Impact of the BCG vaccination policy on tuberculous meningitis in children under 6 years in metropolitan France between 2000 and 2011

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In France, *Bacillus Calmette–Guérin* (BCG) vaccination by multipuncture device was withdrawn in 2006. In 2007, universal mandatory BCG vaccination was replaced by vaccination of high-risk children. To evaluate the impact of these changes on tuberculous meningitis (TBM) epidemiology, data on culture-positive and culture-negative (or unknown microbiological result) TBM in ≤5 years olds were collected from 2000–2011. Ten culture-positive and 17 culture-negative TBM cases were identified, with an annual incidence rate ranging from 0.16 to 0.66 cases per 10 million inhabitants. The average annual numbers of TBM cases were 2.7 and 1.8 from 2000–2005 and 2006–2011, respectively. In Ile-de-France where all children are considered at risk, the overall incidence rates were 1.14 and 0.29 per million for the two periods. In other regions where only at-risk children are vaccinated since 2007, rates were 0.30 and 0.47, respectively. None of these differences were significant. Annual incidence rates for each one-year age group cohort were comparable before and after changes. Childhood TBM remains rare in France. No increase in incidence was observed after changes in BCG vaccination strategy. Ongoing surveillance should be maintained, as a slight increase in TBM in the coming years remains possible, in the context of suboptimal vaccination coverage of high-risk children.

Introduction

Tuberculous meningitis (TBM) is estimated to account for ca 1% of all tuberculosis (TB) cases in developed countries [1,2]. TBM is the most severe form of TB, and it is associated with a high mortality: 7–65% in developed countries, and up to 69% elsewhere [2–4]. The suspicion of TBM is based on a combination of epidemiological, clinical, and preliminary cerebrospinal fluid (CSF) findings. The confirmation of the TB aetiology for meningitis is done by direct isolation of *Mycobacterium tuberculosis complex* in the CSF.

Children aged 6 months to 5 years are among the age groups most frequently suffering from TBM [1,5]. TBM symptoms in these children are not specific and a definite diagnosis, i.e. through smear-positive CSF and/or culture-positive CSF, is a rare event highly dependent on the volume of the CSF sample [6]. New diagnostic techniques based on gene amplification have been developed but their sensitivity and specificity suggest they may not be as helpful as expected [7]. Thus, TBM diagnosis is often based on a bundle of criteria that may vary according to centres, despite a recent effort in diagnosis standardisation.

Bacillus Calmette–Guérin (BCG) vaccination in early childhood is one of several TB control interventions to prevent TBM. Two meta-analyses published in the early 90s have confirmed the effectiveness of BCG against extra-pulmonary TB (mainly meningitis) with an effectiveness varying depending on the study design from 64% to 86% [8,9]. This led the World Health Organization (WHO) to renew its recommendation in favour of BCG vaccination for infants in all countries [10]. Such a strategy has been applied in most countries, including France, where BCG vaccination has been mandatory since 1950 for children entering collective life, i.e. at the latest when 6 years old (age of mandatory schooling). Vaccine coverage at that age has been consistently close to 100%, due to law enforcement by the Ministry of Education [11]. In January 2006, the multipuncture device (Monovax, Sanofi Pasteur MSD, France), which was used for more than 90% of BCG vaccinations, was withdrawn from the French market and replaced by the intradermal BCG device (SSI, Statens Serum Institut, Denmark), the technique recommended by WHO. The difficulty of using the latter technique in young infants by untrained medical staff as well as its less favourable safety profile compared with the multipuncture device, led to a decrease in BCG coverage of

more than 50% in a few months, despite the vaccination still being mandatory [12].

In July 2007 in France, universal mandatory BCG vaccination was replaced by a strong recommendation to vaccinate children at higher risk of TB, as soon as possible after birth. The main rationale for this change was the decreasing incidence of TB in France, with 2002 to 2004 incidences of both sputum smear-positive TB cases and meningitis in children below the thresholds recommended by the International Union against Tuberculosis and Lung Diseases (IUATLD) for considering a possible discontinuation of BCG vaccination [13]. The heterogeneity of the risk of infection, questioning the benefit/risk balance of BCG in low risk children, was also an important factor in the decision [14]. High risk groups targeted by the new vaccination strategy include mainly children born or whose parents were born in highly TB-endemic countries and children living in the two French regions with high incidence rates of TB: French Guiana, located overseas (26.2/100,000 in 2006), and Paris and its surrounding departments known as Ile-de-France region (17.1/100,000 in 2006) [15].

In Ile-de-France, where all children are targeted by the new policy, administrative data, complemented with data from surveys in the public sector, were used to monitor the BCG vaccination coverage. It has progressively increased from ca 50% in children born in 2007 to ca 80% in children born in 2010 [16]. In the rest of France, the vaccination coverage for high risk children was much lower, estimated, in 2008, between 32% and 40% for children followed-up in the private sector [17,18], representing around 90% of the children, and, in 2009, at 62% for those followed-up in Maternal and Child Health Clinics [19].

A simple modelling exercise, carried out before the decision of discontinuation of systematic BCG vaccination, has concluded that the switch to a vaccination strategy targeting high-risk children only could lead to an annual increase, after 15 years, of up to four and nine cases of TBM in children, for vaccination coverages of 95% and 50%, respectively, in those children, and considering an effectiveness of the vaccine of 85% against meningitis in children [14].

In order to assess the impact of the change in the BCG strategy and of the suboptimal vaccination coverage in high-risk children, we conducted a retrospective survey of the TBM incidence in children aged ≤ 5 years for the period 2000 to 2011. Our primary objective was to compare the pre and post 2006 annual incidence rates of TBM in children.

Methods

Tuberculous meningitis data collection

In France, TB has been a mandatorily notifiable disease since 1964 through the Mandatory Notification System

(MNS). For each TB case, each physician or microbiologist has to send a standardised paper notification form to the corresponding Regional Health Authority. After data anonymisation and validation, data are annually transmitted to the National Institute for Public Health Surveillance (Institut de Veille Sanitaire, InVS) in St Maurice. Any patient with clinical and/or radiological signs compatible with TB and treated by an anti-TB treatment should be reported, whether or not there is a culture-positive sample at the time of notification.

In addition to the MNS, a nationwide laboratory network set-up in 1992 for the surveillance of multidrug-resistant TB (MDR-TB), has collected annual data on culture-positive TBM among patients aged ≤ 5 years since the year 2000, from all laboratories performing mycobacteria culture. This network is coordinated by the National Reference Centre (NRC) for mycobacteria and resistance of mycobacteria to anti-tuberculosis drugs, in Paris [20].

All cases of TBM diagnosed in metropolitan France in patients aged ≤ 5 years, and recorded between 1 January 2000 and 31 December 2011 in MNS and NRC databases were included. Because all data were anonymised before recording in both databases, we had to go back to regional health authority data files and to local laboratories to identify cases based on notifying healthcare institution, physician or microbiologist identifiers, and patient birth date. Thereafter, a questionnaire was sent to physicians and/or microbiologists in order to collect additional information, especially on bacteriological results and outcome.

A confirmed case was defined as a patient aged ≤ 5 years with a positive culture of *M. tuberculosis* complex in a CSF sample or a brain biopsy during the study period. Cases notified as TBM but with missing data or negative culture were considered as possible cases. No additional information was recorded for possible cases.

Incidence rates computation

Because the risk of TBM varies with age, even within the 0 to 5 years age group, and of the progressive replacement of the fully vaccinated cohorts by partially vaccinated birth cohorts, we stratified the analysis by age. For each year of age (0–5) defined by the age at diagnosis, we calculated and compared the TBM incidence rates in two groups of children, those born before 1 January 2006, referred to as fully vaccinated cohorts and those born after, referred to as partially vaccinated cohorts. Despite the change in vaccine strategy in 2007, we chose 1 January 2006 as the trade-off between the two cohorts because the vaccine coverage dropped immediately after the withdrawal of the multipuncture device from the French market.

Each case was assigned to one of the two groups depending on their birth cohort: all cases that occurred up to 2005, were assigned to the fully vaccinated

cohorts as well as cases aged 1 year and more in 2006, 2 years or more in 2007, 3 years or more in 2008, 4 years or more in 2009, 5 years in 2010. In 2011, all cases occurred in children belonging to the partially vaccinated cohorts (Figure). Two analyses were performed, one with only confirmed cases and the other with confirmed and possible cases.

The analysis was done separately for Ile-de-France (around 22% of the birth cohorts) where BCG remains recommended for all children, and the rest of the country. Population data for incidence rate computations were annual population estimates obtained from the French National Institute of Statistics and Economic Studies (INSEE, www.insee.fr). Data on the size of each one-year age group, for each year and for each of the two groups of regions were used. We considered TB incidence in the general population to be stable during the study period.

Statistical analysis was performed by using STATA (STATA Corp, College Station, TX, US). Fisher's exact test was used for comparison of incidence rates.

Ethics approval

Approval was obtained from the National Commission for Information Technology and Civil Liberties (CNIL, Number 1375404) in 2010, according to the French law.

Results

From 2000 to 2011, 29 cases of TBM were notified to the MNS. Among them, four were excluded because of duplicate notification ($n=2$), of diagnosis made before 2000 ($n=1$), and of misdiagnosis (viral meningitis) found subsequently to the notification ($n=1$). Two others were not included because they were from French Guiana and Guadeloupe Island, i.e. outside metropolitan France. Consequently, eight confirmed cases (culture-positive TBM) and 15 possible cases (10 culture-negative CSF and 5 with lost records preventing evaluation) were included in the study.

During the same period, the NRC network recorded 12 cases of TBM among children ≤ 5 years old. One was the

patient from French Guiana also identified by the MNS, who did not fulfil inclusion criteria. Nine confirmed and two possible cases (1 culture-negative CSF and 1 with lost records) were thus retained.

A total of seven confirmed cases were identified in both systems; one case was reported only to the MNS, and two were registered only in the NRC network. Consequently, a total of 10 culture-positive cases of TBM were identified by both sources combined between 2000 and 2011. Finally, a total of 27 cases, including 10 confirmed cases and 17 possible cases, were basis for the analysis.

TABLE 1

Characteristics of culture-positive tuberculous meningitis cases in children ≤ 5 years old, metropolitan France, 2000–2011 ($n=10$)

Characteristic	N
Male	6
Age (years)	
0 – < 1	5
1 – < 2	1
2 – < 3	3
5 – < 6	1
Median (months)	8.5
Place of birth	
France	6
North Africa	1
Sub-Saharan Africa	3
HIV status	
Negative	7
Unknown	3
BCG vaccination	
Yes	3
No	6
Unknown	1
Cerebral localisation of TB	
CSF	10
Tuberculoma/nodule	0
Contact with TB patient	9
Extra-cerebral TB manifestations	
None	3
Pulmonary	2
Disseminated	4
Unknown	1
Outcome	
Full recovery	2
Sequelae	6
Death	2

BCG: Bacillus Calmette–Guérin; CSF: cerebrospinal fluid; TB: tuberculosis.

FIGURE

Fully and partially Bacillus Calmette–Guérin-vaccinated cohorts by year of and age at tuberculous meningitis diagnosis, metropolitan France 2000–2011 ($n=25$)

Characteristics of culture-positive tuberculous meningitis cases

Among the 10 identified culture-positive cases, six were French-born, and four were born in Africa (Table 1). Six cases were male. The HIV status was known for seven cases and was negative for all of them. BCG vaccination status was known for nine cases, of which six had not been vaccinated. All six were from outside the Ile-de-France region, five were French-born and one was foreign-born. Two of the six, including the foreign-born case, were born before 2006, i.e. at a time when BCG vaccination was mandatory for all children. Among all 10 cases, nine had an identified putative TB source case, three foreign-born and six French-born cases including the four unvaccinated cases born since 2006. Among the latter four, one had relatives born in Africa, and three had French-born parents without identified risk factors for TB.

A total of seven cases had extra-cerebral manifestations of TB disease, including two with pulmonary TB, four with disseminated TB, and one with an unrecorded site of disease. Most of the cases (n=8) recovered, but 6 had neurological sequelae, and 2 died (Table 1).

TBM incidence rates

From 2000 to 2011, the annual number of confirmed TBM cases varied from 0 to 1, and the annual incidence rate from 0 to 0.17 cases per 10 million inhabitants. The total (confirmed and possible cases) number of TBM cases reported each year to both systems varied from 1 to 4, and the annual incidence rate from 0.16 to 0.66 cases per 10 million. These correspond to annual TBM

incidences in children aged ≤ 5 years below 10 cases per 10 million children (Table 2).

There was no significant time trend related to the initial dramatic drop of coverage in 2006 followed by the change in the vaccination policy, neither for confirmed cases nor for the total (confirmed and possible) number of cases. The average annual numbers of TBM cases (confirmed and possible) were 2.7 and 1.8 in the periods from 2000 to 2005 and 2006 to 2011, respectively.

Incidence rates of childhood TBM by one-year cohorts before and after the change in vaccination policy are provided in Table 3 for all cases. In the Ile-de-France populations, the cohort-specific incidence rates seem lower in partially vaccinated cohorts when compared with fully vaccinated ones, although none of the differences are statistically significant. In the rest of France, cohort-specific incidence rates appear comparable in both groups. A similar conclusion can be drawn when only considering confirmed cases (data not shown).

Discussion

Any change in BCG vaccination strategy is expected to impact paediatric TBM epidemiology because BCG vaccination has been proven to be effective in preventing invasive TB in young children [8,9]. We evaluated the impact on TBM epidemiology of the changes in BCG vaccination strategies implemented in France in 2006 and 2007.

From 2000 to 2011, the annual number of TBM in children aged ≤ 5 years in metropolitan France has remained

TABLE 2

Numbers and annual incidence rates of confirmed, possible and total tuberculous meningitis cases in children ≤ 5 years old, metropolitan France, 2000–2011 (n=27)

Year	Incidence rate of confirmed cases ^a		Per 10 million inhabitants (general population)	Number of possible cases ^b	Total number of cases	Total incidence rate of TBM	
	Number of confirmed cases	Per 10 million children				Per 10 million children	Per 10 million inhabitants (general population)
2000	1	2.32	0.17	1	2	4.64	0.34
2001	1	2.28	0.17	2	3	6.85	0.51
2002	1	2.26	0.17	1	2	4.51	0.34
2003	1	2.24	0.17	1	2	4.48	0.33
2004	0	0	0	3	3	6.67	0.50
2005	1	2.21	0.16	3	4	8.84	0.66
2006	1	4.20	0.16	2	3	6.60	0.49
2007	1	2.19	0.16	0	1	2.19	0.16
2008	1	2.19	0.16	2	3	6.57	0.48
2009	1	2.18	0.16	0	1	2.18	0.16
2010	1	2.16	0.16	0	1	2.16	0.16
2011	0	0	0	2	2	4.29	0.32
Total	10	-	-	17	27	-	-

TBM: tuberculous meningitis.

^a Culture-positive.

^b Culture-negative and undefined.

very low, i.e. from 0 to 1 culture-positive cases and from 0 to 3 additional possible cases. However, definitive diagnosis of TBM in children is difficult and it is estimated that *M. tuberculosis* is not identified in up to 60% of TBM cases [6]. Hence, it is likely that a few cases of TBM were overlooked. However, to address this and minimise underdiagnosis, we combined data from two surveillance systems (MNS, NRC) to improve case ascertainment. We also included cases born abroad for whom the French vaccination strategy may not be applicable. In addition, the inclusion of possible cases in the analysis took into account, at least partially, the difficulties in TBM definite diagnosis [6]. After inclusion of possible cases, the yearly incidence rate of TBM in the period from 2000 to 2011 varied between 0.16 and 0.66 per 10 million inhabitants. Thus it is unlikely that the true incidence rate exceeded the threshold proposed by the IUATLD of 1 case of TBM among <5 years old children per 10 million inhabitants, below which the TBM incidence should remain for at least five years before considering to discontinue BCG vaccination [13].

No increase in TBM incidence has been observed after the shift from universal to selective BCG vaccination in children. In addition, no statistically significant differences could be observed when comparing the age-specific incidences rates among the fully- and the partially vaccinated cohorts. Of note, a recent cross-analysis of the French National Hospital Discharge Database has shown a stable sensitivity of the MNS for all TB cases including TBM, throughout the period from 2000 to 2010 (data not shown). However, the steady incidence rates of TBM across all ages in the recent years, in a context of constant decrease in overall trend in TB [21], call for attention, although the number of confirmed TBM in children is lower than in the 1990s [22].

From 1995 to 2005, vaccination coverage estimates in children aged 24 months in France were around 85% and virtually 100% at 6 years of age [11,23]. After the withdrawal of the multipuncture device in January 2006, coverage decreased immediately for all children

[11]. In Ile-de-France region, where the incidence of TB was 18.2 per 100.000 in 2007 and where all children remain targeted by BCG vaccination, coverage at 9 months of age increased progressively from 73.1% to 80.6% for the 2008 and 2011 birth cohorts, respectively (data not shown). Furthermore, a study conducted in 2010 in Ile-de-France region in children aged ≤5 years has shown that children born to at least one parent originating from a high-TB incidence country were significantly better vaccinated than other children (97.3% vs 78.6%) [24]. This has likely contributed to the absence of increase of TBM in the Ile-de-France region. In the rest of the country, the BCG coverage of high-risk children under the age of 6 years remains insufficient. It was estimated at 40% in 2008 for children followed in the private sector and 62% in 2009 for children followed in Maternal and Child Health clinics, where health professionals may feel more comfortable to perform BCG vaccination, due to the higher number of children they care for [17,19]. Follow-up of BCG sales data are not in favour of a recent increase in coverage (data not shown). Therefore, the absence of increase of TBM outside the Ile-de-France region may be temporary and such an increase may still occur in the future.

The best-documented experience in Europe of shifting from universal to selective vaccination of groups at risk comes from Sweden. Routine vaccination of newborns was discontinued in 1975. After an initial drop in overall vaccine coverage to less than 2%, the coverage increased up to 13.2% of the birth cohort in 1983 and it was estimated that 79% of foreign-born children were vaccinated in 1985. Only one case of TBM was diagnosed from January 1969 to March 1975 and two cases from April 1975 to December 1985 [25]. Other countries such as the UK, Finland or Norway have recently switched from universal BCG vaccination to targeted vaccination [26]. However, data available to date do not allow assessing the impact of this change on the risk of TBM in children.

Our analysis is based on the assumption of a constant risk of infection for children. This simplification has

TABLE 3

Number, and incidence rates per million children for tuberculous meningitis cases^{a,b} in children ≤5 years old, by one-year age cohort and region according to vaccination strategy, metropolitan France, 2000–2011, (n=25)

Age group (year)	Number of one-year age cohorts (birth-cohorts)		Ile de France region					Other regions				
			Number of cases		Incidence rate (per million)		p value	Number of cases		Incidence rate (per million)		p value
	FV	PV	FV	PV	FV	PV		FV	PV	FV	PV	
0–1	13	11	4	1	1.91	0.53	0.2	6	6	0.79	0.91	0.5
2–3	17	7	2	0	0.76	0	0.5	1	0	0.10	0	0.7
4–5	21	3	3	0	0.95	0	0.7	2	0	0.16	0	0.8
All ages	51	21	9	1	1.14	0.29	0.1	9	6	0.30	0.47	0.3

FV: fully vaccinated; PV: partially vaccinated.

^a The exact date of birth was missing for two cases.

^b Possible (culture-negative and undefined) and confirmed (culture-positive).

probably not affected our conclusions because the number of notified pulmonary cases of TB has only decreased by 5% between 2005 and 2011.

In conclusion, childhood TBM remains very rare in France and no increase in incidence rates was observed after two consecutive major changes in BCG vaccination strategies. This favourable result supports the 2007 decision to stop universal BCG vaccination. However, as suggested by modelling of the impact of a selective strategy with sub-optimal coverage, a slight increase in TBM in the 15 years following the change remains possible [14]. Therefore, there is a need for a comprehensive surveillance combining the different sources of data and case definitions, as done in the current analysis, in order to carefully monitor the median and long-term impact of this selective vaccination policy.

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Conflict of interest

None declared.

Authors' contributions

VTB and JR designed the study, collected and analysed data, and wrote the manuscript. DLB, DA, DC participated in the design of the study, in data analysis and in the writing of the manuscript. VJ participated in the design of the study and in data interpretation and final reading of the manuscript.

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