Katarzyna Krysztopa-Grzybowska[1], Iwona Paradowska-Stankiewicz[2], Anna Lutyńska[1]

THE RATE OF ADVERSE EVENTS FOLLOWING BCG VACCINATION IN POLAND

NIEPOŻĄDANE ODCZYNY PO SZCZEPIENIU BCG W POLSCE

Zakład Badania Surowic i Szczepionek[1], Zakład Epidemiologii[2]
Narodowego Instytutu Zdrowia Publicznego – Państwowego Zakładu Higieny w Warszawie

STRESZCZENIE

CEL. Celem pracy była ocena efektywności nadzoru nad odczynami po szczepieniu przeciw gruźlicy w związku ze zmianami dokonywanymi w kalendarzu szczepień.
Częstość niepożądanych odczynów poszczepiennych po szczepieniu szczepionką Bacillus Calmette-Guerin (BCG) w Polsce, podobnie jak w innych krajach stosujących powszechne szczepienia BCG, jest niska. Szczepienia BCG szczepionką zawierającą podszczep *Mycobacterium bovis* BCG Moreau są objęte kalendarzem szczepień w Polsce od 1955 r. Początkowo pierwszą dawkę podawano niemowlętom, a kolejne w 2, 4, 7, 12, 15, i 18 r.ż. Schemat ten obowiązywał aż do późnych lat 90-tych, kiedy to podjęto próbę jego racjonalizacji w kierunku zmniejszania liczby podawanych dawek. Począwszy od 2006 r. zgodnie z zaleceniami Światowej Organizacji Zdrowia, szczepionka BCG jest stosowana wyłącznie w schemacie jednodawkowym – u dzieci do 1 miesiąca życia.
METODY. W pracy przeprowadzono analizę zarejestrowanych niepożądanych odczynów po szczepieniu BCG w latach 1994-2010, szczególnie w odniesieniu do okresów przed i po 2006 r., kiedy były stosowane różne schematy szczepień BCG.
WYNIKI. W Polsce częstość występowania niepożądanych odczynów po szczepieniu BCG wynosiła ok. 0.2‰ w latach 1994-2000 i 0.6‰ w latach 2001-2010, w połowie były to odczyny powstające w miejscu szczepienia, a w połowie zmiany w regionalnych węzłach chłonnych. Wyniki analizy danych zgromadzonych w systemie nadzoru wskazują na podobną częstość występowania niepożądanych odczynów po szczepieniu BCG w okresach przed i po 2006 r., w których stosowane były różne schematy szczepień.
WNIOSKI. Zmiana sposobu gromadzenia danych na temat niepożądanych odczynów z biernego na aktywny oraz wprowadzenie rutynowo stosowanego laboratoryjnego potwierdzania każdego przypadku podejrzenia występowania niepożądanego odczynu po szczepieniu BCG może przyczynić się do rzeczywistej oceny częstości zakażeń, a w perspektywie niezwłocznego przeprowadzenia skutecznej terapii.

SŁOWA KLUCZOWE: *niepożądany odczyn po szczepieniu, szczepionka BCG, nadzór epidemiologiczny*

ABSTRACT

PURPOSE OF THE STUDY. The purpose of the study was to evaluate the capacity of the surveillance system to respond to the schedule changes in the view of TB vaccination uptake.
Complications of Bacillus Calmette-Guerin (BCG) vaccination in Poland are as elsewhere uncommon. In Poland, BCG vaccination with a vaccine produced with *Mycobacterium bovis* BCG Moreau has been a part of the National Immunization Program since 1955. In the beginning the immunization schedule involved several BCG revaccinations in children and youths, with the first dose given to neonates up to 1 month old followed by revaccinations at 2, 4, 7, 12, 15, and 18 years of life. In 90s, the number of BCG doses was reduced and since 2006, according to recommendations made by the WHO, a single BCG dose is given to neonates only.
METHODS. In the study we have analyzed data on adverse events following BCG vaccination registered within a period of 1994-2010, with attention to the periods before and after 2006, when different BCG vaccination schedules were used for immunization.

RESULTS. The frequency of adverse events following BCG vaccination in Poland oscillated within 1994-2000 and 2001-2010 periods around 0.2‰ and 0.6‰ respectively, and in half consisted of local lesions at the injection sites and in half - appeared in the form of the regional lymphadenopathy. The analysis of surveillance data revealed similar rates of adverse events following BCG vaccination in the periods of different BCG vaccination schedules, eg. before and after 2006.
CONCLUSIONS. Improvements in the data collecting manner from passive to active one and the introduction of the routine laboratory confirmation of the infection might evaluate the real prevalence of *Mycobacterium bovis* BCG infections and improve the treatment of adverse events following BCG vaccination cases.

Key words: *adverse event following vaccination, BCG vaccine, surveillance*

INTRODUCTION

Although extensive studies have been performed to develop advanced vaccines against tuberculosis (TB), vaccination with attenuated *Mycobacterium bovis* Bacille Calmette-Guérin (BCG) is the only commercially available vaccine against TB (1). The BCG vaccine is used worldwide; however, its efficacy has been debated as it shows more than 80% efficacy against meningitis and miliary TB in children but 0-80% efficacy against pulmonary TB in adolescents and adults (2). On the other hand, BCG vaccines are generally regarded as being the safest vaccines in use, but the real incidence of disease evoked by BCG strains, e.g. BCG-itis or osteitis, is not known (3). Localized abscesses, regional lymphadenopathy, and disseminated disease in immunocompromised hosts are generally regarded as rare but well recognized complications following BCG vaccination (4). Abscesses at BCG injection sites and in places other than BCG injection sites have also been described in healthy hosts (5, 6).

In Poland, BCG vaccination has been a part of the National Immunization Program since 1951. The nationally produced BCG vaccine with the *M. bovis* BCG Moreau strain has been used since 1955. The immunization schedule up to 90s involved several BCG revaccinations in children and youths, with the first dose given to neonates up to 1 month old followed by revaccinations at 2, 4, 7, 12, 15, and 18 years of life. Then, the number of BCG doses in the schedule was reduced to the first dose given to neonates being followed by revaccinations at 1, 7 and 12 years of life. Currently, since 2006 and according to recommendations given by the WHO, a single BCG dose is given to neonates only. The coverage with the BCG vaccine in Poland is high, and within 2001-2010 oscillated around 93-95% (7).

The aim of this work was the analysis of all available in Poland surveillance data on AEFI (*Adverse Events Following Immunization*) registered after BCG vaccination within a period of 1994-2010, with attention to the periods before and after 2006, when different BCG vaccination schedules were used for immunization to evaluate the capacity of the surveillance system to respond to the schedule changes in the view of TB vaccination uptake.

MATERIAL AND METHODS

National surveillance. An obligatory system of notification of infectious diseases is handled by the Ministry of Health (MOH) through the Department of Epidemiology at the National Institute of Public Health – National Institute of Hygiene (NIPH-NIH), Warsaw since 1958 (8). All data concerning tuberculosis reported are originating from the surveillance performed by the National Tuberculosis and Lung Diseases Research Institute (NTLDRI) in Warsaw. Epidemiological indexes available included: an absolute numbers, rates per 100 000 population, case finding, and treatment outcomes (9). Surveillance on AEFI after BCG vaccination has been introduced officially in 1994 through initiative undertaken by NTLDRI (10). Vaccination coverage and number of BCG AEFI data were collected from '*Vaccinations in Poland*" monographs published yearly by NIPH-NIH (7) on behalf of MOH.

RESULTS

TB and BCG AEFI surveillance. The incidence of TB registered in 1957 (290.4/100 000) decrease above 6 times in 1990 (42.3/100 000) (9). Within 1999-2010 further decrease of incidence has been registered as TB prevalence oscillated between 29.7 and 19.7/100 000. The general data on the number of TB cases in last ten years in Poland with the incidence, number of BCG AEFI registered and hospitalized, level of immunization are presented in the Table I and Figure 1.

Data coming from national surveillance offices in the period of 1994-2000 described 1461 cases of adverse events following vaccination among 7 354 780 of all BCG vaccinated children (11). This estimation allowed

Table I. Surveillance data on TB and BCG AEFI in Poland within 2001-2010[1]

Tabela I. Dane epidemiologiczne zachorowań na gruźlicę oraz niepożądanych odczynów po szczepieniu BCG w Polsce w latach 2001-2010

Year	No. of patients with TB	TB incidence per 100,000	No. of doses BCG	No. of BCG AEFI	No. of BCG AEFI hospitalized	BCG vaccine coverage (%)
2001	10672	27.6	5	133	25	94.9
2002	10475	27.4	4	187	42	95.1
2003	10124	26.5	4	292	66	93.5
2004	9493	24.9	4	321	49	94.1
2005	9269	24.3	4	363	64	94.4
2006	8587	22.5	1	209	63	93.7
2007	8614	22.6	1	133	42	93.3
2008	8081	21.2	1	182	53	93.3
2009	8236	21.6	1	197	60	93.4
2010	7509	19.7	1	176	39	93.4

[1]TB, tuberculosis; BCG, Bacille Calmette-Guérin vaccine; AEFI, adverse events following immunization.

to find AEFI frequency as low as 0.2‰ without osteitis and with a single bcg-itis cases. Most of cases concerned local AEFI (skin ulceration and subcutaneous abscesses) and changes within lymph nodes (lymphadenopathy, suppurative inflammation), which have been observed with the frequencies of 52.9% and 44.3%, respectively. Within a period of 2001-2010 there were registered 2 193 AEFI cases after BCG vaccination with only four cases of bcg-itis in 2009 and 2010. The AEFI frequency estimated from population being vaccinated was found higher than in the previous period (0.6‰) but similar proportions of reactions evoked locally and in lymph nodes was found (Fig.2). Similarly, the number of BCG AEFI cases in the periods of 1994-2000 and 2001-2010 was found at average 200 per year with ¼ of cases hospitalised. Higher rate of Koch phenomenon before but not after 2006 has been recognised.

DISCUSSION

It is generally estimated that local adverse reactions usually occur at the rate of 0.1 to 0.5 per 1000 vaccinations, and serious disseminated complications occur at rate of less than 1 in a million vaccinations (12). Estimations made in Poland by *Szczuka* (10) allow to conclude that the profile of the nationally produced BCG vaccine is safe because of the low rate of the regional lymphadenophaty (0.1‰). It is regarded that upper accepted limit for this complication is 1.0% (12). The average number of BCG AEFI registered cases was 200 per year with one quarter of cases being hospitalized (7). A low frequency of AEFI cases observed in 1994-2000 and 2001-2010 periods in Poland (0.2 ‰ and 0.6 ‰, respectively) was coupled by rarely seen osteitis and bcg-itis cases (five cases) (13). Most of the AEFI cases appeared as local effects and changes within the lymph nodes (lymphadenopathy, suppurative inflammation) (7). The high rate of Koch phenomen cases registered before 2006 might be according *Szczuka* (11) connected

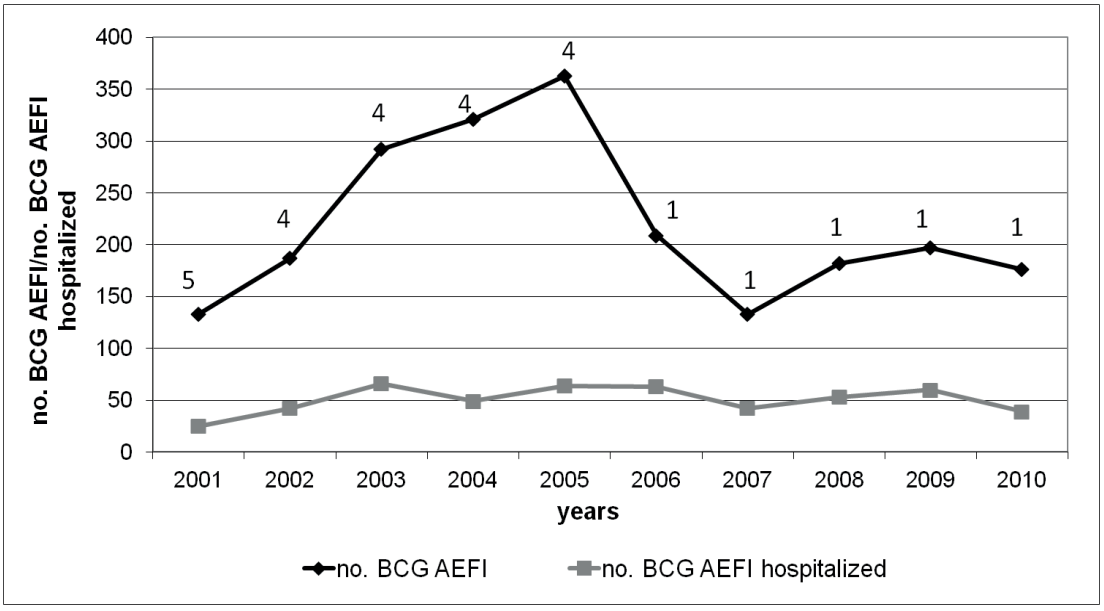

Fig. 1. Number of BCG AEFI cases registered and hospitalized within 2001-2010 in Poland (the number of BCG doses recommended in the schedule was presented above the curve)

Ryc. 1. Liczba zarejestrowanych przypadków niepożądanych odczynów po szczepieniu BCG z uwzględnieniem przypadków hospitalizowanych w latach 2001-2010 w Polsce (nad krzywą podano liczbę dawek szczepionki BCG w obowiązującym schemacie szczepień)

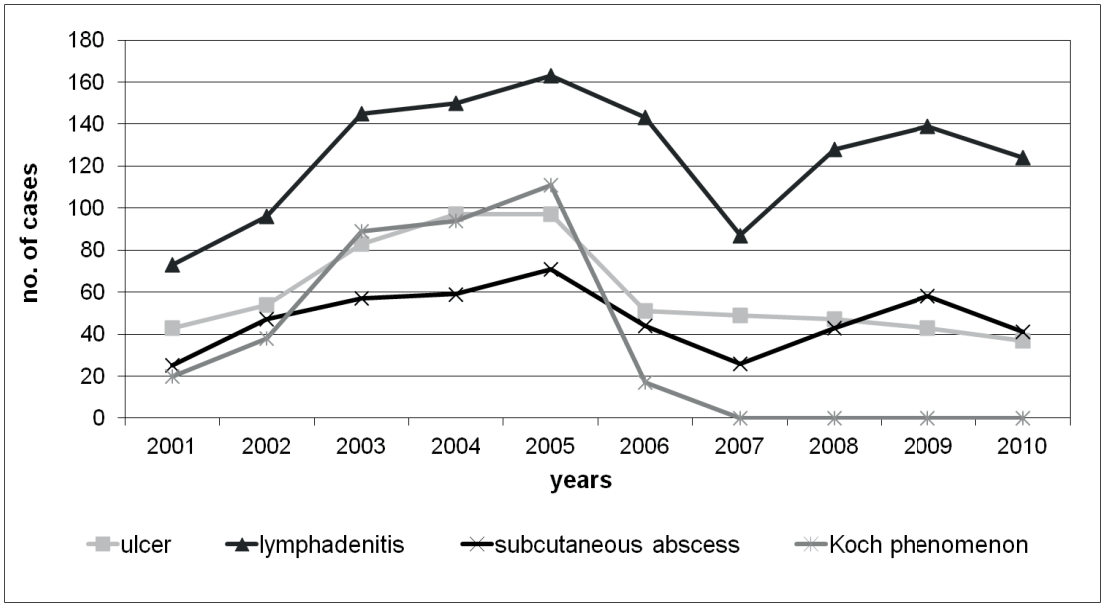

Fig. 2. Characteristics of BCG AEFI cases registered within 2001-2010 in Poland
Ryc. 2. Charakterystyka przypadków niepożądanych odczynów po szczepieniu BCG zarejestrowanych w latach 2001-2010 w Polsce

with improper classification of local adverse events, which has not been observed later. Similar complication rates following BCG vaccination were also found in the literature. *Pankowska* et al. (5) who recognized a low rate of local reactions (0.7‰) that were unrelated to immunodeficiency, mainly in newborns, and rare in revaccinated patients (ulceration and suppuration in vaccination site, suppuration of local lymph nodes with or without fistula) in the period 1994-1995 in Lodz. In 2003-2006, auxiliary lymphadenitis and local subcutaneous abscesses were described in 109 children aged up to 36 months old (6). Furthermore, BCG AEFI in 16 immunodeficient children who had been vaccinated at birth with BCG were described by *Bernatowska* et al. between 1980-2006 (4). The general observation on low level of AEFI found in Poland is in agreement with previous observations. In a clinical trial reported by *Kobierska* and *Stopnicka* (14), the Brazilian substrain, referred to as Moreau, was the safest, inducing suppurative lymphadenitis in only 0.3% of children compared with 2.4% and 4.9% of those immunized with vaccines produced with Danish and French substrains, respectively. Furthermore, trials performed in 1960 in Poland (15) found that the BCG vaccine produced with the French *M. bovis* BCG substrain by the Lublin manufacturer was less reactogenic than those originally produced in France (13.2% versus 8.1%), but more reactogenic than those in *Kobierska* and *Stopnicka's* study (14).

Nevertheless, the rate of AEFI registered after 2006 was unexpectedly found similar to the rate observed before 2006 when vaccination schedule contained several revaccinations. This implies that data on BCG AEFI rate registered, were rather not responding properly to the changes influencing the real rate of possible observations, probably reflective passive not active character of the surveillance. After 2006 only neonates were vaccinated with a single dose of BCG vaccine, thus it would be expected that the number of AEFI cases registered will lower as older groups were not concerned. There was the only one report describing the adverse events rate after BCG in Kujawsko-Pomorskie province between 2006-2010 as lower than in other provinces – but the analysis did not involve comparison with the rate before 2006 (16). Improper vaccine administration was generally suggested as the main reason for AEFI registration (6, 16).

Adverse events following vaccination with BCG, although registered in a national surveillance system, were incidentally confirmed in the laboratory. The differentiation of *M. bovis* BCG from other members of the *M. tuberculosis* complex has previously been regarded as being difficult (17). Recently many tools have been developed to differentiate between and identify particular substrains of *M. bovis* BCG or species within the *M. tuberculosis* complex. Some of them were successfully introduced in BCG vaccine identity testing for purposes of lot release (18). The criteria for the diagnosis of disseminated BCG infection in people with primary immunodeficiency were proposed, including definitive confirmation of *M. bovis* BCG substrain infection by culture and/or standard PCR were proposed (4). However, such diagnostics criteria should be also proposed and introduced for regular confirmation of AEFI after BCG vaccination, as they are able to confirm mycobacterial species, including *M. bovis* BCG substrains. Moreover, new molecular tools might be directly used on clinical material in order to shorten the diagnosis time in comparison to the conventional culture.

In summary, cases of BCG AEFI are rarely recorded in Poland, although *M. tuberculosis* infection could be evoked in vaccinated individuals. A single clinical trial performed in 1965-1977 in Poland on a locally produced TB vaccine showed only 60% efficacy against pulmonary TB in 1-14-year-old children within 6 years after vaccination (15). Moreover currently, the epidemiological profile of TB does not allow to classify the country as a low-burden population. Although TB meningitis is extremely low (six cases of TB meningitis in patients under 5 years of age were registered within the last 10 years), TB culture-confirmed rate, although lowered when compared to the 1980s, is still higher than 5/100 000. Thus, improvement of laboratory diagnostics for BCG adverse events should be considered to allow valid identification of infections in cases of ulcers, abscesses, lymphadenitis and rarely osteitis and BCG-itis, to differentiate the hypersensitivity from infection in large local reactions, and also to confirm or exclude the *M. tuberculosis* infection. Improper identification of mycobacteria makes the real prevalence of BCG infections unknown, and influences negatively the success of therapy. Improvements of surveillance on BCG AEFI by a change from passive into active one are found as more than expected.

Acknowledgments
This study was supported by a grant for scientific research (N N404 207 239) from the Ministry of Science and Higher Education (Poland).

REFERENCES

1. World Health Organization. Global tuberculosis control: epidemiology, strategy, financing: WHO report 2009 [cited 2011 Apr 27]. Available at: http://whqlibdoc.who.int/publications/2009/9789241563802_eng_doc.pdf
2. Brewer TF. Preventing tuberculosis with bacillus Calmette-Guérin vaccine: a meta-analysis of the literature. Clin Infect Dis 2000;31:S64-7.
3. Behr MA. BCG-different strains, different vaccines? Lancet Infect Dis 2002;2:86- 92.
4. Bernatowska EA, Wolska-Kusnierz B, Pac M, et al. Disseminated Bacillus Calmette-Guerin Infection and Immunodeficiency. Emerging Infect Dis 2007;13:799-801.
5. Pankowska A, Rożniecki J. Complications after BCG vaccination in children from Urban area of Lodz in 1994-1995 [in Polish]. Pneumonol Alergol Pol 1997;65:761-6.
6. Gołębiowska M, Andrzejewska E, Stryjewska I, et al. Advers events following BCG vaccination in infants and children up to 36 months of age [in Polish]. Przegl Epidemiol 2008;62:71-5.
7. National Institute of Public Health - National Institute of Hygiene. Vaccinations in Poland [in Polish]. Available at: http://www.pzh.gov.pl/oldpage/epimeld/index_p.html#05.
8. Kostrzewski J, Tomaszunas-Błaszczyk J. Reporting, recording and disseminating information about infectious diseases cases in Polish lands in the 20th century. In: Kostrzewski J, Magdzik W, Naruszewicz-Lesiuk D, eds. Infectious diseases and controlling them in Polish lands in the 20th century [in Polish]. 2dn ed. Warsaw: PZWL; 2001:81-4.
9. National Tuberculosis and Lung Diseases Research Institute, Biuletyn IGiChP [in Polish]. Available at: http://www.igichp.edu.pl.
10. Szczuka I. Safety BCG vaccinations – adverse effects following immunization. Part I. Types, occurrence and registrations [in Polish]. Przegl Epidemiol 2002;56:1-13.
11. Szczuka I. Adverse events following immunization after BCG vaccination in Poland 1994-2000 [in Polish]. Przegl Epidemiol 2002;56:205-16.
12. Lotte A, Wasz-Höckert O, Poisson N, et al. BCG complications. Estimates of the risks among vaccinated subjects and statistical analysis of their main characteristics. Adv Tuberc Res 1984;21:107-93.
13. Kubit S, Czajka S, Olakowski T, et al. Evaluation of the effectiveness of BCG vaccinations [in Polish]. Ped Pol 1983;LVIII:775-8.
14. Kobierska MH, Stopnicka M. Case of pneumonia and pleurisy in a child following BCG vaccination diagnosed as tuberculosis [in Polish]. Pediatr Pol 1951;26(8):855-7.
15. Olakowski T, Iwanova O, Mardoń K. Controlled trials of BCG vaccination of newborn infants with BCG vaccine prepared from the French BCG substrain in Warsaw [in Polish]. Gruźlica 1972;40:403-9.
16. Czaplińska B. Vaccination adverse events after BCG in Kujawsko-Pomorskie province between 2006-2010 [in Polish]. Hygeia Public Health 2011;46(3):362-5.
17. Zwolska Z, Augustynowicz-Kopeć E, Zabost A, et al. Modern microbiological methods in diagnosis of adverse reactions after BCG vaccination. Case reports [article in Polish]. Pneumonol Alergol Pol 2004;72(11-12):505-11.
18. Bedwell J, Kairo SK, Behr MA, et al. Identification of substrains of BCG vaccine using multiplex PCR. Vaccine 2001;19:2146-51.

Received: 24.04.2012
Accepted for publication: 20.06.2012

Address for correspondence:
Anna Lutyńska
National Institute of Public Health
– National Institute of Hygiene
24 Chocimska Street
00-791 Warsaw, Poland
Tel. +48 22 54 21 213
Fax. +48 22 54 21 311
alutynska@pzh.gov.pl