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Deaths reported to national surveillance for adverse events following immunization in China, 2010–2015

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Abstract

Background: The national Adverse Events Following Immunization (AEFI) surveillance system in China (CNAEFIS) has collected AEFI reports -including deaths -following all vaccines used in China since 2008.

Aims: To review reports of AEFI-associated death cases from 2010 to 2015 to assess potential vaccine safety issues.

Methods: Descriptive analysis of epidemiologic characteristic of AEFI-associated death cases and standard causality assessment for reported causes of deaths. To estimate the risk of death after vaccination, we used population data, administered doses and live births to calculate denominators.

Results: During 2010-2015, 753 deaths were reported to CNAEFIS from mainland China. Highest numbers were reported in 2013 and 2014 when reporting peak of AEFI-associated deaths occurred after media reports concerning “death following Hepatitis B vaccination” in China. About 95% of deaths were in children <5 years of age and males accounted for 60%. Most common vaccines associated with reports of fatal AEFIs were vaccines in national immunization schedule. In causality assessment, 120 (16.0%) deaths were classified as vaccine-associated reactions such as anaphylactic reactions and disseminated BCG infections; 594 (78.9%) deaths were identified as coincidental events. The main causes of death were asphyxia, and Sudden Infant Death Syndrome. The overall estimated AEFI-associated death rates were: 0.26 per million vaccination doses administered and 0.09 per million population. The neonatal AEFI death rate was 0.77 per million live births.

Conclusions: These data provide reassuring information about the small risk of death following immunization. They also illustrate sensitivity of passive reporting to public information and that peaks in serious AEFI reports should be interpreted with caution. Continuous monitoring and scientific causality assessment for serious AEFIs, including AEFI-associated deaths is imperative to ensure public confidence in the immunization program.

Key words: adverse events following immunization, deaths

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1. Introduction

China initiated the National Expanded Program on Immunization (EPI) in 1978 and expanded it to cover 14 types of vaccines in National Immunization Schedule in late 2007 [1]. As part of the EPI in China, about 22 vaccine doses are administered during the first year of life [2]. With its 1.3 billion inhabitants and over 17 million annual newborns, China is one of the largest market and manufacturer for vaccines in the world [3]. On average, more than 500 million vaccine doses are administered every year [2]. Deaths that occur after immunization, particularly neonatal or infant deaths frequently attract media attention and cause public concern. Recently, concerns were raised about adverse events following immunization (AEFI) and vaccine safety [4]. After media reports of deaths following hepatitis B vaccine (HepB) administration in Hunan province of China in December 2013, concerns about the vaccine safety increased among parents and the public [4]. However, vaccinations during childhood are common, and determining whether or not they are associated with pediatric deaths is difficult.

All vaccines administered in mainland China are monitored and considered to be safe and effective by the National Regulatory Authority [3]. Since 2008, Chinese Center for Disease Control and Prevention (CCDC) has monitored AEFI reports, which are recorded using a passive AEFI nationwide surveillance program (Chinese AEFI Information System [CNAEFIS]) [5]. Since its implementation, the CNAEFIS has collected information on a large number of AEFI cases associated with vaccines used in China.

To understand the epidemiological characteristics, causes of death, and risk of death following vaccination in China, we reviewed and analyzed reports of deaths after immunization from 2010 to 2015.

2. Materials and methods

2.1 Data sources

The CNAEFIS is a nationwide passive surveillance system for AEFI **[**2, 5]. In 2008, after 3 years of various pilot studies [6-7], the CNAEFIS became an online system covering all provinces. The AEFI surveillance of mass immunization campaigns, including the 2009 A(H1N1) influenza vaccine campaign during 2009–2010 influenza season [8] and measles vaccines campaign, which included more than 100 million children in 10 days in September 2010 [9] were covered by CNAEFIS, strengthening the reporting capacity. In June 2010, Chinese Ministry of Health and the Food and Drug Administration jointly issued a national AEFI guideline that made the CNAEFIS the sole and official surveillance system in mainland China [10].

According to the national AEFI guideline, an AEFI is defined as a reaction or an event after vaccination that is suspected to be related to vaccination. Healthcare facilities, vaccination units, local centers for disease control and prevention (CDCs), adverse drug reaction monitoring agencies, vaccine manufacturers, and their executive staff are responsible for reporting AEFIs. In addition, the public can notify any of these bodies. The data are collated by local county CDCs. These centers verify the AEFI Case Reporting information, which is then entered the CNAEFIS. Duplicate reports are detected and deleted by county-level, prefectural-level and provincial level CDCs. Once a case is reported in the CNAEFIS, it can be viewed online by CDCs, and adverse drug reaction monitoring agencies [10].

2.2 Causality assessment

According to national AEFI guidelines [10], all deaths reported in the CNAEFIS must be investigated. County-level CDCs commence an investigation by collecting relevant data and

completing the AEFI Case Investigation Form, which is entered in CNAEFIS. An ad hoc AEFI Investigation and Diagnosis Expert Committee is then established by the CDCs. The committee includes experts in clinical medicine, epidemiology, laboratory practices, pharmacy, vaccinology, vaccine regulation, and related fields, as needed. In cases of deaths, prefectural or provincial CDCs establish the AEFI Investigation and Diagnosis Expert Committee, which includes experts and committee members related to the case. This Committee then conducts the causality assessment [5,10].

After the causality assessment, the AEFI (including reports of deaths) is classified into one of the following categories [10]: 1) vaccine reactions or vaccine-related reactions, 2) vaccine quality reactions, 3) program errors or immunization errors, 4) coincidental events, or 5) psychogenic reactions or immunization anxiety-related reactions.

2.3 Data collection

Deaths which were suspected to be related to the vaccinations, with dates of death from 1st January 2010 to 31st December 2015, were extracted from CNAEFIS and included in the study. Information collected included age and gender of the patients, vaccines received, results and conclusions of the causality assessments, time intervals from vaccinations to onset of symptoms, clinical diagnoses, and concurrent vaccines administered.

2.4 Calculation of reporting rates

We used the following denominators to estimate the risk of AEFI-associated deaths: 1) administered doses collected from vaccination clinics during the study period, 2) population data from the National Bureau of Statistics of the People's Republic of China, and 3) neonatal death rates after vaccination. For denominator 1 and 2, the numerator was AEFI-associated deaths reported to CNAEFIS during the same period. The rates were calculated per million administered vaccination doses or per million population. For denominator 3, we used administered doses for first dose of HepB vaccine which administered within 24h after birth and vaccination coverage to estimate the number of live births. The numerator was cases who died within 28 days after birth.

2.5 Statistical analysis

All calculations were performed by using R software, version i386 3.2.3; the epitools package was used to calculate confidence intervals for Poisson rates.

3. Results

3.1 Characteristics of AEFI-associated deaths

A total of 753 AEFI-associated deaths were reported during 2010–2015. AEFI-related deaths peaked in 2013–2014 (Fig. 1). The proportion of neonatal deaths varied from 5.0% (2010, 2011) to 16.5% (2013). In 2012–2014, the proportion exceeded 10.0%. All deaths were reported from locations within mainland of China.

During the first quarter of the year (January to March), there were 249 (33.1%) AEFI-associated deaths, followed by 234 (31.1%) during the fourth quarter, 140 (18.6%) and 130 (17.3%) during the third and second quarters, respectively. Fifty-one AEFI-associated deaths were reported in December 2013, and 34 (66.7%) of these were related to HepB vaccine, administered alone or with other vaccines (Fig. 2).

Of AEFI-associated death reports, 293 (38.9%) were females, 635 (84.3%) were aged <1 year, and 82 (10.9%) cases were aged 1–4 years (Table 1). The median age in the group aged <1 year was 68 days, and the median age in the group aged 1–4 years was 1 year old.

Sixty-Nine different vaccines or vaccine combinations were associated with reported deaths. The

most common vaccines or vaccine combinations were 1) HepB (alone) (182, 24.2%), 2) Bacillus Calmette Guerin (BCG) and HepB (116, 15.4%), 3) oral poliomyelitis vaccine (OPV) and diphtheria, tetanus and acellular pertussis combined vaccine (DTaP) (84, 11.2%), 4) BCG (alone) (61, 8.1%), and 5) DTaP (alone) (31, 4.1%) (Table 2).

3.2 Results of the causality assessments

Autopsies were conducted in 257 (34.1%) cases. According to the causality assessment, 120 (15.9%) deaths were classified as vaccine reactions, 594 (78.9%) deaths were due to coincidental events, 38 (5.1%) deaths were classified as indeterminate, and 1 (0.1%) death was due to an immunization error-related reaction. No deaths were classified as due to vaccine quality defect-related reactions or immunization anxiety-related reactions during the study period (Table 2)

3.2.1 Vaccine-related reactions

One hundred-twenty deaths were classified as vaccine-related reactions, with an estimated rate of 0.04 per million doses, using the all vaccination doses as the denominator. Anaphylactic reactions accounted for 55 cases, in which 53 cases occurred within 1 day after vaccination. Anaphylactic reactions take 45.8% of vaccine-related reactions, with estimated rates of 0.02 per million vaccination doses. Nineteen vaccines or vaccine combinations were related to anaphylactic reactions. The average numbers of deaths per year due to anaphylactic reactions post-vaccination was about 9 (range: 6–13 cases). The most common vaccine and vaccine combinations associated with vaccine reactions were HepB (alone) (12 cases), OPV and DTaP (10 cases), BCG and HepB (9 cases).

There were 39 BCG-related deaths (estimated rate: 0.37 per million BCG vaccination doses). Thirty BCG-related deaths were classified as the result of disseminated BCG infections, and nine cases were due to BCG lymphadenitis or other infections (recurring). One death due to vaccine associated Vaccine-Associated Paralytic Poliomyelitis (VAPP) was reported. One case of hemorrhagic measles was reported in which the autopsy and laboratory findings confirmed that this was related to the vaccine virus.

Thirteen deaths were attributed to neurological, illness, of which six cases were meningitis (aseptic or viral), four cases were acute disseminated encephalomyelitis, two cases were encephalopathy, and one case was epilepsy. Seven vaccines and vaccine combinations were administered in these cases, of which the rabies vaccine was the most common vaccine, accounting for five deaths. The average number of deaths per year was three, with a range of two to four in the study period.

Nine deaths were confirmed as status thymicolymphaticus (STL) after autopsies. Other two cases were diagnosed as malaise and vomiting post vaccination, and both died of aspiration asphyxia. In all above 11 cases, vaccination was not the direct cause of death. However, in the causality assessment, the expert committee concluded that vaccination contributed to these deaths and classified the deaths as vaccine-related reactions.

3.2.3 Immunization errors

Only one death was classified as immunization error-related reaction. In this case, the baby had been diagnosed with severe malnutrition prior to immunization, and the immunization nurse had failed to perform a physical examination when the parents requested that the infant be vaccinated. The direct cause of death was severe malnutrition, respiratory failure, and cardiac failure, not vaccine related.

3.2.4 Coincidental events

After causality assessment, 594 deaths were classified as coincidental events. The most common

causes of death were asphyxia, sudden infant death syndrome (SIDS), pneumonia (neonatal and infant), congenital heart diseases, and vitamin K deficiency (which could lead to internal bleeding). In these cases, 577 (97.1%) deaths occurred within 15 days after vaccination. Sixty vaccines and vaccine combinations were administered, the most common were HepB (alone) (163 cases), BCG and HepB (92 cases), OPV and DTaP (65 cases), OPV (alone) (26 cases), and BCG (alone) (24 cases). In 574 (96.6%) cases, the patients aged < 5 years.

3.2.5 Indeterminate cause of death

During 2010–2015, 38 deaths were classified as due to indeterminate causes. There was no clear clinical diagnosis in 25 (65.8%) cases, and for the rest cases there was insufficient evidence available to conduct the causality assessment. All 38 deaths occurred within one-week post-vaccination, and 34 (89.5%) cases aged < 5 years.

3.3 Risk estimation of AEFI-associated deaths

Using all administered doses as the denominator, the average rate of AEFI-associated death was 0.26 per million vaccination doses (range: 0.20-0.32) during the study years. Using population data as the denominator, the average rate was 0.09 per million population (range: 0.07-0.12) (Table 3).

Neonatal deaths accounted for 10.4% (78 cases) of all reported AEFI-associated deaths. The highest rate of reported neonatal deaths after vaccination occurred in 2013 (1.48 per million live births) (Table 4). The rate of neonatal deaths after vaccination in 2010–2011 was significally different from 2013–2014 (Table 4). During 2013–2014, 47 neonatal deaths were reported and 44 (93.6%) of those were related to HepB (with concurrent vaccines). In the causality assessment however, only one of the reported deaths was considered causally related to vaccination.

During 2010-2015, we identified 182 reports of AEFI-associated deaths after vaccination with HepB was the only vaccine used. Of these, 13 were causally related to vaccination in the causality assessment. The annual numbers of causally related deaths during the period were 2,3,2,1,3,2, respectively.

4. Discussion

During six years of AEFI surveillance in mainland China, more than three quarters of reported AEFI-associated deaths were due to coincidental events, and only 16% could be attributed to vaccination by causality assessment. Most of those determined to be causally related to vaccination were related to anaphylactic reactions and disseminated BCG diseases. Although the reporting rates of neonatal deaths increased during 2013-2014, deaths that causally related to HepB were only 1-3 cases during the study years.

Overall, our study provides reassuring information about the small risk of deaths following immunization. Although 5% AEFI-associated deaths were indeterminate cause, the AEFI investigation and causality assessment process provided valuable information to evaluate vaccine safety in China. The reporting peak of AEFI-associated deaths in late 2013 to early 2014, illustrates the sensitivity of passive reporting of serious AEFI to public information and the caution that should be exercised in interpreting peaks in serious AEFI reporting. Our analysis also illustrates progress made with vaccine safety monitoring during recent years in China.

Several limitations should be considered when interpreting the study findings. As CNAEFIS is a passive surveillance, it has inherent limitations, including reporting bias, and lack of control groups [11]. The limitation of denominator-based risk estimation includes different resources to identify the vaccine-administered doses and unknown background information, which make it difficult to compare the observed to the expected, as well as among different settings [12]. In our study, the

denominators used were estimated from different data resources and one should be cautious about comparing the estimated rates with immunization related death rates in other countries. In China, compensation is available for reactions determined to be vaccine-related. When the expert panel finds no other cause of death, it might be concluding that the vaccine or vaccination was a contributor to the death in the causality assessment. In such cases, the families of the deceased are eligible to apply for compensation. This policy might increase the number of reports of vaccine-related reactions.

Regarding the seasonal distribution of deaths during the study period, except for 2013, deaths were more common in winter than in summer months, consistent with findings of similar studies elsewhere [13]. The results showed that children aged <5 years accounted for 95% of AEFI-associated death, which is consistent with Vaccine Adverse Event Reporting System (VAERS) data in the U.S. [14] and the National Immunization Schedule in China. There were also more male than female deaths. This finding is consistent with data reported in the All Cause of Death Surveillance System in China [15]. Of the AEFI-associated deaths, 78.9% were classified as coincidental events. The reported causes of death were consistent with common causes of mortality nationally [16,17]. According to the National Bureau of Statistics of the People's Republic of China (http://data.stats.gov.cn/easyquery.htm?cn=C01), all-cause neonatal death rates during 2010-2014 were 5.9–8.3‰. The estimated neonatal death rates in this study were lower than all-cause neonatal death rates in the general population, suggesting no association of vaccinations with an increased risk of death at the population level.

Generally, parents have their children vaccinated when they are in relatively good health. In situations where the infant dies shortly after immunization, parents and even health providers may blame vaccine [13]. Although vaccines play a vital role in preventing diseases in children, vaccine hesitancy has become an issue in many counties, including China [18,19]. Events in December 2013 in Hunan province of mainland China provide an example of how such concerns was arise [20]. Media reports of 17 infant deaths, including one case of anaphylactic shock following HepB vaccination, raised widespread public concern in China [3,19]. After investigation, The China Food and Drug Administration reported that the deaths were not related to the vaccine, but instead with a variety of problems, including severe pneumonia, suffocation, kidney failure, severe diarrhea and congenital heart disease [3,19,20,21]. In passive surveillance systems, the behavior of parents and vaccine providers behavior may influence the number of reports. This publicity may have increased public awareness and led to a tendency to report deaths after immunization during 2013-2014. Our analysis showed a reporting peak during 2013-2014, in which 94% of the neonatal deaths were reported to be related with HepB. However, vaccine reactions determined to be causally related to HepB were rare during the study years. Although the overall number of all AEFI reports in CNAEFIS increased from 2010 to 2015, the number of serious AEFIs (events causing a potential risk to the health/life of a recipient leading to prolonged hospitalization, disability/incapacity, congenital abnormalities/birth defects or death) has remained constant [9,22-25].

Causality assessments in China are performed in accordance to WHO guidelines [10,26]. The documented causes of death that could possibly occur due to the inherent properties of a vaccine are limited and include anaphylaxis, viscerotrophic disease following yellow fever vaccine, disseminated attenuated live vaccine agent infection in severely immune-compromised individuals and death from intussusception following rotavirusvaccine [27]. In China, yellow fever vaccine is not recommended, and rotavirus vaccines differ from those used internationally. In our study, the

most common causes of vaccine-related reactions and deaths were anaphylaxis and disseminated BCG infections. BCG is recommended at birth, without screening to determine the status of the immune system at that time. In our study, several deaths were due to neurological diseases. There was no solid evidence that these neurological diseases were caused by the vaccines or vaccination, although some studies reported temporal associations of such diseases with various immunizations [28,29]. When no etiologic agent is identified, and the person was healthy prior to immunization, a suspicion may arise in the causality assessment that the vaccine contributed to the death. Several cases with STL was also assessed to be causally related to vaccination during surveillance. STL is associated with immune system dysfunction. As reported previously, mild immune stimulation, such as that produced by minor trauma or immunizations, could give rise to sudden death among individuals with STL [30]. The expert committee concluded that it triggered these deaths, even when neither the vaccine nor the vaccination was the direct cause. Case causality assessments are extremely difficult. Strengthening the capacity of AEFI investigation and causality assessment is very important in the field of vaccine safety surveillance and evaluation in China. In 2018, WHO issued revised classification for causality assessment [31] which could be adopted and modified for the Chinese setting in future.

5. Conclusions

Vaccines are among the safest medical products in use. However, parents will naturally become concerned when serious adverse events occur after vaccination, even though the event may only be temporally related to immunization [32]. A functional vaccine safety surveillance system and thorough AEFI investigation for causality assessment can provide valuable information for both national regulatory authorities and the public [27]. Our study showed that the risk of death following vaccination was extremely small and did not identify specific safety concerns with vaccines used in China. Because passive surveillance might be stimulated by media reports and public concerns, continuous monitoring and scientific causality assessment of serious AEFI reports, including AEFI-associated deaths, is imperative to ensure public confidence in the immunization program.

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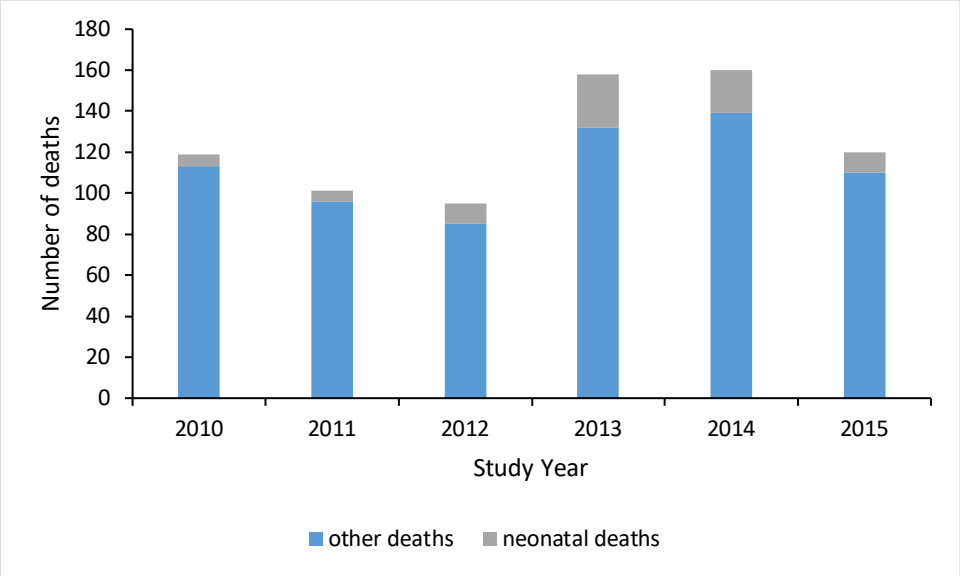

Figure 1 Reports of AEFI-associated deaths by year, 2010-2015

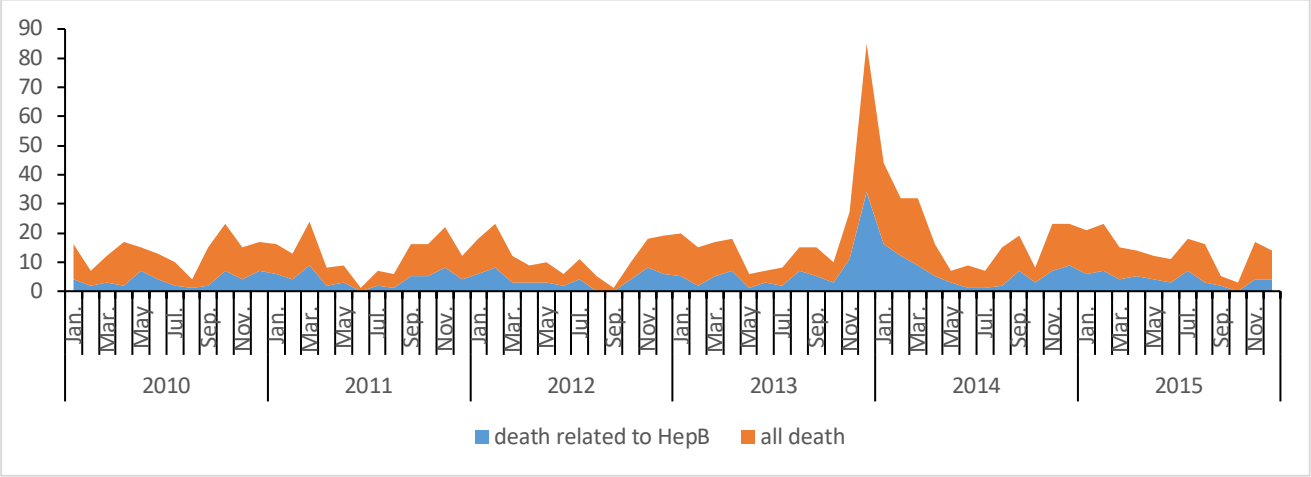

Figure 2 Seasonal distribution of AEFI-associated deaths, 2010-2015

Table1 AEFI-associated deaths by year of death, age and gender, 2010-2015

	<1		1-4		5-9		10-17		18-64		≥65		Total	
	N	Female %	N	Female %	N	Female %	N	Female %	N	Female %	N	Female %	N	Female %
2010	84	44.05	20	50.00	3	0	2	50.00	9	44.44	1	0	119	43.70
2011	90	44.44	8	37.50	1	0			1	100	1	100	101	44.55
2012	79	27.85	12	25.00	2	50.00			1	0.00	1	0	95	27.37
2013	139	36.69	13	38.46			2	0	2	50.00	2	50.00	158	36.71
2014	141	39.01	15	40.00	3	0					1	100	160	38.75
2015	102	42.16	14	42.86	1	100			2	0.00	1	0	120	41.67
Total	635	39.06	82	40.24	10	20.00	4	25.00	15	40.00	7	42.86	753	38.91

Table 2 AEFI-associated deaths by vaccine and vaccine combination, and the causality assessment classification, 2010-2015

Vaccines and vaccine combinations	vaccine reaction	immunization error	coincidental events	indeterminate	Total
HepB	13		163	6	182
BCG+HepB	16	1	92	7	116
OPV+DTaP	13		65	6	84
BCG	34		24	3	61
DTaP	7		22	2	31
OPV			26	1	27
HepB+OPV	2		17		19
RabV	7		8	3	18
JE-L	4		12	1	17
OPV+DTaP+Hib	1		12		13
Other 59 vaccines and vaccine combinations	23		153	9	185
Total	120	1	594	38	753

Table 3 Estimated overall AEFI-associated death rates using different denominators, 2010-2015

Year	No. of deaths	All vaccination doses (millions)	Estimated rates by vaccination doses		Total population (millions)	Estimated rates by total population	
			Deaths rates (per million vaccination doses)	95% *CI*		Deaths rates (per million population)	95% *CI*
2010	119	427.88	0.28	0.23-0.33	1340.91	0.09	0.07-0.11
2011	101	461.44	0.22	0.18-0.27	1347.35	0.07	0.06-0.09
2012	95	478.97	0.20	0.16-0.24	1354.04	0.07	0.06-0.09
2013	158	489.21	0.32	0.27-0.38	1360.72	0.12	0.10-0.14
2014	160	495.74	0.32	0.27-0.38	1367.82	0.12	0.10-0.14
2015	120	504.23	0.24	0.20-0.28	1374.62	0.09	0.07-0.10
Total	753	2857.49	0.26	0.25-0.28	8145.46	0.09	0.09-0.10

Table 4 Estimated neonatal deaths rates after vaccination, 2010-2015

Year	No of Neonatal death	Vaccination doses of 1st dose of Heptitis B (million doses)	Vaccination coverage %	estimation of live birth (million live birth)	Neonatal death rates (per million birth)	95% CI
2010	6	17.16	99.81	17.19	0.35	0.13-0.76
2011	5	17.5	99.86	17.53	0.29	0.09-0.67
2012	10	18.68	99.87	18.71	0.53	0.26-0.98
2013	26	17.48	99.77	17.52	1.48	0.97-2.17
2014	21	15.18	99.84	15.2	1.38	0.86-2.11
2015	10	15.75	99.87	15.77	0.63	0.30-1.17
Total	78	101.75	-	101.91	0.77	0.61-0.96