Comparing the reporting rates of adverse events following immunization in Albania with those from other countries through a systematic review of AEFI internationally

Abstract

Background: Adverse Events following Immunization are becoming day after day an increasing concern all over the world. Different countries have implemented various post-vaccination surveillance systems to detect, treat and prevent AEFI. AEFI surveillance systems are passive or active. The AEFI reporting rates will differ dependently by the post vaccination surveillance system type and other factors related to methods used to investigate AEFI. AE reporting rates vary among different cultural differences in various countries. Geographical variations in AE reporting are a known phenomenon.

Objective: The main objective of this study is to confront the nature, design and performance of AEFI surveillance system in Albania with other countries.

Methods: This comparison will be done extracting various indicators from studies found in the literature and confronting them with those obtained by the analysis of the AEFI database of Albania, in order to highlight differences and similarities and try to configure reasons that support them.

Conclusion: The completeness and accuracy of information in the Albanian vaccine safety surveillance system still needs to improve. It should be emphasized that the reporting rates in passive surveillance systems cannot be considered as incidence rates. To complete the safety profile of each vaccine, additional methods are necessary.

Keywords: AEFI, Post marketing surveillance, Vaccines, Rates of AEFI, Reporting AEFI
Introduction

Joelson et al. (1997) showed that adverse events reporting rates fluctuated between 17% and 68% in 13 different countries, with certain AEs being a particular focus for some countries (such as respiratory events in English-speaking countries). This variation should be considered when comparing the safety results from clinical trials with diverse geographical areas which have different cultural settings as reporting of adverse events is subjective as much as it is objective, and it is influenced by perceptions and mentality of a population. The heterogeneity in the reporting rates among countries is defined by various factors such as: different definitions of AEFI, serious events, vaccine type, number of events, number of administered or distributed doses, age, gender and study period. Taking in consideration that no vaccine is safe perfectly, it is important to identify the “normal” rates of vaccine reactions extracted from different studies in this field and to estimate whether rates of AEFI of a country lay in this range. This estimation will help not only to evaluate the safety of vaccines in that specific country, but also to assess the reporting frequency and quality. Through this article we are trying to identify factors associated with differences in AEFI reporting rates between Albania and other countries, and also suggest methods to improve the reporting of AEFI in Albania.

Data and Methods:

Through a systematic review of published studies which documented the AEFI rates in different countries at regional or national level, in different surveillance systems: active surveillance and passive surveillance, a total of 31 articles were chosen for full reading of the content.

Inclusion and exclusion criteria

The included articles were in English or Italian language and included reporting rates of AEFI by vaccine, category of reaction or age. The Pubmed, Web of Science and Embase databases were searched for all published studies regarding the reporting of AEFI in all countries and regions. The keywords of the search included “post marketing surveillance”, “adverse events following immunization”, “immunization”, “vaccines”, “surveillance systems”, “rates of AEFI”, “reporting AEFI”. These keywords were combined with specific vaccine categories such as DTP, BCG, MMR, HepB, OPV (or polio, or IPV), in order to detect studies dealing with events reported for specific vaccine categories. The focus was on finding studies having the same type of surveillance system and having the same reporting method. Nevertheless, other types of surveillance systems were taken in consideration in order to give a general outlook of the AEFI rates and trying to identify factors influencing the heterogeneity. The final studies were selected based on pre-defined criteria: only studies in English and Italian languages were taken in consideration. Studies were based on population and vaccines included were one of the following: DTwP vaccines, DTwP-HepB-Hib, Hib, HepB, OPV, IPV, DT, Td, PCV, MR, MMR, or BCG.

The results were filtered for English and Italian language. The surveillance type was not important; it could be passive or active, based on clinical findings or hospital admission data. It should, nevertheless be a post-marketing surveillance type. Studies were included if they reported reporting rates or incidence rates of adverse events following immunization and for serious or non-serious events. The reporting rate of AEFI could be population based or setting based. All studies conducted in different settings such as hospital, vaccination centers and maternity hospitals were included. The AEFI rate could be calculated on distributed doses, administered doses or number of vaccinated subjects.

Only vaccines pertaining to the Albanian National Immunization Program were considered for comparison. These vaccines include DTwP, BCG, Hep B, OPV, IPV,
MMR, DT, Td, DTP-HepB-Hib.
Studies were excluded if they were in other languages other than English and Italian, if they did not report rates or incidences of any AEFI, if they reported events of vaccines not included in the Albanian NIP and if they were pre-marketing studies. Post marketing studies that focused on drugs were excluded. Studies dealing other problems related to vaccination such as incidence of vaccine preventable diseases or vaccination coverage were excluded too. Information materials other than scientific studies and AEFI periodic reports were excluded.

If more than one study resulted for the same country or region in different, they were both accepted. Studies from the same country, from different authors and having different results reflect the influence of different variables in the AEFI rates and also bias of the author. If for one country there were more than one study from one author conducted at different periods, the study covering the period more approximate to ours was selected. For events considered as serious there was a further comparison with background rates reported by WHO in 2000 in the vaccine information sheet.

Data analysis
The preliminary searching yielded 530 studies of which only 50 were selected to be related to our study design and aims. The references of each study were checked for other studies not tracked from our first search and a total 67 studies were extracted. From these only 15 seemed to fit our objectives. Finally, after reviewing the full text of the 75 retrieved studies, only 30 of them adhered to our inclusion criteria (Table 8.1). From each study the overall reporting rates of AEFI were extracted. Other data extracted from each study were: study period, country, region, setting, type of AEFI surveillance, study design, vaccines included in the study, target population, vaccine responsible for most of the cases reported, the most reported event, year of AEFI surveillance system establishment and percentage of serious events. Reporting rates were calculated using either the administered doses or distributed doses as the denominator. The reporting rates for total AEFI and serious cases were compared between countries. Age groups, type of vaccines included in the study, the most reported event and also the type of study were considered for comparison.

Results
Overall AEFI reporting rate
The overall reporting rates were calculated differently in various countries. In some of them, distributed doses were taken as numerator, in some others the type was not specified and only in few of them administered doses were used. In a few other studies rates of AEFI were calculated taking in consideration the number of population vaccinated. All the characteristics extracted from these studies are summarized in the table 1. As it is observed from the table, Albania has the lowest reporting rate of all countries and regions reviewed. This rate; 3.9/100,000 administered doses comes closer with that of Switzerland (Schumacher et al., 2010) which has a rate of 2.7/100,000 distributed doses and that of Zhejiang Province of China which had a rate of 9.2/100, 000 administered doses.

Vaccines under study
Most of the studies reported rates for all the vaccines of the immunization schedule in children, just a few of them reported rates for one or two vaccines.

The three studies in Brazil (Cunha, & Dourado, 2004); (Fernandes, et al., 2005); (Cunha et al., 2013) reported rates of more vaccines than those included in the immunization schedule; Yellow Fever, Influenza, and Rabies. These vaccines which are responsible for most of the AEFI reported and of clinical relevance might have contributed to the higher reporting
rates of AEFI in this country. Denmark which had also a high reporting rate included these vaccines too (Folkenberg et al., 2011). Cuba which was the only country that reported rates for DTwP vaccine rather than for DTPa reported also high rates (Galindo et al., 2012). This clearly demonstrates that countries which have a high overall reporting rate coincide with a low frequency of serious events as all events are reported equally. While countries which have problems with underreporting, report high percentage of serious events as they tend to predominate over the total number of the events reported. Moreover the definition of serious events and what is considered a serious event differs from country to country.

**The most reported event**

Fever was the most reported event in Albania. This was consistent with studies from Denmark, Singapore, Australia, India, Italy, Democratic Republic of Congo, Cuba, Spain, Australia, and USA. Vaccines studied were generally all the vaccines of immunization schedule, except the study from Republic of Congo which studied OPV vaccine.

Although fever was the most reported event in other countries too like it was in Albania, the percentage of cases with fever differed from one country to another. Fever (58% of all reactions) in Albania case represented 58% of total reactions (247/422) and it appeared in 80.2% (247/308) of the cases. Otherwise resulted in other countries such as Australia where fever represented 24% of the AEFI events, USA fever frequency was 25.8% of all reports, in Canada fever comprised 23% of the events and in China 46.2% of the events. This high percentage in Albania is another indicator for underreporting and reflects the low knowledge of the reporters about what to report. This shows somehow the lack of knowledge of health workers about events that should be reported, their detection and appropriate identification.

**Vaccine associated with most of the events**

Obviously the vaccine associated with most of the events was DTwP in Albania which was consistent with reported events from Cuba where the same result was obtained (Galindo et al., 2012).

There are countries like Switzerland where the most reported AEFI are other than the common and known events reported after administration of a vaccine. In Switzerland AEFI after administration of yellow fever vaccines minimize AEFI from other vaccines (Schumacher et al., 2010). Tick borne encephalitis and yellow fever vaccines are those for which there are the highest reports.

**Target population**

The target populations in the Albanian study were children aged from 0 to 18 years old because this is the age of the children covered by the Albanian National Immunization Schedule. Some of the other studies regarded all ages of population while some others children less 7 years old. Increasing the range of age included in the population, increases the number of doses administered and the denominator of the reporting rates, thus influences the final value of the AEFI rate. It is well known that most of the adverse events after immunization are reported in children <7 years and limiting the analysis of AEFI data in this group means to decrease the denominator and having approximately the same numerator which increases the reporting rate.

**Discussion**

It is observed from the above analysis that countries which have the highest reporting rates and the higher quality of data were those in which the Vaccine safety surveillance system has started early and those that integrated passive and active surveillance. Moreover, studies that covered longer periods of time were more close to the true results than those which covered shorter periods of time.
The variation in rates of AEFI is due to different reporting requirements, different case definitions and different compliance of the reporters. The result from our study stated that fever was the most reported event and it was mostly reported after DTP-containing vaccines. Many other studies have reported such result. Fever and injection site reactions might be characteristic of DTP containing vaccines.

As it is observed from the results higher reporting rates were associated with active surveillance systems or integrated systems in which active and passive surveillance are complementary. This is the case of Canada (AEFI reporting rate: 17/ 100,000 DD) in which passive surveillance is integrated by active surveillance which is performed by 12 pediatric hospitals across the country under IMPACT (Scheifele & Halperin, 2003). Albania has the lowest reporting rate of all countries and regions reviewed. This rate; 3.9/100,000 administered doses comes closer with that of Switzerland (Schumacher et al., 2010) which has a rate of 2.7/100,000 distributed doses and that of Zhejiang Province of China which had a rate of 9.2/100,000 administered doses. The definitions and interpretation of an AEFI varied across countries and studies (Table1). The reporting rate of 3.9/100 000 administered doses in our study is not surprising taking in consideration the nature of the surveillance system. The mean reporting rate of Liguria Region in Italy in the period 2009–2012 was 1.7 reported AEFI for 100 000 administered doses of vaccine while after the implementation of educational activities and the active surveillance project in 2013, the reporting rate was estimated to increase to approximately 14.0 for 100 000 administered doses (Alicino et al.,2015).

Problems with underreporting are highlighted also by other countries where the incidence of AEFI cannot be measured even in highly developed countries. In a study aimed to report the sensitivity of surveillance system in the United States, demonstrated that sensitivity varied widely, ranging from 72% for vaccine associated with poliomyelitis to less than 1% for acute thrombocytopenic purpura following the MMR vaccine and hypotonic hyporesponsive episodes following the DTP vaccine. This reflects the underreporting of known outcomes in the passive surveillance system (Rosenthal & Chen, 1995).

The proportion of serious AEFI among all AEFI varies considerably in national surveillance systems. These differences reflect variability in reporting regulations but also point to a bias towards reporting serious AEFI which in general have been found to be significantly lower in active surveillance systems and in clinical trials compared to passive surveillance systems (Heininger et al., 2007). During passive surveillance the reporting of non serious events is neglected and the proportion of serious ones is higher, while during active surveillance both serious and non serious reactions are reported at high percentages and the proportion of serious reactions diminishes.

The patterns of AEFI in Albania were close to the patterns of AEFI in other countries with similar surveillance system. In a prospective, single center, observational study in a hospital of India was reported that fever was the most common AEFI followed by an excess cry. Moreover, the incidence of fever reported was significantly high following DTP vaccine. Like in Albania, cases of BCG vaccine were not reported (Amol et al., 2015).

The same study in Denmark reported that one third of AEFIs were classified as serious and the annual number of serious AEFIs remained constant during the study period. The most frequently reported AEFIs were febrile seizures and local reactions which is similar to the situation in Albania. The majority of serious AEFI of a neurological nature were convulsions likewise in Albania (Folkenberg, et al., 2011). In a study conducted in a middle-sized city in Brazil , it is noted that data related to BCG like BCG lymphadenopathy, local abscess and
ulcer are still reported (Fernandes et al., 2005). Differently happens in Albania where there are no reports about this vaccine.

Nevertheless, systemic events from this study are approximately the same as those in Albania where DTP-fever, hypotonic-hipporesponsive episode (HHE), convulsion and persistent crying are the most reported events. A transient increase in reporting of AEFI following the introduction of DTPa-IPV combination vaccines in November 2005 was observed also in Australia and the most reported event was injection site reaction after DTPa-IPV vaccine. The same situation was observed in Albania when pentavalent vaccine was added to the immunization schedule (Lawrence et al., 2007).

The patterns of AEFI in Albania were closer to those countries which had the same system and approximately the same economic level. However, there were some other characteristics that were shared with developed countries. This shows the good will of vaccine safety stakeholders in Albania to conduct AEFI surveillance in accordance with international requisites. The different sensitivity of various surveillance systems to detect and report AEFI is attributed to different criteria adopted for diagnosing and recording cases.

**Advantages of Surveillance System in Albania**

The Albanian surveillance system considers the number of doses actually administered rather than the number of doses distributed, thereby improving the accuracy of the estimated rate of reported AEFI cases. However, rates of AEFI using these denominators cannot be interpreted as incidence rates due to under-reporting, bias in reporting which compromises the quality and completeness of information (Mahajan et al., 2012). Moreover, when necessary, the vaccination methods in Albania include not only routine vaccination but also the mass vaccination campaign which increases the sensitivity of the surveillance system because rare events might be investigated. The characteristics of events which are less likely to be reported include: delayed onset after vaccination and event not recognized to be associated with vaccination. It is observed from the table above that studies based on active surveillance reported a higher reporting rate of AEFI compared with those from passive surveillance and record based.

**Conclusion**

The completeness and accuracy of information in the Albanian vaccine safety surveillance system still needs to improve. It should be emphasized that the reporting rates in passive surveillance systems cannot be considered as incidence rates. To complete the safety profile of each vaccine, additional methods are necessary. The observed rates should be compared with the expected rates calculated from the health databases. Epidemiological and analytical studies which assess the exposure of the individual and outcome are also important. The Albanian surveillance system considers the number of doses actually administered rather than the number of doses distributed, thereby improving the accuracy of the estimated rate of reported AEFI cases. Moreover, when necessary, the vaccination methods in Albania include not only routine vaccination but also the mass vaccination campaign which increases the sensitivity of the surveillance system because rare events might be investigated. The reporting bias include the underreporting of common and mild events and stimulated reporting that might occur due to intense media attention and increased public awareness (Rosenthal & Chen, 1995). Another limitation of passive surveillance system is the incapacity to detect new AEFI not documented previously.
References


References


References


Table 1. Characteristics of AEFI in different countries | DA: Administered doses, DD: Distributed Doses

<table>
<thead>
<tr>
<th>National/Regional/Local</th>
<th>Country</th>
<th>Type of AEFI surveillance</th>
<th>Type of study</th>
<th>Vaccines</th>
<th>Rates</th>
<th>Year</th>
<th>Target Population</th>
<th>Vaccine responsible for highest no of reports</th>
<th>Most reported event</th>
<th>Year of AEFI surveillance starting</th>
<th>Serious events</th>
</tr>
</thead>
<tbody>
<tr>
<td>All country</td>
<td>Albania</td>
<td>Passive</td>
<td>Record based descriptive study</td>
<td>BCG, DTwP,OPV,IPV, HepB, MMR,DT,DTwP-HepB-Hib, PCV,TT,</td>
<td>3.9/100 000 DA</td>
<td>2003-2015</td>
<td>0-18 y</td>
<td>DTP</td>
<td>Fever (58% of all reactions)</td>
<td>2003</td>
<td>21%</td>
</tr>
<tr>
<td>All country</td>
<td>Oman (Al Awaidy et al., 2010)</td>
<td>Passive</td>
<td>Record based descriptive study</td>
<td>BCG, Hib,MR,MMR,OPV,DT,TT,DTP,DT-P-Hib-HBV</td>
<td>10.8/100 000 DA</td>
<td>1996-2005</td>
<td>children &lt; 6 y</td>
<td>BCG</td>
<td>BCG adenitis</td>
<td></td>
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<tr>
<td>Hamedan Province</td>
<td>Iran (Khazaei et al., 2016)</td>
<td>Passive</td>
<td>Record based descriptive study</td>
<td>DTP,MMR,BCG,</td>
<td>11.8/10,000 doses</td>
<td>2014</td>
<td>children &lt; 7 y</td>
<td>DTP</td>
<td>Lymphadenitis</td>
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<tr>
<td>Liguria Region</td>
<td>Italy (Alicino et al., 2013)</td>
<td>Passive</td>
<td>Record based descriptive study</td>
<td></td>
<td>14.1/100 000 DA</td>
<td>2011-2013</td>
<td>All ages</td>
<td>BCG</td>
<td></td>
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<td></td>
<td>Guatemala(Asturias et al., 2013)</td>
<td>Active surveillance</td>
<td>prospectve cohort study</td>
<td>Quinvaxem</td>
<td></td>
<td>2008-2010</td>
<td>children aged 0 -- 17 years</td>
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<tr>
<td>Emiglia Romagna</td>
<td>Italy (Gatti,n.d)</td>
<td>Record based descriptive study</td>
<td></td>
<td>BCG, Hib,MR,MMR,OPV,DT,DT,DTP,Yellow Fever, Influenza, Pneumococcus, HBV,Rabies, Measles</td>
<td></td>
<td>2006-2009</td>
<td>children aged 0 -- 17 years</td>
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<tr>
<td>Location</td>
<td>Country</td>
<td>Study Type</td>
<td>Vaccines/Conditions</td>
<td>Vaccine coverage</td>
<td>Age(s)</td>
<td>Hypotonic-hyporesponsive episodes (HHEs), fever &gt;39.5°C, febrile convulsion, generalized exanthema</td>
<td>Year(s)</td>
<td>Notes</td>
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<tr>
<td>Rondonia State</td>
<td>Brazil (Cunha et al., 2013)</td>
<td>Passive</td>
<td>BCG, MMR, DTP, DTP+Hib, Yellow Fever, Hib</td>
<td>52.7/100,000 DTP, 70.6/100,000 DTP+Hib</td>
<td>0-7 y</td>
<td>DTP, DTP+Hib</td>
<td>2000-2008</td>
<td>1998 in this state, 2000 all over the country in Brazil</td>
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<tr>
<td>Brazil</td>
<td>Brazil (Cunha &amp; Dourado, 2004)</td>
<td>Passive</td>
<td>DTwP/Hib</td>
<td>44.2/100,000 DA 67.7/100,000 first 47.9/100,000 second 21.0/100,000 third</td>
<td>&lt;1 y</td>
<td>DTwP/Hib</td>
<td>2003-2004</td>
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<tr>
<td>Denmark</td>
<td>Denmark (Folkenberg et al., 2011)</td>
<td>Passive</td>
<td>MMR, HPV, Yellow Fever, Influenza, Pneumococcus, HBV, Rabies, Measles, Meningococcus</td>
<td>MMR: 70.6 per 100,000 doses</td>
<td>1998-2007</td>
<td>children aged 0 -- 17 years</td>
<td>MMR, DTaP-IPV-Hib</td>
<td>Febrile convulsions, pyrexia, injection-site reactions and rash.</td>
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<tr>
<td>Calabria Region</td>
<td>Italy (Staltari et al., 2013)</td>
<td>Passive</td>
<td>Hib, MMR, DTaP, HBV, PCV, Men C, Varicella, Influenza, HPV, IPV</td>
<td>2012</td>
<td>All ages</td>
<td>Pain, redness, and swelling in the site of administration, seizures</td>
<td></td>
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<tr>
<td>Singapore</td>
<td>Singapore (Thoon et al., 2014)</td>
<td>Passive</td>
<td>BCG, HBV, DTP, PCV, MMR, RV</td>
<td>2010-2012</td>
<td>All ages</td>
<td>BCG lymphadenitis, fever, afebrile seizures,</td>
<td>2007</td>
<td></td>
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<tr>
<td>Veneto Region</td>
<td>Italy (Micheletti et al., 2011)</td>
<td>Passive</td>
<td>23/ 100,000 doses</td>
<td>1992-2008</td>
<td>All ages</td>
<td>MMRV vaccine (23.1), followed by varicella (10.5), tetravalent DTaPHB (9.4), BCG (8.6) and hexavalent (8.5) vaccine.</td>
<td>Injection site reactions and fever as the most frequently reported events</td>
<td>5, 6%</td>
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<tr>
<td>All country</td>
<td>Australia (Lawrence et al., 2007)</td>
<td>Passive</td>
<td>Record based descriptive study</td>
<td>MMR, DTPa-IPV, DTPa-IPV-HBV, DTPa-IPV-HBV-Hib, MenCCV, varicella, 7vPCV, Hib, Hib-HepB.</td>
<td>3.8/100 000 population 12.5/100 000 doses</td>
<td>2006</td>
<td>All ages and children &lt;7 y</td>
<td>DTPa-IPV injection site reaction following a fourth or fifth dose of acellular pertussis-containing vaccine (70 reports per 100,000 doses)</td>
<td>2000</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td>All country</td>
<td>Australia (Mahajan et al., 2012)</td>
<td>Passive</td>
<td>Record based descriptive study</td>
<td>MMR, DTPa-IPV, DTPa-IPV-HBV, DTPa-IPV-HBV-Hib, MenCCV, varicella, 23vPCV, Hib, Hib-HepB.</td>
<td>10.4/100,000 population</td>
<td>2011</td>
<td>All ages and children &lt;7 y</td>
<td>DTPa-IPV ISR (46%), fever (24%), allergic reaction</td>
<td>2000</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>All country</td>
<td>India (Joshi et al., 2013)</td>
<td>Passive</td>
<td>Active prospective study, telephone</td>
<td>99.2/1000 doses</td>
<td>2011</td>
<td>0-14 y</td>
<td>DTP, BCG, Hepatitis-B Fever, injection site inflammation</td>
<td>1985</td>
<td>0.70%</td>
<td></td>
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<tr>
<td>Karnataka one region</td>
<td>India (Amol et al., 2015)</td>
<td>Prospective, single center, active surveillance</td>
<td>Februar-Apr 2014</td>
<td>&lt;5 y</td>
<td>DTP</td>
<td>Fever, persistent crying</td>
<td>1985</td>
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<tr>
<td>All country</td>
<td>Italy (AIFA, 2012)</td>
<td>Passive-Active surveillance</td>
<td>Record based descriptive study</td>
<td>13.5/100,000 doses</td>
<td>2012</td>
<td>Pediatric age</td>
<td>Hexavalent: DTP-IPV-HBV-Hib</td>
<td>Pyrexia</td>
<td>15%</td>
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<tr>
<td>Emilia Romagna</td>
<td>Italy (Gatti, n.d)</td>
<td>Passive</td>
<td>Record based descriptive study</td>
<td>Difterite - Tetano - Pertosse , Polio, HBV, Hib, PCV, MenC, HPV, influenza, Varicella</td>
<td>46/100,000 doses</td>
<td>2006-2011</td>
<td>0–17</td>
<td>Hexavalent</td>
<td>Ipersensibilità Febbri importanti</td>
<td>10.00%</td>
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<tr>
<td>All country</td>
<td>Switzerland (Schumacher et al., 2010)</td>
<td>Passive</td>
<td>record based descriptive study(sys tematic analysis)</td>
<td>BCG, DTP(a/wc)/dT, Hib, OPV or IPV, tick-borne encephalitis (TBE), hepatitis A and/or B, MMR, yellow fever,</td>
<td>2.7/ 100,000 DD</td>
<td>1991-2001</td>
<td>tick-borne encephalitis and yellow fever vaccines</td>
<td>1988</td>
<td>21.8%</td>
<td></td>
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<tr>
<td>Country</td>
<td>Study Details</td>
<td>Vaccine Schedule</td>
<td>Durations</td>
<td>Adverse Reactions</td>
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<td>All country</td>
<td>Democratic Republic of Congo (Nzolo et al., 2013)</td>
<td>OPV</td>
<td>Mar-Jun 2011</td>
<td>Headache, abdominal pain, fever, diarrhea, and asthenia</td>
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<td>Babol, Mazandaran.</td>
<td>Iran (Barari-Savadkou et al., 2016)</td>
<td>BCG</td>
<td>2011-2013</td>
<td>0.93% presented with lymphadenitis, 99% with lymphadenopathy, lymphadenitis,</td>
<td></td>
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<tr>
<td>All country</td>
<td>Cuba (Galindo et al., 2016)</td>
<td>Record based descriptive study</td>
<td>1999-2008</td>
<td>DTwP fever, local reactions at injection site</td>
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<tr>
<td>All country</td>
<td>Czech Republic (Danova et al., 2017)</td>
<td>Active study based on hospital record</td>
<td>2011-2013</td>
<td>0-10</td>
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<tr>
<td>All country</td>
<td>Poland (Krysztopa-Grzybowska et al., 2012)</td>
<td></td>
<td>1994-2010</td>
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<td>Madrid</td>
<td>Spain (Carrasco-Garrido et al., 2004)</td>
<td>DTPa + Hib (IM) OPV Meningococcal C (IM) MMR (SC) HBV (IM)</td>
<td>Jan-Dec 2002</td>
<td>0-14</td>
<td></td>
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<tr>
<td>New South Wales</td>
<td>Australia (Mahajan et al., 2013)</td>
<td>Injection site reaction, syncope, pyrexia, rash</td>
<td>2012-2013</td>
<td>0-10</td>
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</table>

Note: The table provides a summary of studies conducted in different countries, including the vaccines used, adverse reactions, and study durations.
<table>
<thead>
<tr>
<th>Province of Manitoba</th>
<th>Canada (Roberts et al., 1996)</th>
<th>Passive, population-based and active, hospital-based</th>
<th>DT,(DPTP),(IPV),MMR, Td.</th>
<th>1987-1989</th>
<th>1990</th>
</tr>
</thead>
<tbody>
<tr>
<td>National USA (Zhou et al., 2003)</td>
<td>Passive, population-based and active, datalink</td>
<td>Record based descriptive study</td>
<td>11.4/ 100,000 DD</td>
<td>January 1, 1991, through December 31, 2001</td>
<td>all ages</td>
</tr>
<tr>
<td>National China (Hu et al., 2013)</td>
<td>Passive</td>
<td>Record based descriptive study</td>
<td>9.2 / 100,000 doses.</td>
<td>2008-2011</td>
<td>DTP,MM,DT.</td>
</tr>
</tbody>
</table>

**Table:**

- **Province of Manitoba**
- **Canada (Roberts et al., 1996)**: Passive, population-based and active, hospital-based. DT, (DPTP), (IPV), MMR, Td. 1987-1989.
- **USA (Zhou et al., 2003)**: Passive, population-based and active, datalink. Record based descriptive study. 11.4/100,000 DD. January 1, 1991, through December 31, 2001. All ages.
- **Canada (Public Health Agency of Canada, 2006)**: Passive, population-based and active, hospital-based. Tdap, td, MenC, MenP, PneumoC, Pneum oP, Varicella, HBV, M, MR, MMR, OPV, IPV-DTaP, DTP, DT-P-IPV, Hib. 17/100 000 doses. 1992-2004. Local reactions (32.4% of 3,625), allergic reactions including rash (31.7%) and fever (23%).
- **ZHEJIANG PROVINCE**: Passive. Record based descriptive study. BCG, DT, DTP, MM R, MM, MR, OPV, pandemic H1N1 influenza, Japanese encephalitis virus live attenuated vaccine (JEV). 9.2 / 100,000 doses. 2008-2011. DTP, MM, DT. Fever (46.2%; 2,894/6,265), followed by injection site reaction (ISR) (39.4%) and allergic reaction (7.2%).
| 5 Counties | **China (Guo, 2013)** | Passive, population-based and active | cross-sectional descriptive analytic study | **BCG, HepB, OPV, DTPa/DTap/DTwP, MV, DT, MMR/MM/MV, Men-A, Men-A+C, HepA-a, JEV-a, HepA-a** | August 2007 to July 2009. | **DTwP/DTap and MCV** | injection reaction’ (0.19%) and ‘program error’ (0.18%) for total events | 2005 |