601001.

0264-410X/$ — see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.vaccine.2008.02.038

fatal adverse events has been rarely reported, ranging from 0.01 to 43.4 cases per million vaccines. Such severe adverse events usually occur in infants with impaired immunity [4].

In Western Europe the most frequently reported adverse event is suppurative lymphadenitis; osteitis and occasionally disseminated BCG infection have also been reported [5,6].

The decrease in overall incidence of TB in industrialised countries, together with the increasing concern for adverse events following immunization (AEFI), has led to important modifications of BCG policies in the last decades [7,8]. BCG vaccination has been discontinued or has been limited to children 'at risk' in a growing number of countries in the European Union (EU) [9]. Policy changes are currently under discussion in other EU countries.

Decision on discontinuing universal BCG vaccination should rest upon a cost—benefit analysis taking into account several variables, namely the expected number of severe TB cases in children, the expected number of AEFI, and the number needed to vaccinate per severe TB case prevented.

We provide a theoretical model to assess cost—benefit of different options of BCG vaccination strategies in low to intermediate TB burden countries with respect to prevention of severe TB cases in childhood.

Methods

We aimed at adapting a model that would allow us to estimate the effects of withdrawal or change in BCG vaccination strategy in low to intermediate TB prevalence settings.

Methodological background

Published models for assessing the impact of BCG can be grouped under two different approaches: (1) *a surveillance-based model* that has been previously described in the literature [10,11] and (2) *an annual risk of infection (ARI)-based model* that has been previously adopted by various authors [3,12—14].

For the purposes of this work we used the second (ARI-based) approach since the first one requires access to a surveillance system that is able to capture severe forms of TB (TB meningitis and possibly miliary TB) in children.

We took into consideration the 27 European Union countries plus two EEA countries (Norway and Iceland).

We established that the model should estimate a number of outcomes that would allow a cost—benefit comparison under the different BCG strategies in various epidemiological settings. We established that the following outcomes would be needed:

- Estimated number of TB meningitis and miliary TB cases (*severe TB cases*) prevented in a cohort of children for the first 5 years of life.
- Estimated number of BCG vaccinations required to prevent one case of TB meningitis or miliary TB (*number needed to vaccinate—NNV*).
- Number of BCG adverse event per case prevented.

The methodology previously developed by Fine et al. [14] and by Trunz et al. [3,13] was adapted for calculating the selected outcomes.

We considered the number of severe TB cases prevented (assuming an hypothetical 100% BCG coverage), as the main outcome of the model. In order to reach this estimate, we started with calculating the ARI from the smear positive (infectious) TB prevalence as indicated in Trunz et al. work:

$$\mathrm{ARI} = \beta p_{\mathrm{sm+}}$$

in which β (contact rate) represents the number of new infections generated by a prevalent smear positive case per year and $p_{\mathrm{sm+}}$ is the prevalence of smear positive cases in 2004. For the purpose of this work a contact rate of 6 was selected [3,13].

The outcome estimated by the model have been calculated in 5 theoretical epidemiological settings that could represent the variability within the selected 29 European countries.

The TB prevalence (SS + per 100,000 population) in the selected European countries ranges between 1.0 and 88.0 [15].

In order to define 5 hypothetical settings, that may describe the various epidemiological situations in Europe, the 5th, 25th, 50th, 75th and 95th percentiles have been calculated based on the actual distribution of TB prevalence. Starting from the TB prevalence values calculated in such way, 5 theoretical settings (namely A—E) have been derived applying the ARI model, as described below.

The number of expected cases of TB meningitis was calculated given the known proportion of childhood infections that lead to tuberculous meningitis (ρ_{men}). This proportion has been previously published and falls in the range of 0.7—1% [3,13,16,17]. For the purpose of the proposed model the upper limit of this range (1%) has been selected.

The total expected cases of TB meningitis — for each of the 5 settings — was calculated for a period of 5 years (representing the peak period of risk for developing severe disease) in a hypothetical birth cohort of 100,000 children.

The number of severe TB cases (meningitis and miliary TB) was calculated by adding to the number of TB meningitis the estimated military TB cases based on a ratio of 1:2. This represents the upper limit of the expected ratio of miliary to meningitis TB cases (range 1:4—1:2) [3,13].

A BCG efficacy of 80% against both meningitis and miliary TB, was applied to estimate the number of severe cases prevented under a hypothetical 100% BCG coverage [4].

The number needed to vaccinate was calculated by dividing the birth cohort (100,000 children) in each setting by the estimated number of severe TB cases prevented.

The number of adverse events following BCG vaccinations was estimated from the available evidence in literature applicable to the European context.

Literature search provided several different results on BCG adverse events in European settings [5,6,18,19].

For the purpose of this work we assumed an incidence of disseminated BCG infection of 4 per 100,000 and an incidence of suppurative lymphadenitis of 1 per 1000 [5].

Validation of the model

We utilized two methods for validating the ARI based model:

a. We compared data from French surveillance report for the 2000–2002 period [20] to the estimates obtained through the ARI model using the French data (birth cohort and TB prevalence) for the year 2004 [15,21].
b. We selected a setting (Italy) where no BCG vaccination is performed in the 0–4 age group [22] and we compared the average TB meningitis cases in the 1999–2003 period [23] to the estimate obtained through the ARI model using the Italian data (birth cohort and TB prevalence) for the year 2000 [15,21].

95% confidence intervals have been calculated assuming that TB severe cases follow a Poisson distribution. An Excel worksheet has been used to this purpose.

Selective versus universal vaccination strategy

We also proposed a calculation for comparing a universal BCG policy (100% coverage of the whole birth cohort assumed) versus a selective BCG policy (100% coverage of the children within the birth cohort belonging to a specified high-risk group).

The number needed to vaccinate has been calculated in three hypothetical settings where high-risk groups represented 5%, 10% and 20% of the entire population, respectively.

Decrease (%) in number needed to vaccinate — switching from universal to selective vaccination policy under these three different levels in the general population — has been calculated in relation to the proportion of TB severe cases belonging to high-risk groups.

Calculation of prevented primary TB cases in the first 15 years of life and prevented adult cases

Prevented cases of primary TB in children under 15 years of age was also calculated based on the model by Fine et al and assuming a BCG efficacy of 50% in preventing all primary TB in children under 15 [4].

Results

Main outcomes of the model applied to the 5 settings are showed in Table 1.

TB prevalence (SS + per 100,000 population) ranges from 1.7 (setting A, 5th percentile) to 33.4 (setting E, 95th percentile), corresponding to ARI values ranging from 0.01 to 0.20 per 100,000 population.

The number of prevented severe TB cases in the hypothetical 100,000 children birth cohort (100% vaccine coverage, 80% vaccine efficacy) ranges from 0.6 to 12.0, with a NNV ranging from 161,499 to 8317. The expected number of disseminated BCG-itis per severe case prevented ranges from 0.3 to 6.5. The number of expected suppurative lymphadenitis per severe TB case prevented ranges from 8 to 161.

Table 1 Outcomes for the 5 selected settings from the ARI model applied for a cohort of 100,000 children

Setting	Percentile	TB Prevalence[a]	ARI (%)	Expected severe TB cases (TB meningitis)[b]	Prevented severe TB cases (TB meningitis)	Number of BCG vacc. per severe TB prevented	Expected disseminated BCG-itis per severe TB case prevented	Expected supp. Lymphadenitis per severe TB case prevented	Prevented primary TB cases (children under 15 years)
A	5th	1.7	0.01	0.8 (0.5)	0.6 (0.4)	161,499	6.5	161	3.8
B	25th	2.9	0.02	1.3 (0.9)	1.0 (0.7)	95,785	3.8	96	6.5
C	50th	4.7	0.03	2.1 (1.4)	1.7 (1.1)	59,102	2.4	59	10.6
D	75th	15.0	0.09	6.8 (4.5)	5.4 (3.6)	18,519	0.7	19	33.8
E	95th	33.4	0.20	15.0 (10.0)	12.0 (8.0)	8,317	0.3	8	75.2

[a] Prevalence of sputum smear positive TB per 100,000 population.
[b] Calculated from $Tb_{sev\text{-}exp} = (1 + k)\ (5B\beta\ p_{sm} + \rho_{men})$ and $Tb_{men\text{-}exp} = (5B\beta\ p_{sm} + \rho_{men})$ extrapolated from formula in Box 1.

Box 1
Calculation of severe TB cases prevented based on the annual risk of infection (figures used appear in italics).

$Tb_{sev\text{-}prev} = (1 + k)\ (5B\beta\ p_{sm} + \rho_{men}) \times \varepsilon$
$Tb_{sev\text{-}prev}$ = severe TB cases prevented in a birth cohort for the first 5 years of life
B = births in a given year (*100,000*)
β = contact rate (*6*)
p_{sm+} = prevalence of smear positive disease (*range 1.7—33.4 per 100,000*)
$\beta\ p_{sm+}$ = annual risk of infection
ρ_{men} = proportions of infections leading to Tb_{men} (*0.01*)
k = ratio of miliary TB cases to TB meningitis cases (*1.5*)
ε = BCG efficacy against severe TB cases (0.8)

The number of prevented primary TB cases in the same cohort for the first 15 years of life ranges from 3.8 to 75.2.

Number of tuberculous meningitis (TBM) cases in absence of BCG vaccination estimated by the INVS on the 2000/2002 French birth cohorts are 11—16 (interval). Number of TBM estimated applying the ARI model to the 2004 French birth cohort is 15 (95% CI: 8.4—24.7) (Table 2).

According to the data provided by the hospital records system of the Italian Ministry of Health during the period 1999/2003 the annual number of reported TBM cases has been 5.6 on average. The number of expected TBM cases calculated applying our ARI model to the 2004 Italian birth cohort is 4.6 (95% CI: 1.4—10.9) (Table 2).

Finally, the percentage decrease in NNV has been used as a parameter for comparing a selective BCG policy (100% coverage of the children within the birth cohort belonging to a specified high-risk group) versus a universal BCG policy (100% coverage of the whole birth cohort assumed).

Fig. 1 shows three different hypothetical situations where respectively 5%, 10% and 20% of the entire population belongs to TB high-risk groups. The figure intends to show the percentage decrease in number of children needed to be vaccinated (NNV) under different proportions of high-risk individuals in both the general population and among cases.

The ARI model applied to these settings shows how the decrease in NNV is very favourable in those situations where high-risk groups represent the 5% of the entire population, even if the percentage of cases belonging to such groups is low. On the other hand an important decrease in NNV (>60%) is evident in all three settings when the proportion of cases belonging to the high-risk population is over 50%. On the other hand, when the proportion of population belonging to high-risk groups is high (20%), the NNV under selective vaccination paradoxically increases — when compared to universal vaccination (% decrease is a negative value on the *Y*-axis) — if the number of cases belonging to high-risk groups is less than 20%.

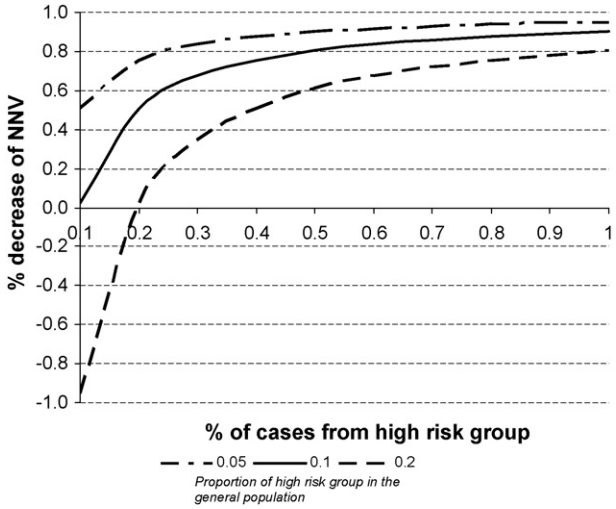

Figure 1 Percentage decrease in number needed to vaccinate (switching from universal to selective vaccination) under different assumptions of proportion of cases belonging to high-risk groups, and proportion of high-risk group individuals in the general population (three assumptions have been used namely, 5%, 10% and 20%).

Table 3 shows how in high prevalence settings (setting D and E) selective vaccination could lead to a low effectiveness of the program with the majority of cases unprevented (from 4.6 to 10.8 per 100,000 population). This finding is related to the fact that most of severe TB cases occur outside the high-risk group. In low prevalence settings the number of unprevented cases would range between 0.3 and 0.9 per 100,000 population. In addition the NNV in settings D—E paradoxically increases switching to selected vaccination when the proportion of population belonging to high-risk groups is around 20%.

Discussion

The purpose of our work was to adapt a model that would estimate the effects of withdrawal or change in BCG vac-

Table 2 Comparative validation of the model

Model	Expected cases TBM	Prevented cases TBM[a]	Methods/source
INVS 2000/2002	11—16	9—13	Surveillance based method/notifications
ARI based (cohort 2004)	15 (95% CI: 8.4—24.7)	12 (95% CI: 6.2—20.9)	ARI based model
Italy[b]	5.6	NA	Hospital records
ARI based (cohort 2004)	4.6 (95% CI: 1.4—10.9)	NA	ARI based model

[a] Under universal BCG coverage.
[b] Average of hospitalised cases during the period 1999/2003.

Table 3 Comparison of universal vs. selective high-risk groups BCG vaccination under different assumptions in settings A–E

Setting	Percentile	% of cases belonging to high-risk groups[a]	Severe TB cases prevented under *universal* BCG vaccination	Severe TB cases prevented under *selective* BCG vaccination	Number of BCG vacc. per severe TB prevented under *universal* BCG vaccination	Number of BCG vacc. per severe TB prevented under *selective* BCG vaccination (under three different assumptions of proportion of population belonging to high-risk groups 20%)		
						20%	10%	5%
A	5th	50	0.6	0.3	161,499	64,599	32,300	16,150
B	25th	50	1	0.5	95,785	38,314	19,157	9,579
C	50th	50	1.7	0.8	59,102	23,641	11,820	5,910
D	75th	15	5.4	0.8	18,519	24,691	12,346	6,173
E	95th	1	12	1.2	8,317	16,633	8,317	4,158

[a] Average % of cases belonging to high-risk groups in EU countries in the range of prevalence A–E, according to the EURO TB report 2005 [24].

cination under different settings. We did not specifically address the issue of deriving ARI from prevalence of disease but we merely applied previously developed methodologies. We recognize that prevalence estimates carry a degree of uncertainty. Furthermore, calculations were made on the basis of smear positive prevalence only, disregarding the possible transmission from smear negative cases.

The model has been deliberately biased to maximize the effect of BCG in preventing tuberculosis. On the other hand, we did not further discuss the impact of BCG vaccination on primary TB in children under 15 years of age, in view of the uncertainties around both the proportion of infected children developing primary TB, and the variability in efficacy of the vaccine against this form of disease [4].

In addition we also felt that severe forms of TB have a relative higher weight in cost–benefit analysis.

Another limit of the model might be related to the wide confidence intervals of the estimates, particularly evident in the calculated number of TB meningitis reported in Table 2. This is a consequence of the low incidence of the disease in these countries.

Particularly the following assumptions might influence the results towards overestimation of the number of cases prevented:

- High contact rate
  In the proposed model we have used an average contact rate of 6. This figure is probably overestimating the real contact rate in low prevalence countries [3,13]. Hence, the consequently overestimated ARI derived from the prevalence of infectious disease will have the effect of maximizing the number of potential TB arising in children and the number of cases prevented by BCG.
- Upper end of efficacy range in preventing both severe forms and pulmonary forms
  The assumptions of 80% protection against severe forms of disease in children under 5 years of age represent the higher end of the efficacy range.
- Assumption on the annual reduction in the risk of infection
  To simplify the model, and in view of the lack of recent data (in low prevalence countries) on the annual reduction in risk of infection we have assumed the annual reduction of ARI to be negligible (0%). This might have had the effect in our model of maximizing the number of potential severe TB cases and hence overestimating the number of cases prevented in the vaccinated cohort.
- Proportions of childhood infections leading to tuberculosis meningitis
  Similarly, the assumption on the proportion of childhood infections that lead to tuberculous meningitis (0.7–1%)% might be an overestimate of the current value in Europe, since it derives from observations performed in the pre-chemotherapy era [3,13,16,17].

The model has its weaknesses in the number of assumptions made to reach the estimated number of severe forms of TB in the under 5s population.

Through the model we are assuming a homogeneous ARI throughout the population at national level. However, it is clear from current notification data [24] that cases are often concentrated in high-risk population. It is therefore likely

that the risk of infection in such sub-population well exceeds the calculated average.

Given the above limits, nevertheless this model provides good estimates when compared with surveillance data from France and Italy, and it could represent a valid tool to start a decision making process on BCG vaccination in European countries.

The model shows that a universal BCG programme can be definitely beneficial in setting E (95th centile of the 29 European countries with prevalence level around 30 SS + per 100,000). In this setting the number of adverse events per case prevented, as well as the number needed to vaccinate, are reasonably low.

In setting D (75th centile, prevalence level around 15 per 100,000 pop) the benefit of universal BCG vaccination is questionable. Hence, in this settings other factors play a major role in the decision making process.

In setting A—C (5th to 50th centile, prevalence level under 5 per 100,000) it appears that universal vaccination might lead to an excess of adverse events per case prevented (more than 2.4 BCG-itis and more then 59 lymphadenitis). It becomes important in these settings to evaluate the distribution of cases between general population and high-risk groups, and eventually assess the applicability of a selective vaccination.

When the model is applied to compare the effect of universal versus selective vaccination (perceptual decrease of number needed to vaccinate) in a setting with a range of percentage of general population belonging to an identified high-risk group from 5 to 20% the following can be observed:

- In the case of over 50% of cases belonging to the high-risk group, selective vaccination is beneficial (60% and more decrease) regardless of the composition of the population (Fig. 1).
- The weight of the high-risk group within the population plays a more important role when less than 50% of cases belong to the risk group. In this case the smaller the high-risk population (within the general population) the greater the benefit will be.
- Under selective vaccination most cases remain unprevented in high prevalence settings, with a paradox effect of NNV increase.

Conclusion

In our work we aimed at providing a tool to facilitate assessment of BCG policies in low to intermediate burden settings.

The theoretical model we discussed is particularly relevant to the European countries where smear positive TB prevalence ranges from 1 to 88 per 100,000. According to the model, in European countries, where the prevalence level is under 5 per 100,000, it appears that universal vaccination might lead to an excess of adverse events per severe TB case prevented. In countries with prevalence rates around 15 per 100,000 (75% percentile) the value of universal BCG vaccination is questionable.

In these settings it becomes important to assess the applicability of a selective vaccination that seems to be very favourable in those situations where high-risk groups represent at least 5% of the entire population or when the proportion of cases belonging to the high-risk population is over 50%.

Switching to selective vaccination of high-risk groups requires a remarkable effort. Proper surveillance systems must be in place to be able to detect and identify populations with relative higher TB rates than the general population.

This represents a major challenge, as the definition of a high-risk population and the classification of an individual as such pose several difficulties. Operational feasibility of such definitions should be assessed and easily recognizable high-risk groups identified.

It should also be remarked that the results obtained through the model are based on an assumption of 100% coverage in both scenario. This is most probably not achievable; particularly under a selective vaccination programme which targets hard to reach populations. Nevertheless, the model provides a theoretical background to identify key issues for consideration in the decision making process of selective versus universal vaccination.

From an operational point of view reaching specific population groups requires intensive and dedicated interventions by the public health force. On the other hand effective selective immunization programmes have been successfully implemented in Europe [25,26].

Calculation of the benefits of BCG selective vaccination should also take into consideration that the ARI in the high-risk population might be several times higher than the average estimates applied to the general population in our model.

Our model adds to previously elaborated criteria for discontinuation of BCG vaccination in low prevalence countries by the International Union Against Tuberculosis and Lung Disease (IUATLD) [27], by recognizing the heterogeneity of the population in terms of risk of TB (particularly severe TB).

We believe that a selective immunization programme should be integrated into a comprehensive TB control approach aiming at maximizing case finding and ensuring the highest standards of care in high prevalence populations. Such an effort is worthy to be endured, since resources freed after BCG vaccination policy change could be reutilised in a more effective way.

In conclusion, the decision on BCG policy changes in countries with intermediate TB prevalence should be taken after an accurate assessment of the epidemiological situation, but also on the basis of a thorough knowledge of the capacity of the local public health system to specifically address vulnerable and high-risk populations.

Acknowledgments

The authors would like to thank Dr. Victoria Romanus and Dr. Bernadette Bourdin-Trunz for commenting and providing valuable suggestions on the early draft of the work.

References

[1] No author listed. BCG Vaccine. Weekly epidemiological record 2004;79:25—40.

[2] Colditz GA, Berkey CS, Mosteller F, Brewer TF, Wilson ME, Burdick E, et al. The efficacy of bacillus Calmette-Guerin vaccination of newborns and infants in the prevention of tuber-

culosis: meta-analyses of the published literature. Pediatrics 1995;96(1):29—35.
[3] Trunz B Bourdin, Fine PE, Dye C. Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness. Lancet 2006;367:1173—80.
[4] Fine PEM, Carneiro IAM, Milstien JB, Clements CJ. Issues relating to the use of BCG in immunization programmes. A discussion document. WHO Geneva. 1999. Last accessed at WHO web site http://whqlibdoc.who.int/hq/1999/WHO_V&B_99.23.pdf on 20 January 2007.
[5] Romanus V, Fasth A, Tordai P, Wiholm BE. 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.
[6] 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(4):288—92.
[7] Trnka L, Dankova D, Zitova J, Cimprichova L, Migliori GB, Clancy L, et al. Survey of BCG vaccination policy in Europe: 1994—96. Bull World Health Organ 1998;76(1):85—91.
[8] Trnka L, Dankova D, Svandova E. Six years' experience with the discontinuation of BCG vaccination. 1. Risk of TB infection and disease. Tuber Lung Dis 1993;74(3):167—72.
[9] Infuso A, Falzon D. European survey of BCG vaccination policies and surveillance in children, 2005. Euro Surveill 2006;11(3):6—11.
[10] 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 littérature et analyse des données disponibles [in French]. Last accessed at http://www.invs.sante.fr/publications/default.htm on 20 January 2007.
[11] Rahman M, Sekimoto M, Takamatsu I, Hira K, Shimbo T, Toyoshima K, et al. Economic evaluation of universal BCG vaccination of Japanese infants. Int J Epidemiol 2001;30(April (2)):380—5.
[12] Romanus V, Svensson A, Hallander HO. The impact of changing BCG coverage on tuberculosis incidence in Swedish-born children between 1969 and 1989. Tuber Lung Dis 1992;73(June (3)):150—61.
[13] Trunz B. Bourdin. Global impact of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis. Report for M.Sc. thesis. London School of Hygiene and Tropical Medicine, 2004.
[14] Rouillon, et al. BCG vaccination and epidemiological sitaution; a decision making approach to the use of BCG. Adv Tuberc Res 1976;19:64—196.
[15] WHO online Global Tuberculosis Database http://www.who.int/globalatlas/dataQuery/default.asp last accessed on 02 July, 2007.
[16] Styblo k, Meijer J, Sutherland I. The transmission of tubercle bacilli. Bull Int Union Tuberc Lung Dis 1969;42:1—73.
[17] Styblo K, Sutherland I. Epdemiology of tuberculosis in children. Bull Int Union Tuberc Lung Dis 1982;57:133—9.
[18] No authors listed. Tuberculosis, place ov vaccination in control of the disease. INSERM Colective Expert Report, 2004. http://ist.inserm.fr/basisrapports/tuberculose/tuberculose-synthese-anglais.pdf, last accessed 25 January 2007.
[19] Tala-Heikkila M, et al. Evaluation of the Finnish newborn BCG vaccination programme. 2001. Last accessed at http://www.ktl.fi/publications/2001/b12.pdf on 25 January 2007.
[20] Dr. Levy-Bruhle. Personal communication.
[21] EUROSTAT website http://epp.eurostat.ec.europa.eu/portal/page?_pageid=1996,45323734&_dad=portal&_schema=PORTAL&screen=welcomeref&open=/&product=Yearlies_new_population&depth=2.
[22] DECRETO DEL PRESIDENTE DELLA REPUBBLICA 7 novembre 2001, n. 465 - Regolamento che stabilisce le condizioni nelle quali è obbligatoria la vaccinazione antitubercolare, a norma dell'articolo 93, comma 2, della legge 23 dicembre 2000, n. 388 (Gazzetta Ufficiale n. 7 del 9/1/2002).
[23] http://www.ministerosalute.it/programmazione/sdo/ric_informazioni/default.jsp [last accessed 19 May, 2007].
[24] EURO TB and the national coordinators for tuberculosis surveillance in the WHO European Region. Surveillance of tuberculosis in Europe. Report on tuberculosis cases notified in 2005.
[25] Bakshi D, Sharief N. Selective neonatal BCG vaccination. Acta Paediatr 2004;93(9):1207—9.
[26] Romanus V. Selective BCG vaccination in a country with low incidence of tuberculosis. Euro Surveill 2006;11(3):14—7.
[27] International Union Against Tuberculosis and Lung Disease.Criteria for discontinuation of vaccination programmes using Bacille Calmette Guerin (BCG) in countries with a low prevalence of tuberculosis. Tubercle and Lung Disease 1994;75:179—181.