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ORIGINAL RESEARCH ARTICLE

Bacillus Calmette-Guérin (BCG) Vaccine Adverse Events in Victoria, Australia: Analysis of Reports to an Enhanced Passive Surveillance System

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Abstract

Background Bacillus Calmette–Guérin (BCG) vaccine is used worldwide, with high efficacy against childhood *Mycobacterium tuberculosis* (TB) meningitis and miliary TB. BCG vaccine is considered safe, with serious systematic adverse events following immunization (AEFI) of immunocompetent recipients being rare, although adverse event rates vary between differing BCG strains. In Victoria, Australia, AEFI are reported to SAEFVIC (Surveillance of Adverse Events Following Vaccination In the Community), an enhanced passive surveillance system operational since 2007.

Objective To describe the epidemiology of reported BCG AEFI in Victoria, Australia, particularly following the 2012 recall of Connaught BCG vaccine, substitution with Denmark-SSI vaccine and subsequent programme delivery adjustments.

Methods Retrospective analysis of reported BCG AEFI in Victoria, Australia, for the 6-year period 2008–2013. Incidence rates were calculated using available doses-distributed, doses-administered and population data denominators with 95 % confidence intervals.

Results The predominant BCG AEFI reported were abscess and lymphadenopathy, with higher reports for males than for females ($p = 0.039$).The rates of AEFI per 10,000 doses distributed were similar for the Connaught and Denmark-SSI strains, at 11.6 and 15.4, respectively

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Key Points

The Bacillus Calmette–Guérin (BCG) vaccine recall in 2012, global BCG vaccine supply shortages and subsequent unplanned BCG vaccine strain changes required effective adverse events following immunization (AEFI) surveillance to monitor the changes.

AEFI surveillance in Victoria, Australia, was inadequate for meaningful interpretation of results, but new practices described will maximize data completeness and facilitate future investigations.

The Australian experience and lessons learned serve as a timely reminder to BCG vaccination programmes worldwide to review AEFI surveillance systems.

($p = 0.414$). When doses administered rather than doses distributed were considered, the rate of reported Denmark-SSI AEFI was much higher, at 62.8 per 10,000 doses administered. Meaningful result interpretation was hampered by a lack of a BCG vaccination register, multiple disparate providers and absent doses-administered data prior to the recall.

Conclusion Effective AEFI surveillance is of paramount importance as countries are faced with unplanned vaccine strain changes following the 2012 BCG recall and subsequent global vaccine supply shortages. The Australian experience and lessons learned serve as a timely reminder to BCG vaccination programmes worldwide to review AEFI surveillance systems.

1 Background

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, is a leading cause of death worldwide. Asymptomatic infection affects approximately one third of the world's population, with 5–10 % developing clinical disease during their lifetime [1]. In Australia, the incidence is low, with reported cases in 2009 of 6.0 per 100,000. Overseas-born cases constituted 86.4 % of these notifications, suggesting the TB burden in Australia is largely from overseas transmission [2].

The bacillus Calmette–Guérin (BCG) vaccine, first used in 1921, is currently the only licensed vaccine against TB. There are five widely used strains derived from the original vaccine [3], with variations in global strain usage as well as efficacy and adverse event profiles [4]. It is a live attenuated vaccine administered via intradermal injection, typically to the upper arm [5]. Globally, the vaccine reaches approximately 100 million neonates each year [1]. In Australia, a single dose of BCG is recommended for high-risk populations such as Indigenous neonates, children under 5 years travelling or living in high-risk countries for an extended period, and children born to parents with leprosy or a family history of leprosy [6, 7].

Almost all BCG vaccinations are associated with mild local reactions, with typical formation of a papule with progression to the characteristic BCG scar in 70 % of persons vaccinated [5, 8]. Adverse reactions can be infectious, non-infectious, local or systemic and are age and dose dependent [9]. Serious complications following vaccination are rare, with disseminated disease largely restricted to the severely immunocompromised [10, 11]; a French study estimated the prevalence rate of idiopathic disseminated infection at 0.59 per 100 million vaccinations [12]. A number of disseminated BCG cases in immunocompromised First Nation Inuit people of Canada (1993–2002) led to cessation of the neonatal BCG vaccine programme in this special risk group [13, 14]. Likewise, BCG vaccination is contraindicated in the severely immunocompromised and in infants with high suspicion of, or testing positive for, HIV [7, 15].

In Australia, the Sanofi Pasteur BCG Connaught vaccine (Sanofi-Pasteur Limited, Canada, derived from Connaught strain and supplied in 10-dose vials) has been used since 1996 and cessation of Australian-manufactured vaccine (New York strain) [16]. In June 2012, Connaught BCG vaccine manufacturing was halted and four batches (C3787AA, C3787AC, C3787AE and C3787AG) were recalled following a flood at the manufacturing plant, leading to a possible breach in sterility [16, 17]. Connaught vaccine was recalled in Australia, New Zealand and Canada, with three adverse events possibly linked to the recalled batch in Canada [18]. From September 2012, Australia used an interim vaccine supply, Denmark-SSI (Danish strain 1331, manufactured by Staten Serum Institute Denmark, supplied in 100-dose packaging), until issues with the Sanofi Pasteur Connaught vaccine production were resolved [19]. To maximize efficiency with the Denmark-SSI vaccine multi-vial packaging, BCG administration of publicly supplied vaccine was restricted to two specialist clinics as of 1 September 2012. Private travel clinics were also able to purchase Denmark-SSI vaccine from vaccine wholesalers.

Denmark-SSI is a frequently used vaccine strain globally [4, 20] but is reportedly more reactogenic than Connaught vaccine [8, 16, 21], raising concern within Australia about a potential increased incidence of adverse events following immunization (AEFI) with the Denmark-SSI vaccine.

Since 2007, in Victoria—the second-largest state of Australia (population 5,623,492 [22])—AEFI have been reported to Surveillance of Adverse Events Following Vaccinations in the Community (SAEFVIC), an immunization safety collaborative service combining enhanced passive surveillance with integrated clinical services [23]. AEFI are defined as 'an unwanted or unexpected event' following vaccination [24]. SAEFVIC obtains reports on AEFI such as BCG reactions and provides tertiary hospital clinical review to help manage the AEFI as required.

The potential manufacturing quality issue and resultant strain change heightened the need for effective BCG AEFI surveillance.

We therefore aimed to describe the epidemiology of BCG AEFI in Victoria, Australia; to inform immunization policy and providers of any potential impact on expected AEFI following the change from Connaught to Denmark-SSI vaccine strain; and to review the current passive

surveillance capacity to support evaluation of the three events occurring in 2012: product recall, vaccine strain substitution and programme delivery adjustment.

2 Methods

De-identified data on adverse events following BCG immunization were extracted from the SAEFVIC database on 20 May 2014 for all reports received by SAEFVIC from 1 January 2008 up to and including persons vaccinated prior to 31 December 2013. Where the locally administered BCG strain was not identifiable, the date of vaccination was used to assume that the vaccinee had received either Connaught strain (vaccination up to and including August 2012) or Denmark-SSI strain (vaccination during September 2012–December 2013). Ethics approval was granted (reference DA017-2013-03).

Prior to data extraction, all reports received were accessed and attempts were made to ascertain any missing information (provider details, vaccinee demographics, batch number).

Reports were excluded if the vaccine was administered overseas and the vaccine strain was not known ($n = 3$); a normal BCG injection site response was considered as 'expected' ($n = 7$); and following a Mantoux tuberculin skin test ($n = 1$). Reports arising from drug administration errors not resulting in an AEFI ($n = 2$), or where BCG was administered concomitantly with other vaccines and the AEFI was either at the non-BCG vaccination site or was clinically assessed and determined to be not associated with BCG immunization, were described but excluded from numerical analyses.

Australian Bureau of Statistics population census data were used as the denominator for demographic analyses by age and sex [22]. Multi-dose vials-distributed data from 2008 to 2013 by month and BCG vaccine brand were provided by the Department of Health, Victoria. Rates of reported AEFI per 10,000 doses distributed were calculated, assuming 10 doses per vial for Connaught strain and 100 doses per 10-vial pack of Denmark-SSI vaccine distributed.

Doses-administered data were obtained from the two specialist BCG vaccination clinics that administered all publicly subsidized BCG vaccine from September 2012 to the end of 2013.

Surveillance capacity to inform on BCG AEFI was assessed for reporting timeliness and ability to interpret data, considering completeness of data fields and available denominators for rate calculation.

Descriptive and statistical analyses were conducted in Excel 2010 (Microsoft, Redmond, PA, USA) and STATA version 13 (StataCorp, College Station, TX, USA).

3 Results

SAEFVIC received 62 reports of persons experiencing an adverse event following BCG administration that met the study criteria: 52 following Connaught strain and 10 following Denmark-SSI strain vaccination. The reported number of BCG AEFI cases increased over the first 5 years of SAEFVIC operation but declined in 2013 (Fig. 1).

A majority ($n = 39$, 63 %) of AEFI reports were for males, with a male-to-female ratio of 1.7:1 ($p = 0.039$). Sixty vaccinees were aged less than 5 years (median age 5 months, range 22 days to 3 years 8 months). The remaining two vaccinees were aged 5 and 19 years.

The 62 AEFI case reports described 72 reactions, of which abscess was the most frequent (64 %), followed by lymphadenopathy (32 %) [Table 1; Fig. 2]. No deaths were reported. Three cases with abscess were hospitalized during the course of their treatment. None were reported as immunosuppressed.

Six AEFI reports were received where BCG was administered concomitantly with other vaccines and the reactions occurred at the non-BCG vaccination site or were attributed to the other vaccines: fever ($n = 2$), hypotonic–hyporesponsive episode ($n = 1$), injection site reaction—minor ($n = 3$), nodule at injection site ($n = 2$) and urticaria ($n = 1$).

Five reports pertained to drug administration errors [incorrect administration site ($n = 2$) and overdose ($n = 3$)], of which three involved an abscess at the site of administration. All five errors arose from vaccination administered in the community setting prior to September 2012.

3.1 Surveillance Attributes

The time to symptom onset was unstated for 20 reports (32 %); for the remainder, the time from vaccination to

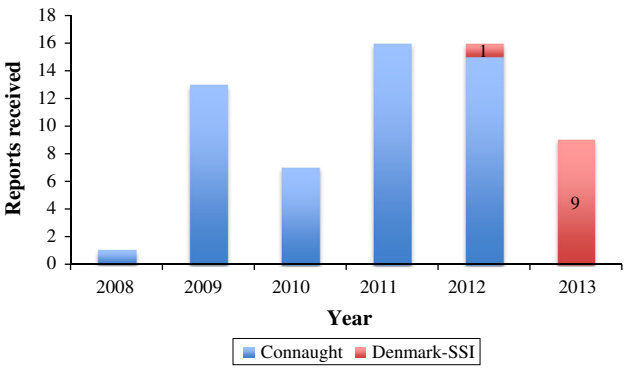

Fig. 1 Reported bacillus Calmette-Guérin (BCG) adverse events following immunization (AEFI) cases, by year and vaccine strain, Victoria, 2008–2013

Table 1 Adverse events following immunization (AEFI) reactions reported by bacillus Calmette-Guérin (BCG) vaccine strain, Victoria, 2008–2013

AEFI reaction	Total	AEFI reactions, by vaccine strain		
		Connaught	Denmark-SSI	*p* value for test of proportions
Abscess	46 (64 %)	34 (59 %)[a]	9 (82 %)	0.1455
Erythema nodosum	1	1		
Lymphadenopathy	23 (32 %)	21 (37 %)	2 (18 %)	0.2449
Nodule at injection site	1	1		
Urticaria/allergic rash	1	1		
Total	72	58[a]	11	

[a] Excludes three abscesses attributed to vaccine administration errors

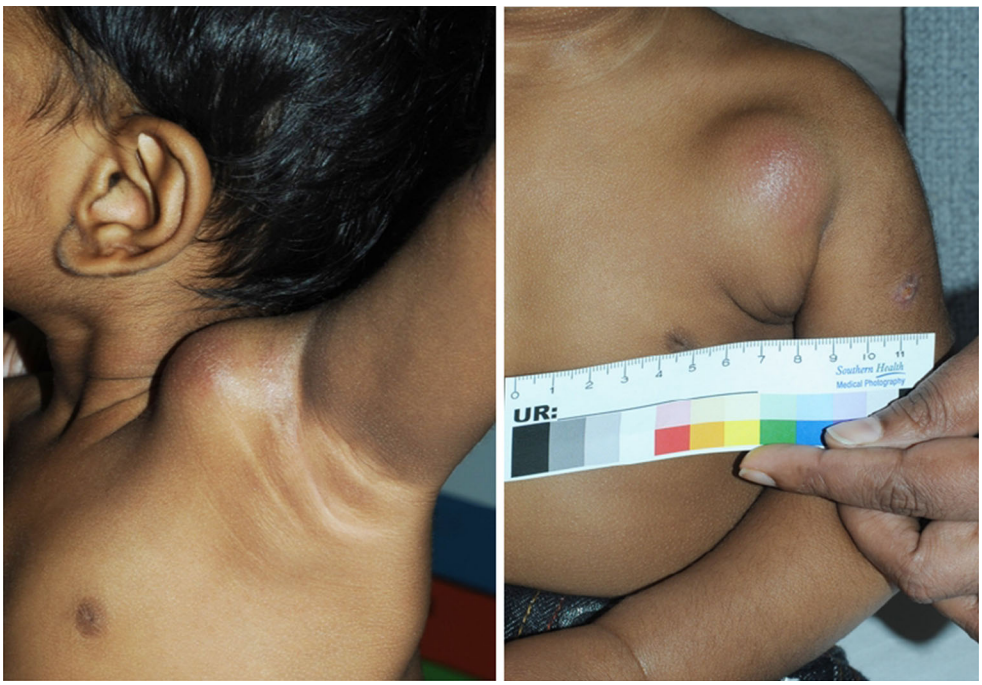

Fig. 2 Axillary lymphadenopathy following bacillus Calmette-Guérin (BCG) vaccination

symptom onset ranged from 48 hours to 168 days (median 35 days, interquartile range 26–56 days). The time to report from the onset of symptoms ranged from 0 to 953 days (median 45 days, interquartile range 23–79 days), with more than 80 % of all reports—and 100 % of Denmark-SSI AEFI reports—being received within 100 days of symptom onset (Fig. 3).

Vaccine batch information was completed for approximately half of all reports (53 %), increasing from 0 % in 2008 to 100 % of reports with batch details accessible following the programme change in 2012.

Three of the four recalled batches had been distributed in Victoria between April 2011 and June 2012: C3787AA (3,090 doses), C3787AC (8,290 doses) and C3787AG (220 doses). Batch C3787AE was not distributed in Victoria.

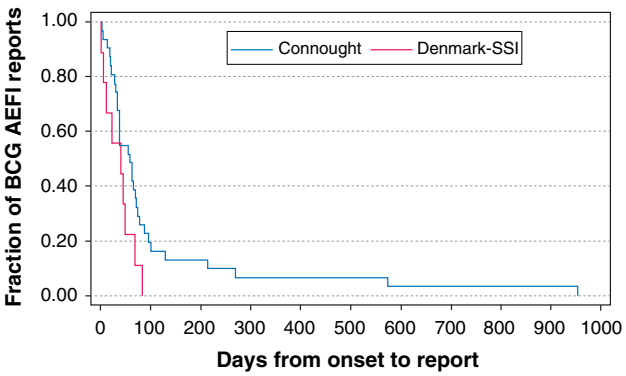

Fig. 3 Kaplan–Meier analyses of bacillus Calmette-Guérin (BCG) adverse events following immunization (AEFI) showing time from symptom onset to reporting, by vaccine strain, Victoria

Eight AEFI reports, related to two of the batches [C3787AA ($n = 2$) and C3787AC ($n = 6$)], were received. The reactions, all reported in 2012, were as follows: for C3787AA, lymphadenopathy ($n = 1$) and nodule at injection site ($n = 1$); and for C3787AC, abscess ($n = 5$) and lymphadenopathy with nodule at injection site ($n = 1$). Three additional reports of expected BCG site reactions were received directly as a result of notification of the batch withdrawal but were not included in the study analysis.

Further retrospective follow-up of cases and ascertainment of vaccine batch data were hampered by insufficient information being available: provider details being unavailable for almost one third (27 %) of cases.

3.2 Data Interpretation and Denominators

Overall, the incidence of reported BCG AEFI cases per 10,000 doses distributed varied by year (Table 2). The estimated rate of reported AEFI cases per 10,000 doses distributed was 11.6 for Connaught strain and 15.4 for Denmark-SSI strain (ratio 0.756, 95 % confidence interval 0.38–1.67; $p = 0.414$).

Calculation of more accurate rates for reported AEFI cases, using doses-administered denominator data for Connaught strain, was not possible in the absence of a consistent database or record of BCG vaccine administration prior to September 2012. Following the change of vaccine strain and service delivery in September 2012, the two accredited tertiary specialist clinics recorded 1,593 doses of Denmark-SSI administered (53 % to males) from 1 September 2012 to 31 December 2013. Ten AEFI reports (0.6 %) were received by 20 May 2014 (20 weeks post-vaccine period), giving an incidence rate of 62.8 reported AEFI cases per 10,000 doses administered. This confirmed usage of only 25 % of available Denmark-SSI doses occurred despite batching of BCG vaccinees in central clinics. The usage of available Connaught doses by the minimum 99 documented providers receiving publicly funded vaccine supply is unknown.

4 Discussion

We retrospectively reviewed and summarized BCG AEFI reported to a passive surveillance system in Victoria, Australia, over the 6-year period 2008–2013, and we assessed the capacity of the surveillance system to inform on BCG AEFI in the context of a product incursion, strain substitution and programme delivery adjustment.

BCG AEFI reporting increased over the initial 5 years from 2 to 16 reports annually, before a marked drop in 2013, coinciding with programme delivery changes. While the increase in AEFI reporting was broadly in step with increasing BCG vaccine distribution, an observed increase in all vaccine AEFI reporting occurred over the same time period as awareness of reporting AEFI to SAEFVIC, which commenced in May 2007, improved [23]. Despite the increase, it remains likely that these reports represent an underestimation of AEFI because of the nature of passive reporting coupled with the ongoing lack of clarity over what constitutes an AEFI with BCG [10, 25]. The BCG recall was likely a contributing factor for the higher rate of reported AEFI cases per dose distributed—for both the newly introduced Denmark-SSI vaccine and retrospectively for recently administered Connaught vaccine—seen in 2012.

A majority of AEFI reports were for infants, consistent with the patient population expected for BCG administration in Australia [7]. More AEFI reports were received for males than for females, which was in contrast to both the population sex ratio at birth (male:female 1.05:1) and AEFI in young children reported in Victoria for all vaccines (male:female 1.2:1 [22, 26]) but is an anomaly that has been observed before in a BCG AEFI study in Oman [27].

Table 2 Bacillus Calmette-Guérin (BCG) vaccine doses distributed and reported adverse events following immunization (AEFI) cases per 10,000 doses distributed, by year, Victoria

Year	Estimated individual doses distributed (reported AEFI cases)		Incidence risk per 10,000 doses	95 % confidence interval
	Connaught	Denmark-SSI		
2008	8,800 (1)		1.1	(0.03–6.3)
2009	9,570 (13)		13.6	(7.2–23.2)
2010	10,340 (7)		6.8	(2.7–13.9)
2011	11,680 (16)		13.7	(7.8–22.2)
2012[a]	4,340 (15)		34.6	(19.4–56.9)
		1,000 (1)	10.0	(0.3–55.6)
2013		5,500 (9)	16.3	(7.5–31.0)
Total	44,730 (52)		11.6	(8.7–15.2)
		6,500 (10)	15.4	(7.4–28.3)

[a] Includes stimulated AEFI reporting following BCG vaccine batch recall

A marginal male preponderance was observed in the doses-administered data for 2012–2013 (for which accurate sex data were available), where 53 % of vaccinees were male. BCG vaccination is reserved for high-risk populations in Australia; if more males are being vaccinated, it would be interesting to determine the factors underlying this. Subjective hypotheses include the following: the threshold for reporting AEFI may be lower in males; male infants may be favoured for travel for parental homeland visits; more males are born in the populations with highest utilization of BCG vaccination [28]; or male vaccinees have a higher risk of AEFI.

AEFI reactions of abscess and lymphadenopathy reported in Victoria were consistent with the known common reactions experienced post-BCG immunization [16, 29, 30]. However, comparisons of AEFI proportions or rates were limited because of the different methodologies and cohorts used in published studies and the lack of consistent application of case definitions [9, 10]. A prospective Australian study of 1,246 BCG recipients conducted after the change to Connaught strain in 1996 recorded lymphadenitis in 1 % and abscess in 2.5 % of the 918 recipients who completed follow-up. However, the study population included adult defence force personnel and is not immediately applicable to the current Australian BCG vaccination recommendations, which focus on children [16].

It is possible that AEFI involving lymphadenopathy occurred after the data extraction for this study or had occurred but not yet been reported. However, this risk was minimized, as 20 weeks had elapsed between the end of the study period (31 December 2013) and data extraction (20 May 2014), a period four times greater than the median time to symptom onset and the period in which a majority of reactions are reported to occur [16].

BCG is administered intradermally, which is a more technically complex mode of administration than intramuscular vaccination and requires expert immunizer training. Technique errors are known factors for adverse reaction occurrence [10]. Therefore, it is possible that more of the reported abscess and local reactions were in fact due to poor administration technique than was documented [3 abscesses were attributed to incorrect administration: intramuscular ($n = 1$) and overdose ($n = 2$)]. Attempts to ascertain administration issues or to analyse AEFI by provider type were restricted by poor reporting of provider type or contact details for further follow-up.

The catalyst for this review of adverse effects following BCG vaccination in Victoria arose following the 2012 recall of Canadian Sanofi Pasteur vaccine, secondary to a possible breach in sterility. This study identified eight adverse reactions associated with two of the four recalled batches. However, batch number was poorly recorded, with almost half of the reports having no batch information available, despite considerable efforts by the SAEFVIC clinical team to follow up individual patients. Some of the difficulty in obtaining batch details arises from vaccine being administered overseas. However, without this key information in situations where a recall is necessary, any comment on a change in adverse events relating to a particular batch is not possible.

The analysis would be strengthened if the number of reports received were presented as rates. Two denominator options are ordinarily available: (1) doses administered and (2) doses distributed. In Australia, BCG doses-administered data are not readily available, as BCG is not included in vaccinations compulsorily recorded in the national Australian Childrens Immunisation Register (ACIR), which records selected vaccinations given to children under 7 years of age [31]. Therefore, the rates are routinely calculated as AEFI per doses distributed, as a proxy. However, in the case of BCG, this would be particularly misleading, as distributed doses would not account for vaccine wastage arising from BCG vaccine being supplied in multi-dose vials. In Australia, Connaught vaccine was available in a 10-dose vial, so a single vial could account for between 1 and 10 vaccinations delivered. Denmark-SSI vaccine is available only in 100-dose packaging, comprising multiples of 10 × 1 mL vials, with each vial being 10–20 doses, depending on recipient age. If vials are not fully used for vaccine administration, this will lead to underestimation of AEFI rates. Therefore, the similar reported AEFI rates of 15.4 and 11.6 per 10,000 doses of Denmark-SSI and Connaught vaccine distributed, respectively, become difficult to interpret and may in fact be a fallacy of the multi-dose vial packaging variances. The documented wastage of 75 % following centralization of BCG in September 2012 may indeed be lower than the wastage of Connaught BCG, which was provided to multiple providers who may have been more likely to immunize individual patients 'on demand', rather than batching into clinics to maximize vial usage.

Following the programme delivery changes and restriction of BCG administration to specialized clinics, accurate data on doses administered were available. These data provided a Denmark-SSI reported AEFI rate of 62.8 per 10,000 doses administered, a figure four times that obtained using doses distributed. However, our finding of 0.5 % AEFI with Denmark-SSI doses administered remained lower than those reported in a 2007 Netherlands strain-specific study, where abscess was reported in 2.5 % and lymphadenitis in 0.1 % [30], but this may be reflective of under-reporting to our retrospective passive surveillance system, compared with their active cohort follow-up.

It is important to ascertain accurate BCG AEFI profiles to permit strain selection for TB control programmes and,

in particular, in advance of possible advocacy for broader usage of BCG immunization for potential 'non-specific' immunological advantages [32, 33] or in HIV patients, where Denmark-SSI strain has had higher reported AEFI rates than other strains [34].

5 Conclusion

BCG AEFI in Victoria, Australia, mainly consist of abscess and lymphadenopathy, with higher reports for males than for females. The capacity of surveillance to evaluate adverse events in the Australian BCG immunization programme was found wanting in 2012, just as it had been at the time of the previous strain change in 1996 [16]. Passive AEFI surveillance was inadequate for meaningful interpretation of results, with the capacity to inform on AEFI rates or to compare AEFI profiles between BCG vaccines derived from different strains being severely limited by the lack of adequate denominator data and poor timeliness of reporting. Estimations of AEFI rates varied depending on the calculation method used.

In Victoria, Australia, new practices implemented, with BCG vaccination being limited to specialist provider sites, will maximize data completeness, provide timely AEFI management and reporting, and facilitate future investigations. The other states in Australia have variable practices with regard to BCG administration and AEFI follow-up, so national co-ordination is required. This study highlights the potential benefit of expanding the Australian Childrens Immunisation Register to include all vaccinations, as well as encompassing all-of-life, as previously advocated, in order to provide adequate vaccine delivery and programme evaluation in Australia [35].

Robust and effective AEFI surveillance is of paramount importance as countries are faced with unplanned vaccine strain changes following the BCG recall in 2012 and subsequent global vaccine supply shortages. The Australian experience and lessons learned serve as a timely reminder to BCG vaccination programmes worldwide to review AEFI surveillance systems.

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