REVIEW OF THE EPIDEMIOLOGY OF DIPHTHERIA – 2000-2016

Kristie E. N. Clarke, MD MSCR, FAAP

US CENTERS FOR DISEASE CONTROL AND PREVENTION

Background

Diphtheria was one of the leading causes of childhood death in the pre-vaccine era[1]. However, after the diphtheria toxoid vaccine was invented in 1923, and subsequently was used on a large scale in the United States and other industrialized countries in the 1940s-1950s, incidence in these nations quickly declined. There was a continued decline after the launch of the Expanded Programme on Immunization (EPI) in 1977 (Figure 1). As a result, physicians in many nations have never seen a case of diphtheria and may be unaware that there are approximately 5000 cases of diphtheria reported worldwide each year[2].

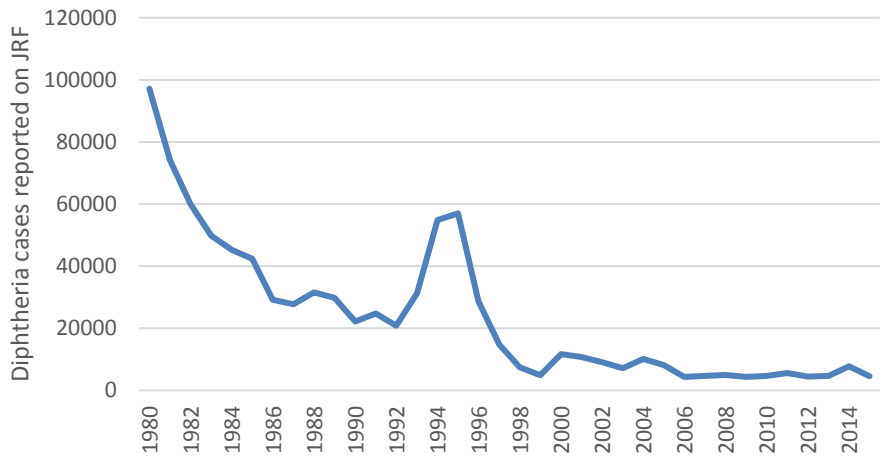


Figure 1- Reported cases of diphtheria worldwide- 1980 -2015

Diphtheria surged into the spotlight with a spike in incidence in the 1990s (Figure 1), representing a widespread epidemic in the Russian Federation and the former Soviet Republics, which left in its wake over 157,000 cases and 5,000 deaths[1]. Cases tended to be much older than those in other contexts, with 64-76% among those aged 15 years and older[3]. This outbreak demonstrates the potential for severe outbreaks when a community has both a large population of non-immune adults and poor vaccination coverage among children. The outbreak began in major urban centers in Russia at the end of the 1980s, but it was not readily acknowledged or addressed, and spread to all 15 post-Soviet Republics by 1995[4]. Reasons for the outbreak were rooted in falling support for vaccination among both parents and health care providers in the 1980s, with over 50 diagnoses listed as contraindications to vaccination and up to 50% of children in some areas receiving the less immunogenic adult formulation Td instead of the recommended DTP due to concerns about complications[5, 6]. The decision of the Soviet Union in 1986 to delay the booster dose at school entry (age 6) to age 9 was also found to increase risk of infection in this population of children[7, 8]. While there were high attack rates among many age groups, the highest incidence and highest proportion of severe cases were among 40-49 year olds, who were young children when DTP was being introduced in the Soviet Union. Many were not immunized as children and were also not exposed to the disease as incidence subsequently declined[3]. Meanwhile, cases did occur among younger adults who had been immunized, but these tended to be milder due to immunologic memory. With the breakup of the Soviet Union, there were also environmental conditions favorable to an outbreak, including large population migrations, declining socio-economic conditions, and disruptions of vaccination supply chains and programs in the former Soviet republics[4, 7]. Importantly, serologic and case control studies at the time showed high vaccine effectiveness, proving that failure to vaccinate was the problem rather than vaccine failure[9]. The recommended response included the mass immunization of the entire population with at least one age-appropriate dose of diphtheria-containing vaccine, with those showing the lowest levels of immunity (30-50 yo adults) receiving a full 3 dose series of Td[5]. While the epidemic peaked at over 39,000 cases in 1994[3], the effects were long lasting. As late as 2001 these nations accounted for over 12% of the cases of diphtheria reported worldwide (in 2015 this figure was just 0.2%)[2].

Patterns of epidemiology are known to have changed over time due to introduction of vaccination as well as changing socioeconomic conditions in countries. In the pre-vaccine era, children were exposed early; by 15 years of age, 80% of children were immune to diphtheria from either overt or subclinical infection. There was some age shift in diphtheria cases prior to the vaccine era. In Poland, >70% of cases in the 1890s were in children under 5, shifting to only 43% by the 1930s. This pre-vaccine era age shift has been attributed to an increased standard of living, smaller families, less overcrowding, and improved hygiene conditions. However, prior to vaccine introduction at least 40% of cases were still in children under 5, and 70% were in children under 15 years of age[4]. While children were susceptible, ongoing circulation served to naturally boost the immunity of adults.

After the introduction of vaccine in a population where diphtheria is endemic, the epidemiologic patterns have been described as following a two-stage process. In the first stage, the disease shifts to a greater proportion of cases in schoolchildren than described in the pre-vaccine era. In the second stage, cases are seen primarily in adolescents and young adults over age 15. In the aftermath of the 1990s outbreak, it was generally thought that in developing countries the pool of immunized individuals was still small enough that immunity would be maintained among adults by natural circulation. In developing countries in warm climates, cutaneous diphtheria, which serves to boost immunity without the symptoms or risks of classic diphtheria[10], was an element of this continuing circulation. Cutaneous diphtheria does not meet the WHO case definition[11], so it is not reported as diphtheria on the JRF. It is also similar in appearance to, and may co-exist with, other cutaneous infections[10] and is frequently not diagnosed. As a result, patterns of cutaneous disease among populations over time are not known or tracked.

In areas where diphtheria has been well controlled, immunity is known to wane in late childhood or adolescence depending on the schedule of immunization[8]. In many industrialized nations there are known gaps in immunity among the adult population, particularly those that were not exposed to the disease in their environment as children. The precise ages of adults most at risk varies by the country and timeline on which immunization for diphtheria was introduced[4]. In some countries, the immunity gap has been shown to be larger among women as compared to men; this had been attributed to booster vaccines received upon entry into military service or greater incidence of injury requiring tetanus vaccination[7, 8, 12]. One of the lessons from the 1990s outbreak is that while a large group of susceptible adults does signal a potential for an outbreak, this is much less likely if the immunization coverage among children is strong. In the 1990s, there were many cases of imported cases of diphtheria to nearby countries such as Poland and Finland. However since these countries had maintained childhood immunization coverage of over 95%, there was no secondary transmission or local outbreaks as a result of these imported cases[5]. It is worth noting that marginalized or difficult to access populations in industrialized countries may still be at risk. In the US, toxigenic diphtheria had not been found to be circulating in national surveillance data, however on a Native American reservation in 1996 a strain was detected that was closely related to a strain seen in the same area in the 1970s, signaling likely continued undetected transmission[7]. Outbreaks in the 1980s were seen in the US and Europe among socioeconomically disadvantaged groups living in crowded conditions, primarily those with comorbid substance abuse[4]. While booster doses have been implemented in many countries and have the potential to address the known gaps, these have been difficult to monitor[6]. Despite the low compliance with the booster doses, the US Advisory Committee on Immunization Practices (ACIP) has continued to recommend decennial boosters despite controversy, in part due to the need to bolster diphtheria immunity among adults of all ages[13]. Another option to reach adults is to replace boosters of TT (such as after injury) with Td, although this can be slow to take effect. In 1991, the ACIP recommended adult vaccination with Td rather than TT be given at every opportunity due to increased

protection with only a marginal price difference; however, as late as 2000, 20% of adults were still receiving TT boosters[7]. Over time demand continued to drop and TT has not been available from manufacturers in the US since 2015.

With the exception of the universally recommended 3 dose primary series in infancy, the current WHO recommendation on diphtheria vaccine depends on the epidemiologic pattern of disease in each country. The first priority is attainment of 90% coverage for the primary series, with subsequent consideration of doses at the end of the second year of life and possibly additional doses at school entry and school leaving. Booster doses are especially recommended for industrialized countries which need to compensate for the loss of natural boosting from the environment. Those living in non-endemic or low endemic areas may require additional boosters at 10 year intervals[10]. There has recently been a call to reconsider these recommendations, with authors in some endemic countries noting a resurgence of the disease or a shift to older populations[14, 15], as well as anecdotal reports in the public health community of an age shift in developing countries that may be similar to that seen in previous years in industrialized countries. Therefore, this review gathered available case-based data regarding age distribution and vaccination status of infected persons. These data were analyzed in the context of available aggregate surveillance and coverage data in an attempt to shed light on the epidemiological patterns of diphtheria after the year 2000 and offer an evidence base for future recommendations.

Methods

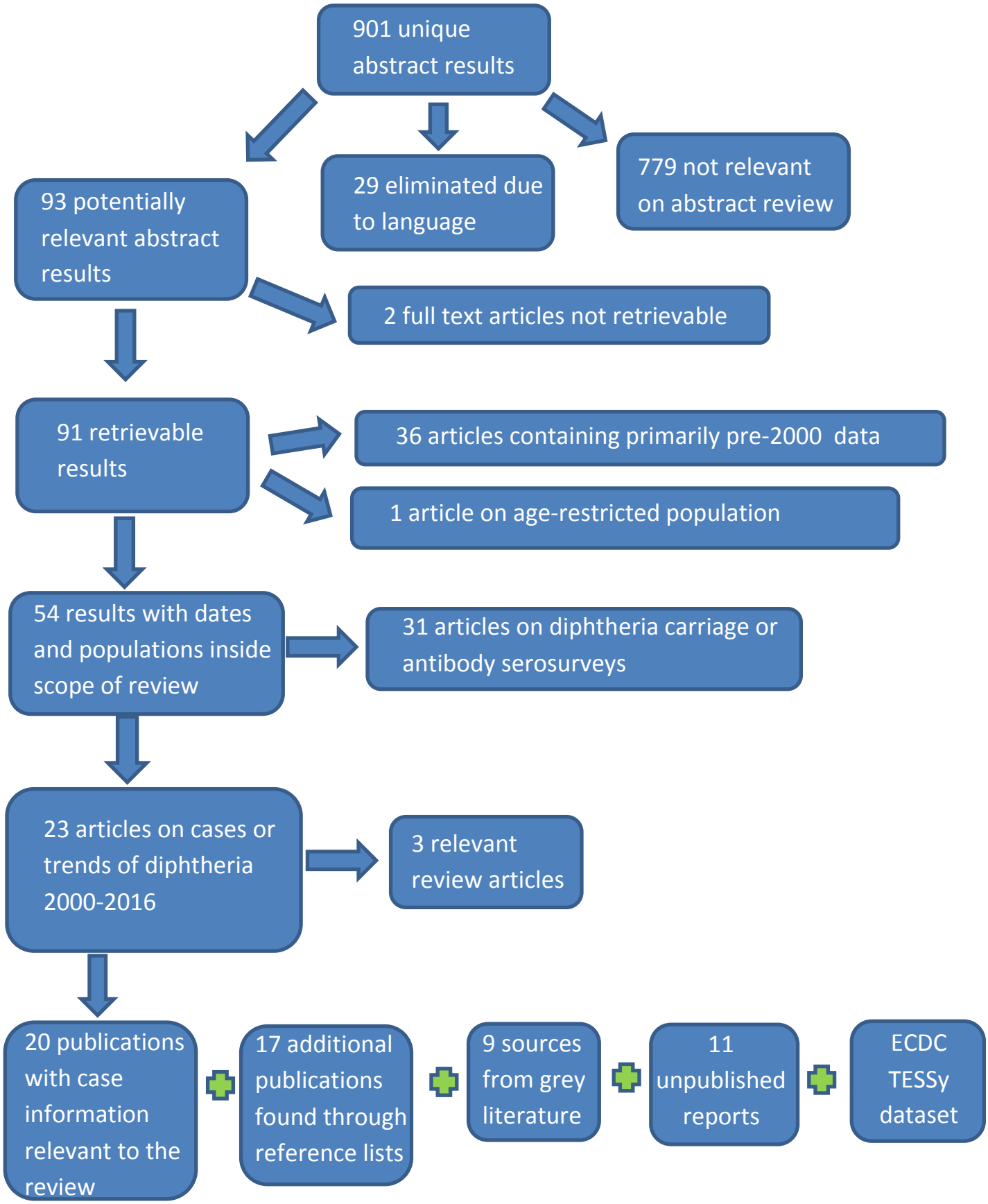
First, JRF data were examined for general epidemiologic trends of incidence over time and across regions. Recent patterns in immunization coverage and incidence were examined more in depth for the 10 countries reporting the most cases from 2010-2015. To contextualize the discussion of immunization recommendations, available databases and other information on national immunization schedules were compiled.

Next, since there is no repository of data on the age or vaccination status of cases of diphtheria, one was created using any accessible published or grey literature. An initial search was run on Medline and Embase with the assistance of a library sciences professional using the search terms diphtheria AND outbreak, cluster, OR epidemic. Once results were reviewed, a secondary search was performed to widen the scope of results on the Medline, Embase, Global Health, CINAHL, Cochrane Library, LILACS, and Scopus databases. See Appendix A for full search terms. The two searches returned 901 unique abstracts. Each abstract was reviewed by 2 members of the literature review team; any discrepancies in classifications were discussed until consensus was reached.

- *Inclusion criteria:* Publications containing age and/or vaccination status information on cases of respiratory diphtheria caused by *C. diphtheriae* between the years of 2000-2016
- *Exclusion criteria:* Publications not containing data on age or vaccination status variables, publications not available in English or Spanish in full text, those dealing exclusively with cutaneous diphtheria or diphtheria caused by another toxin-producing *Corynebacterium* species (e.g., *C. ulcerans*), publications discussing primarily cases diagnosed prior to 2000, and those reviewing outbreaks in age-restricted populations which are therefore not applicable to epidemiologic trends in the general population.

Three review articles were identified from the search [1, 12, 16] and used to inform the background and analysis strategy in this report. Twenty publications with data on case age and/or vaccination status were identified[14, 17-35]. Each was reviewed by at least two investigators, and relevant data were compiled in an Excel database.

Figure 2: Flow chart of literature review and sources for data used in analysis



During the review of the full-text articles, an additional 17 published manuscripts were identified through the reference lists[15, 36-51]. A review of the grey literature resulted in 9 additional sources[52-60], and communications with colleagues and partners in the field resulted in access to 11 unpublished reports containing relevant data[61-71]. In addition, diphtheria data from The European Surveillance System – TESSy, were provided by Spain, Latvia, Germany, Italy, Lithuania, the Netherlands, the United Kingdom, Finland, Sweden, France, Austria, and Belgium and released by the European Centre for Disease Prevention and Control[72]. See Figure 2 for the full flow diagram of the literature search and compilation of other sources. Due to the multiple data sources, care was taken that cases reported from the same country in the same year were not duplicates; if unclear, we conservatively excluded the case from the dataset.

The number of cases on the JRF for each country in the same year or set of years was included in the dataset for comparison. Since DTP3 coverage has been shown to be an important factor in the containment or spread of an outbreak, the average of the national WHO-UNICEF estimates of DTP3 coverage[73] for the previous 5 years were taken for each set of reported cases and included in the dataset. Countries with data included in the review were classified by the following categorical variables of interest (see Appendix B for a full list of variables and datasets created for this analysis):

- *Frequency of cases:* Higher case count countries (defined as reporting at least 10 cases in at least 3 years of JRF incidence data between 2000 and 2015) versus countries with sporadic cases
- *Vaccination schedule type:* Classified by age at last scheduled dose as 3 dose primary series in infancy only; Last booster dose at <6 years old; Last booster dose between 6 and 17 years of age, and Adult boosters (at least one dose of diphtheria-containing vaccine given at or after age 18).

The dataset was examined for patterns in both the age and vaccination status of reported cases. This analysis was complicated by three main factors. First, the age distribution analysis was complicated by the diverse ways in which age data were aggregated in sources. Our analysis used cutoffs at 5 years and 15 years for aggregation of age data since these were most frequently mentioned in the historical literature as benchmarks for the age shift in diphtheria incidence over time. In the 5 year analysis classifications were made using available cutoffs in the sources between 3 to 6 years of age; in the 15 year analysis classifications were made using cutoffs from 9 to 20 years of age depending on available data. Second, sources also aggregated vaccination status data differently. Cases with partial vaccination were grouped with fully vaccinated cases in several sources; these were conservatively designated as 'partially vaccinated' in the main dataset for aggregate analysis. Reports of cases with unknown vaccination status or partial vaccination were grouped with unvaccinated cases in other sources. These cases were conservatively designated as 'unvaccinated' in the main dataset for aggregate analysis. Finally, most reports or manuscripts did not have data that linked the age and vaccination status of cases or groups of cases; even if vaccination data and age data were available, it was not stated what percentage of cases in a specific age group were vaccinated, for example.

To analyze trends despite these limitations, 4 datasets were compiled for sensitivity analyses (see Appendix B):

- Dataset "5 Year" included all cases with clear age data of cases around the 5 year cut-off (±1 year), excluding reports without age data.
- Dataset "15 Year" included those with clear case age data around this cutoff (±1 year), excluding reports without age data.

- Dataset “Vaccine”, includes only those cases that were clearly categorized as unvaccinated, partially vaccinated, and completely vaccinated cases, as well as those with unknown vaccination status.
- Dataset “Age and Vaccination Status” included data from sources that reported the vaccination status of cases within each age group.

Incidence data were abstracted from the database of WHO Joint Reporting Form (JRF) results[2] and compared to the cases found in the literature over the same period as a measure of dataset completeness. Since it was being used as a metric for the dataset, the completeness of the JRF data itself was also examined.

Three key countries representing different regions and a range vaccination schedules which offered more complete and in-depth data are presented as case studies. For these countries, DTP3 coverage data from the WHO-UNICEF estimates were compared with incidence data from the JRF and the case datasets. If regional data on vaccination coverage and incidence were available, these were also compiled and factored into the analysis.

Distribution of cases by age and vaccination status were analyzed for all cases and across categories using basic descriptive methods. Sensitivity analyses looked for consistency of trends among cases with enhanced precision of data around each variable. Due to the heterogeneity of data, a valid meta-analysis could not be performed.

Results and Discussion

General epidemiologic trends, 2000-2015

After EPI implementation began in 1977 with diphtheria vaccine as one of the original six EPI antigens, the incidence of diphtheria worldwide dramatically decreased (Figure 1). We looked at reported diphtheria cases worldwide from JRF data as 5 year averages. Reported diphtheria cases declined from almost 10,000 cases per year during 2000-2004 to 5288 per year during 2005-2009. However, since 2009 annual reported cases have levelled off (Figure 2).

The South-East Asia region is the primary driver of global diphtheria incidence, especially since 2005 (Figure 3). Meanwhile, cases reported from the European and African regions have decreased.

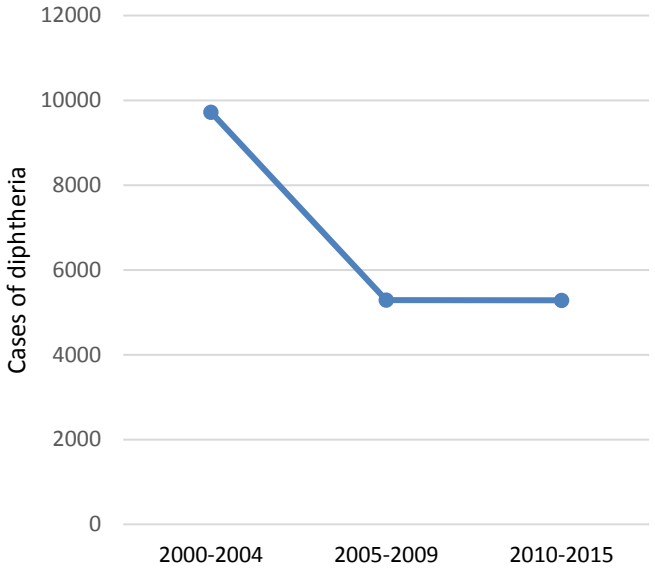


Figure 2: Reported cases of diphtheria per year worldwide by 5 year average

Among countries with the top 10 case counts since 2000, India has the largest number of reported cases, with Indonesia and Nepal being the other main sources of diphtheria cases from the region (Figure 4). The Russian Federation and Ukraine were large contributors from 2000-2004 while the impact of a large outbreak during the 1990s was still attenuating; smaller numbers of cases were reported from other post-Soviet republics. A large number of cases was also reported from Nigeria in 2000-2004 but it does not figure prominently in the other time periods. However, this is likely an artifact of poor surveillance and reporting. Nigeria also has missing diphtheria data on the JRF for 11 years from 2000-2016, despite published cases in the literature for these years[15, 43, 48]. Three other countries had large outbreaks during this time period: Madagascar and Papua New Guinea (with average DTP3 coverage of 72% and 61%,

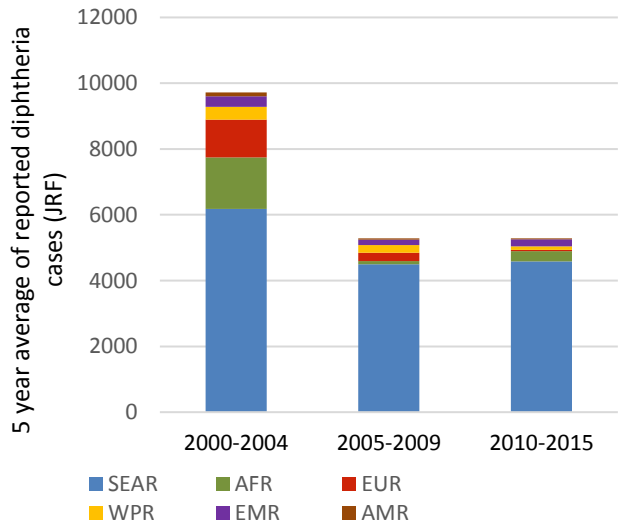


Figure 3: Cases of diphtheria by region by 5 year averages, 2000-2015

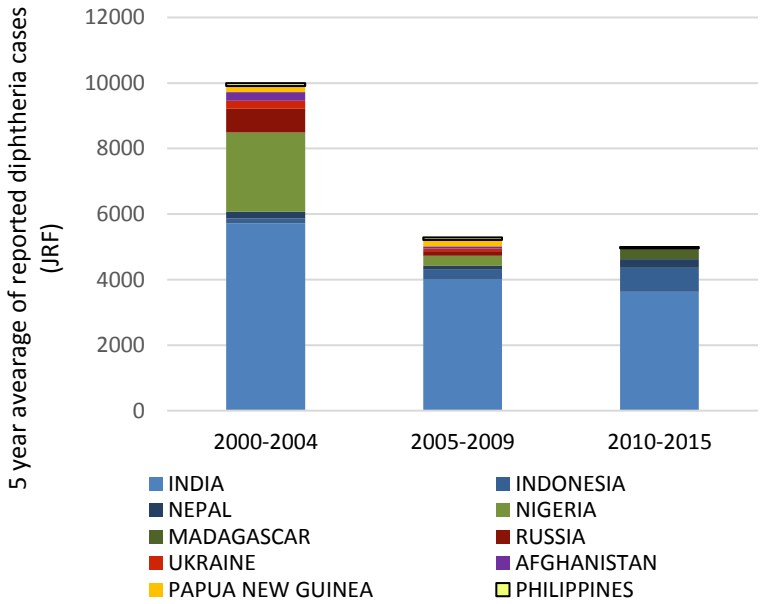


Figure 4: Reported diphtheria cases in the 10 highest case count countries by 5 year average - 2000-2015

respectively, prior to their outbreaks) and Nepal (90% DTP3 coverage). All three of these countries recommend 3 dose primary schedule without booster doses.

National vaccination schedules, 2016

Use of WHO recommended immunization schedules, after the 3 dose primary series, is dependent on country context. When the data from published manuscripts and grey literature were combined with data from online databases[74, 75], it was evident that countries recommend a wide variety of vaccination schedules. 49 countries (25%) administer only the 3 dose primary series, and 40 countries (21%) recommend at least one adult booster dose at or after age 18 (Figure 5).

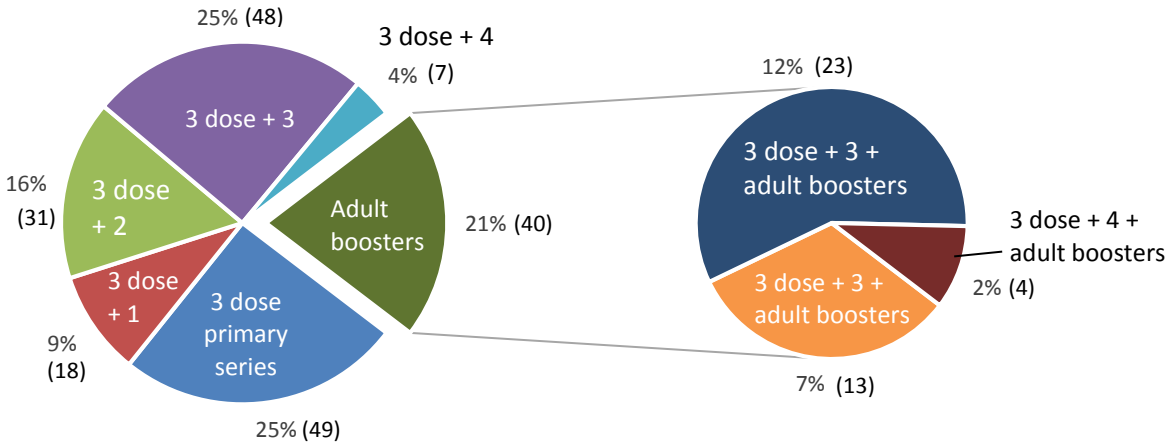


Figure 5: Percentage (number) of countries with each diphtheria vaccination schedule - 2016

The ages at which booster doses are administered are highly variable even among countries recommending the same number of booster doses (Table 1).

Vaccination Schedule	Median age (in years) at last scheduled childhood dose	Range of age at last scheduled childhood dose
3 dose primary series	N/A	N/A
3 dose + 1	5	1-15
3 dose + 2	6	<1-16
3 dose + 3	13	6-17
3 dose + 4	14	7-17
3 dose + 2 + adult boosters	12	5-15
3 dose + 3 + adult boosters	14	10-16
3 dose + 4 + adult boosters	16	14-17

Table 1: Median age at last childhood dose (and range) among countries recommending the same type of vaccination schedule

Although 25% of countries include only the primary schedule in their vaccination program, 6 of the 10 countries (60%) with highest reported numbers of diphtheria cases since 2011 recommend only the 3 dose primary series (Table 2). Of the 9 countries with a clear outbreak from 2005-2015 (defined as at least 2 years of reported case counts <10 followed by a year with >30 cases), 6 countries (67%) follow a 3 dose schedule, 2 follow a 3 +1 schedule, and 1 (Brazil) follows a 3 dose + 2 schedule. A historical record of changes to national schedules of diphtheria-containing vaccines is not available, so data reflect only current schedules as of 2016. Of note, 6 countries recommend 3 or 3 + 1

diphtheria vaccination schedules in which TT boosters are administered without a diphtheria vaccine component in later childhood or adolescence.

Country	Reported diphtheria cases (2011-2015)	Vaccination schedule	Age at last booster dose	Mean DTP3 coverage (2011-2015)
India	18350	3 dose + 2	5	84%
Indonesia	3203	3 dose + 4	8	82%
Madagascar	1633	3 dose	-	72%
Nepal	1440	3 dose	-	91%
Iran	513	3 dose + 2	6	99%
Lao PDR	344	3 dose	-	84%
Pakistan	321	3 dose	-	72%
Sudan	222	3 dose	-	93%
Myanmar	180	3 dose	-	79%
Thailand	157	3 dose + 2	4	99%

Table 2: Vaccination schedules and DTP3 coverage for the 10 countries reporting the most cases of diphtheria in 2011-2015

Availability of data on age and vaccination status of diphtheria cases, 2000-2016

Since only aggregate data are available from the JRF, we had to use other sources to compile the dataset for this review. After an extensive search for data on the age distribution and/or vaccination status of diphtheria cases from 2000-2016, a total of 10,919 cases of diphtheria from 33 countries were identified. By comparison, 106,750 diphtheria cases were reported from 97 countries on the JRF from 2000-2015. To better understand data availability and to contextualize our findings, we looked at data completeness in two ways- by country-year and by case numbers.

Over the period from 2000-2015, each country (with the exception of South Sudan) had the opportunity to submit 16 years of JRF data on diphtheria incidence to the WHO, for a maximum of 3092 potential country-years of data submitted. We assessed the completeness of the dataset created for this review as compared to the JRF incidence data. We also assessed the completeness of JRF diphtheria incidence data itself, since these data were being used as a metric of dataset completeness and represent the most thorough existing database for worldwide incidence. We classified each country-year into one of three categories: zero-reporting (the country included a report of zero diphtheria cases for that year), non-zero (for which a country reported a number of cases greater than zero), and missing (the country did not submit diphtheria incidence data for that year). Nonzero country-years were further separated into non-zero years with data captured in the review and non-zero years without data captured in the review. If at least one case reported from that country and year was included in the review dataset it was counted as a captured country-year, even if the number of cases in the review dataset did not equal the number of cases reported on the JRF. Overall, 63% of country-years were zero-reporting, 19% were non-zero and 18% were missing (Figure 6). Missing JRF diphtheria incidence data was not equally distributed among regions, with highest percentage of missing country-years in the African and Eastern Mediterranean regions. Therefore, even with the most complete data available we do not have a full picture of worldwide incidence.

Of the 600 country-years in which at least one case was reported, 85 (14%) were captured in the review dataset. The largest proportions of non-zero country-years with at least some data captured in the review dataset were in Europe (24%), South-East Asia (18%), and the Americas (12%). It is notable that 8,196 of the 10,919 cases in

the main review dataset (75%) were from India. However, this is proportionate to their overall contribution to case numbers worldwide (52-82% of globally reported cases each year from 2005 to 2015).

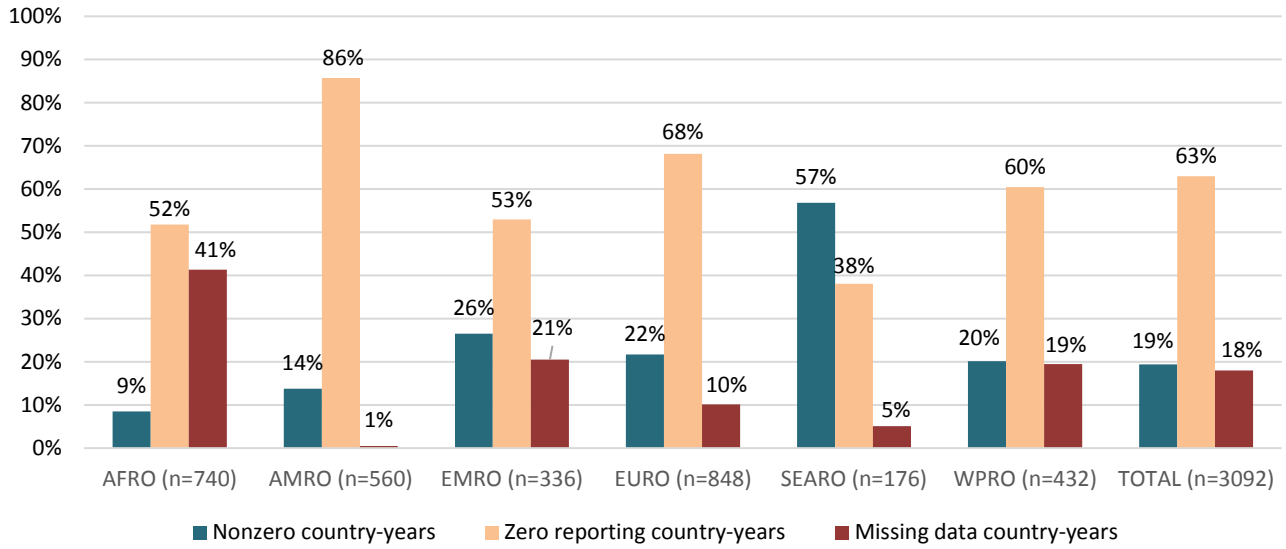


Figure 6: Summary of completeness of JRF diphtheria data by country-year – 2000-2015

There was much variability between regions in the completeness of cases included in the dataset. Data were most complete from the Americas and the Western Pacific region, with the number of cases captured in the review dataset totaling 34% and 20%, respectively, of the total incidence reported in those regions from 2000-2015 (Table 3). Because JRF data are aggregated, there is no way to ascertain how many of the same cases were captured by both datasets versus cases appearing in one dataset but not the other. This comparison also likely overestimates dataset completeness, since the dataset includes cases with 2016 data available, while the JRF data are only available up to 2015.

Region	Cases in review dataset	Cases reported from region, 2000-2015	Proportion of case number potentially captured in review
AFRO	133	10182	1%
AMRO	372	975	38%
EMRO	456	3785	12%
EURO	239	7244	3%
SEARO	8981	80866	11%
WPRO	738	3698	20%
TOTAL	10919	106750	10%

Table 3: Completeness of review dataset, by case numbers - 2000-2015

Finally, the years and countries with cases in the review dataset were cross-referenced with JRF data. In Figure 7, a subset of these data are shown for case counts under 150. Data points falling precisely on the diagonal line indicate a perfect concordance between the case number recorded in the review dataset and the number of diphtheria cases reported by the same country on the JRF during the same year. Data points under the line represent instances in which the country reported more cases on the JRF than were captured by the review; this is not surprising, as many manuscripts were regional rather than national in scope. Points over the line represent instances in which the number of cases found by the review exceeded those reported by the country on the JRF; these are concerning and indicate poor reporting or surveillance. Overall, in 26 instances case data were included in the review from countries and years that had missing data or reported 0 cases for the corresponding year. In 7 additional cases, the number of cases found in the literature for a given country and year exceeded the nonzero number reported on the JRF.

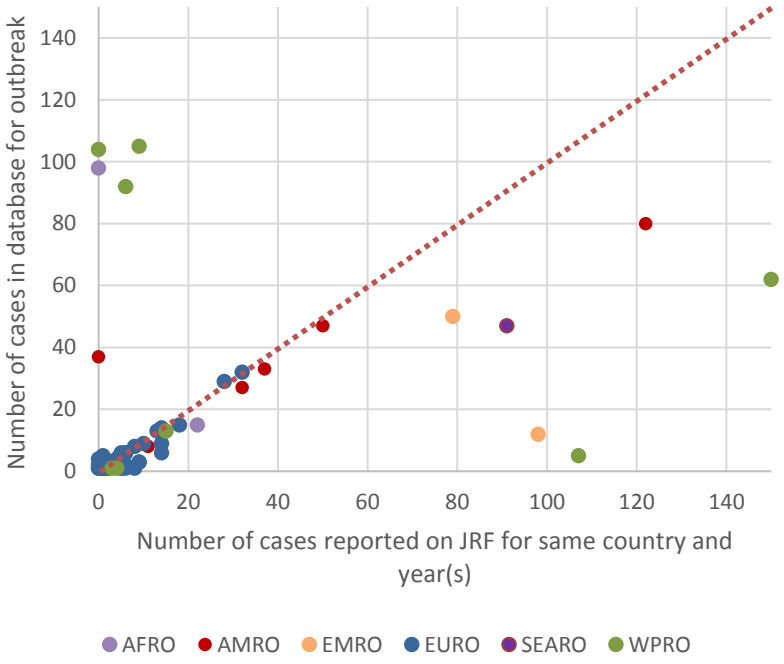


Figure 7: Concordance of cases captured in review and JRF reports
*for readability, depicts a subset of data with case counts under 150

Overall, the most salient points from this portion of the analysis include the poor availability of case-based data for review and the lack of representativeness of these data on a global scale due to overrepresentation of some regions. The review of JRF data demonstrated the lack of completeness, and at times accuracy, of diphtheria data submitted to the WHO, highlighting regional differences in surveillance and reporting quality.

Quality of data on age and vaccination status of diphtheria cases, 2000-2016

Several datasets were created for sensitivity analyses due to the wide variety of categories used by authors to aggregate cases by age and/or vaccination status. The main review dataset includes 10,919 cases; 10,517 (96%) of these have some data on a younger age cut off near age 5 years, 10,625 (97%) have data on an older age cut off near age 15 years, and 6,808 (62%) have at least some vaccination data available. In the "5 Year" dataset, there are 10,385 cases (95%) with data on an age cutoff at 5 (±1) years; in the "15 Year" dataset, there are 5544 cases (51%) with data on an age cutoff at 15 (±1) years. In the "Vaccine" dataset, there are 1360 cases (12%) with data that distinguishes clearly between fully, partially, and unvaccinated cases, as well as those of unknown vaccination status. Finally, in the "Age and Vaccination Status" dataset there are 3719 cases (34%) with some data on both age and vaccination status in endemic or high case count countries. See Appendix B for full details on the datasets used and sample size for each.

Numerous challenges in the quality and comparability of diphtheria case-based data across outbreaks were identified. While the overall case count in the review dataset is large, the sample size substantially decreases in some datasets demanding a higher level of clarity around specific variables.

Age distribution of diphtheria cases

In an overall analysis, 82% of cases worldwide were aged 5 years and older, while 42% were aged 15 years and over. These findings were consistent with those seen on sensitivity analyses of the "5 Year" and "15 Year" datasets.

Age distribution in high case count countries v. sporadic incidence countries

Similar age distributions are seen for the 5 year age cutoff in high case count countries and those with sporadic incidence in analysis of the main dataset, although on sensitivity analysis with the "5 Year" dataset, age distributions in sporadic incidence countries jump to 92% in the over 5 age group (See Appendix B for definitions of these variables and sample size of each group).

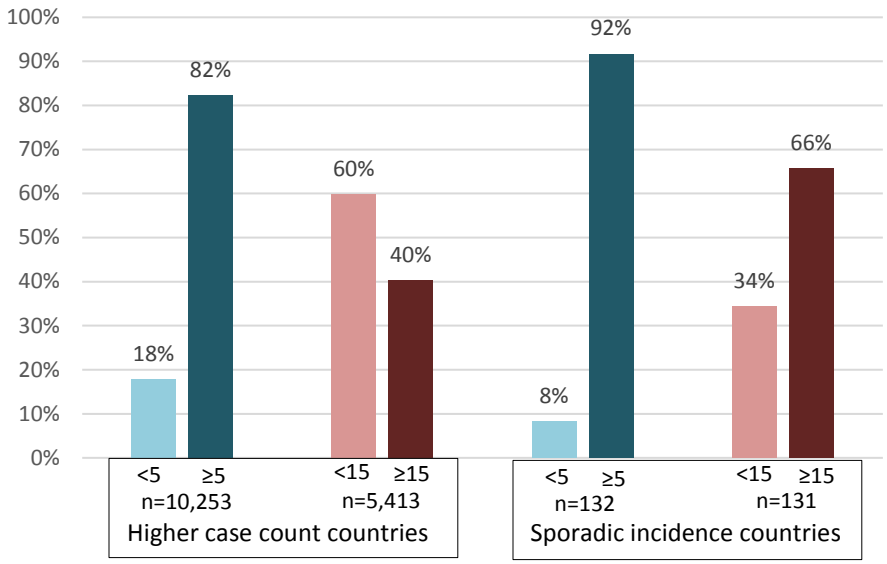


Figure 8: Sensitivity analysis of age distribution in higher case count versus sporadic incidence countries (using "5 Year" and "15 Year" datasets)

Age distributions are different across the 15 year age cutoff. In high case count countries, approximately 60% of cases are in those under 15, while in sporadic incidence countries the proportions were reversed- 66% of cases were in those 15 and older. This was consistent across sensitivity analyses (Figure 8).

In summary, while age distributions in both categories show the effects of vaccination, countries with higher case counts appear more likely to be in the first stage of the shift in age distribution post-vaccine introduction, in which the preponderance of cases occur in school-age children. By contrast, in countries with sporadic incidence the second stage of the shift in age distribution seems more common, with most cases in older adolescents and adults.

Age distribution by national vaccination schedule

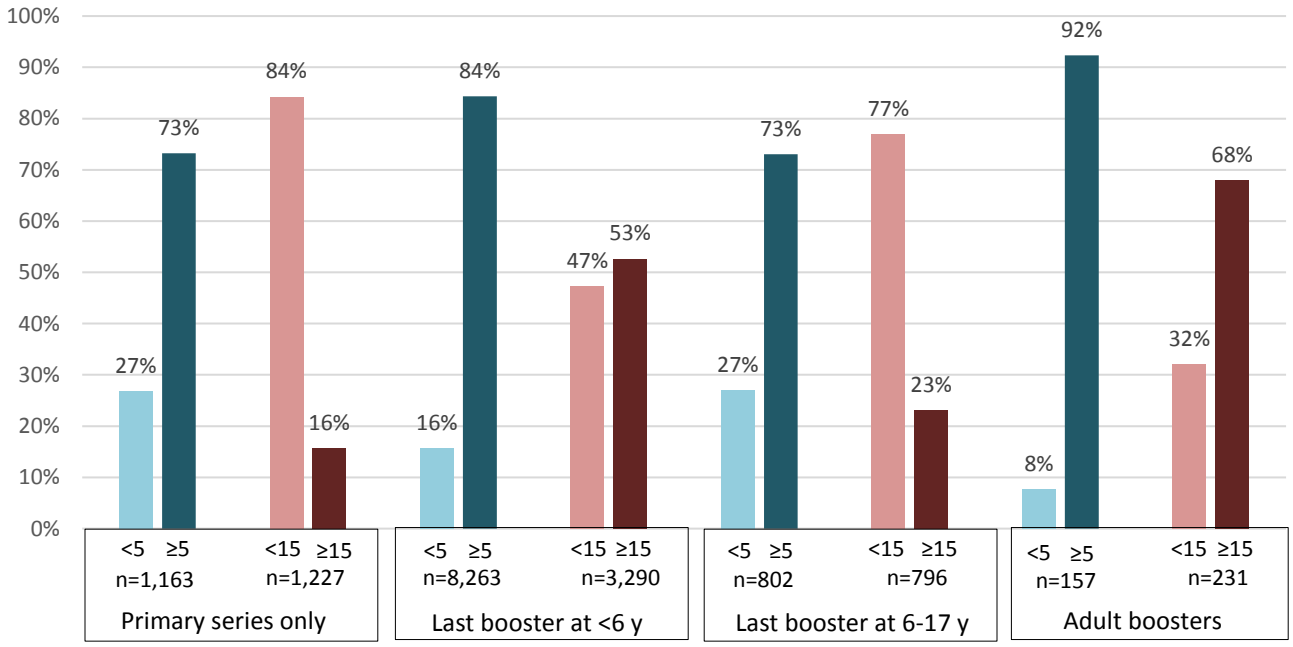


Figure 9: Sensitivity analysis of age distribution by vaccination schedule type (using "5 year" and "15 year" datasets)

Regardless of vaccination schedule, cases were predominantly (>70%) aged 5 years or older across sensitivity analyses. There was more variability of proportions across the 15 year age cutoff. There was

a predominance of cases among persons aged 15 and over only from countries offering adult boosters. In contrast, a larger proportion of cases occurred among persons under 15 years of age in countries offering just the primary series and those offering the last booster between 6-17 years of age. The age distribution of cases in countries offering the last booster before 6 years of age was more evenly split around the 15 year cutoff. However, this group was largely dominated by cases from India (75%) and might better represent the trends from one nation rather than countries using the vaccination schedule as a group. These cases showed a slight predominance (54%) of cases under 15 on analysis of the main dataset, which switched to a predominance of cases 15 and up (53%) on sensitivity analysis with the "15 Year" dataset (Figure 9).

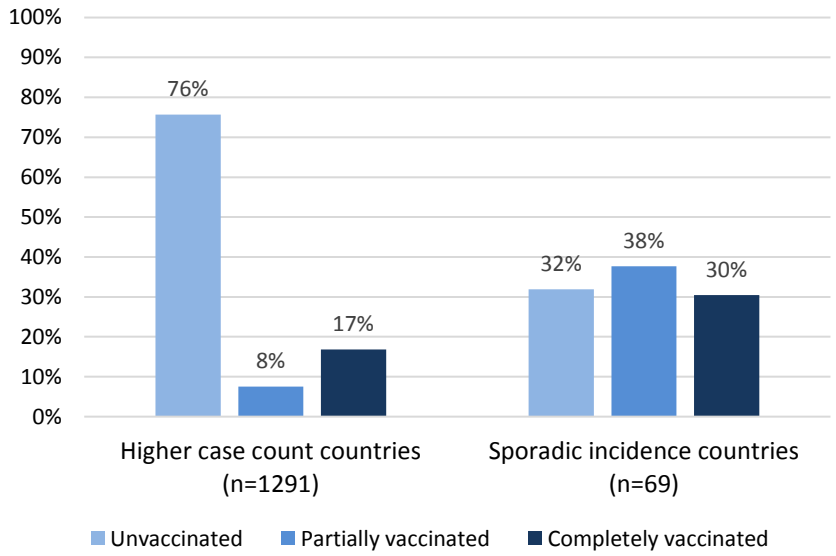
Overall, the first stage of the age shift (predominance of cases in school-age children) seems to apply to countries in the dataset recommending either the primary schedule or giving the last booster to school-age children. The group of countries giving the last dose prior to age 6 years (predominantly India) had a pattern in which case counts were similar above and below age 15 years; this could potentially suggest a transition between the first and second stage of the age shift, in which more cases are occurring in older adolescents and adults but they still do not represent the majority of cases.

Vaccination status of diphtheria cases

On analysis, 65% of cases were unvaccinated, 12% were partially vaccinated, and 23% were fully vaccinated. On sensitivity analysis with the "Vaccine" database, the proportion of unvaccinated cases rose to 73%, while there were lower proportions of cases that received vaccines. It is notable that different sources had different definitions (when stated) for "fully vaccinated" depending on the vaccination schedule of the country or preferences of the investigators. However, in general fully vaccinated can be considered as receiving at least all 3 doses of the primary series.

Vaccination status of cases in high case count countries versus sporadic incidence countries

In countries with high case counts, the majority of cases were unvaccinated in both analyses (65% in the main review dataset and 76% in the sensitivity analysis with the "Vaccine" dataset). In countries with sporadic incidence, about one third of cases each were unvaccinated, partially vaccinated, and completely vaccinated on both the main and sensitivity analysis (Figure 10).



These findings may indicate that the main challenge in countries with high case counts is achieving adequate coverage with the primary series. In countries with sporadic incidence, the predominance of older cases taken together with the relatively even distribution of vaccination status indicate that waning immunity might be a bigger issue.

Figure 10: Sensitivity analysis of vaccination status of cases in higher case count versus sporadic incidence countries (using "Vaccine" dataset)

Vaccination status of cases in countries with different vaccination schedules

In countries with all vaccination schedules, ≥39% of cases were unvaccinated on all analyses. This percentage was 70% or over for countries offering the primary series, 66%-88% for those offering a booster before 6 years of age (depending on dataset used), and 39%-58% for those offering a booster after 6 years of age. Among cases in countries offering adult boosters in all analyses, 48% were unvaccinated, 26% were partially vaccinated and 26% were fully vaccinated (Figure 11).

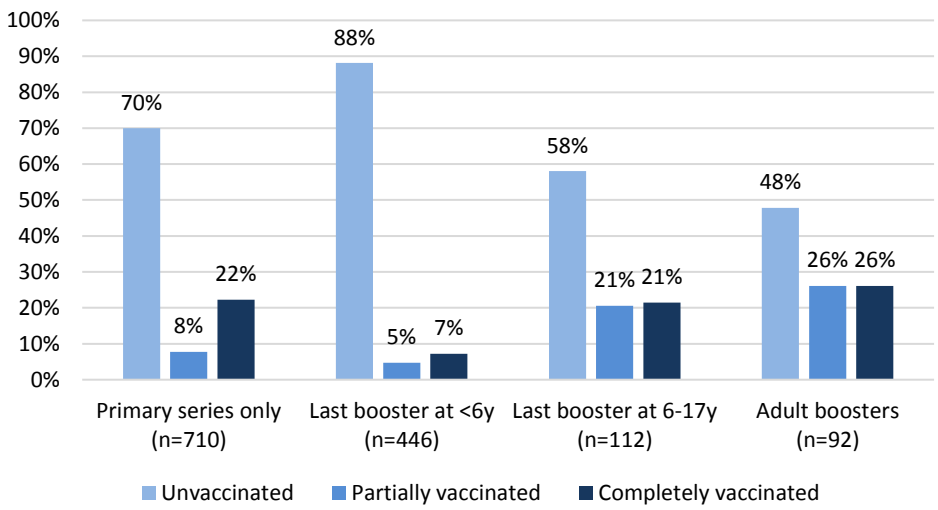


Figure 11: Sensitivity analysis of vaccination status of cases by vaccination schedule (using "Vaccine" dataset)

Overall, countries offering the primary series or boosters only before the age of 6 had a higher proportion of unvaccinated cases as compared to those offering later boosters, including adult boosters. This might indicate that countries using vaccination schedules in which the last diphtheria-containing dose was administered at a younger age have not added doses because they are still striving to achieve optimal coverage with the current schedule.

Relationship between age distribution and vaccination coverage

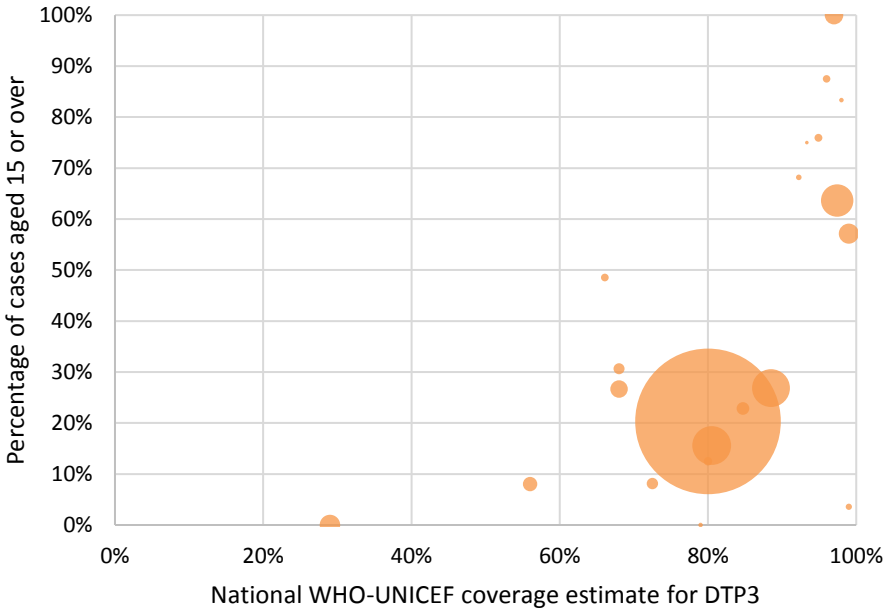


Figure 12: Percentage of diphtheria cases reviewed aged 15+ by national DTP3 coverage

Since vaccination coverage with the primary series has been highlighted as a factor influencing age distribution, this was specifically examined in these data. The total cases for each country were combined, and the average of the 5 years of DTP3 coverage (per WHO-UNICEF estimates) for the year(s) in question was taken. Countries with under 5 cases were excluded from this analysis. The percentage of cases aged 15 or over are plotted on the y axis, and DTP3 coverage on the x axis. Each dot represents a country, and its size is proportionate to the total number of cases reported from the country. In both the main dataset and a sensitivity analysis run on the "15 year" dataset, there is a visible trend toward a higher percentage of cases aged 15 and over in countries with higher DTP3 coverage. In both analyses, countries with DTP3 coverage over 90% tend to have over half of their cases in people aged 15 or over (Figure 12).

Relationship between age distribution and vaccination status of individual cases

In the dataset "Age and vaccination status" there are 3719 cases for which data on both age and vaccination status are available. The age and vaccination status aggregation challenges mentioned previously for the entire dataset also apply to this subset of data. Data are included from Nigeria, Myanmar, the Philippines, India, Haiti, Indonesia, Latvia, and Brazil. The majority of cases in each age group were unvaccinated; the largest proportion of unvaccinated cases were seen in the 15 and up age group. About a third (30%) were completely vaccinated, with most of these cases being in individuals over the age of 5.

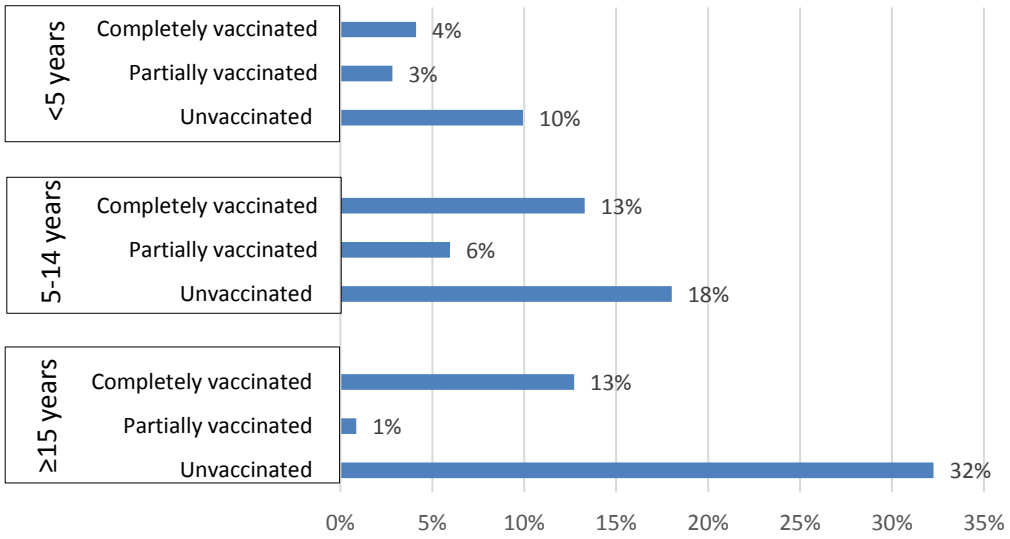


Figure 13: Distribution of age and vaccination status among all cases with vaccination status for each age group (n=3719)

Among countries in this dataset following the primary series only (Nigeria, Myanmar, and the Philippines), 69% of cases were unvaccinated. Among completely vaccinated cases (24%), the largest proportion were among those aged 5-14 years (Figure 13).

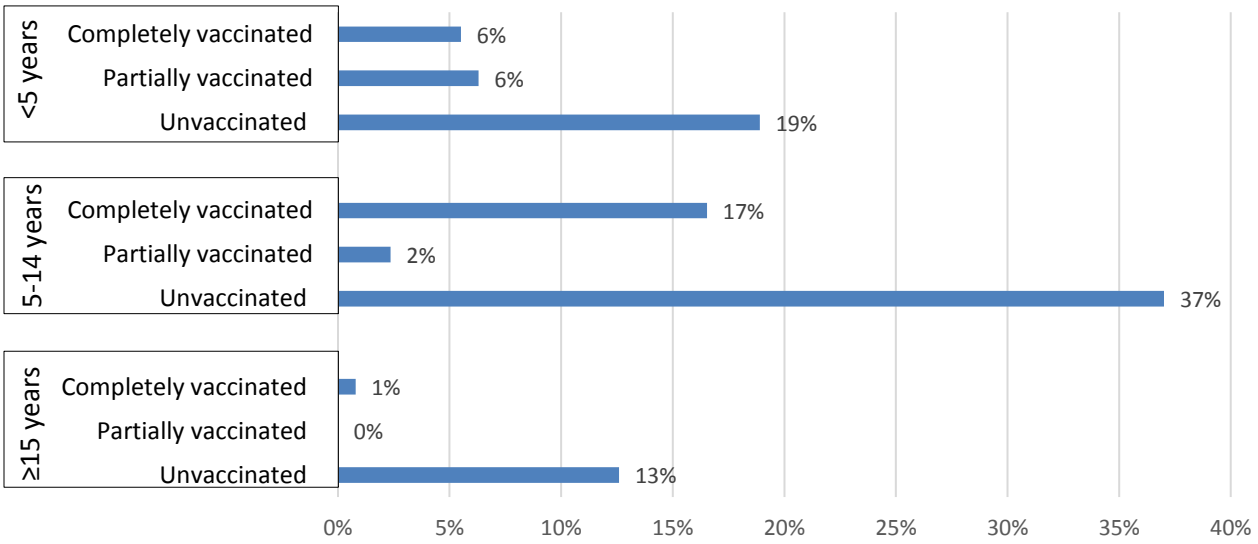


Figure 14: Distribution of age and vaccination status among cases in countries offering the primary series only (n=127)

These data indicate that the lack of vaccination with the primary series tends to be the principal risk factor for infection, yet also support evidence that immunity does wane and booster doses may be relevant. Among countries using the primary vaccination schedule, the fact that the largest proportion of completely vaccinated cases is among school-age children is not surprising, as immunity may wane at this age if the last dose of vaccine is given in the first year of life[8]. It is also an age when children are at high risk of transmission of infectious disease in a school setting. Of note, other vaccination schedule groups were dominated by cases from a single nation, and will be discussed below in the case studies.

Case studies

India

India has followed a 3 + 2 dose schedule since EPI was launched in the country in 1978, with the boosters given at 1.5 and 5 years of age[76]. Despite great progress in both vaccination coverage and reduction of incidence in

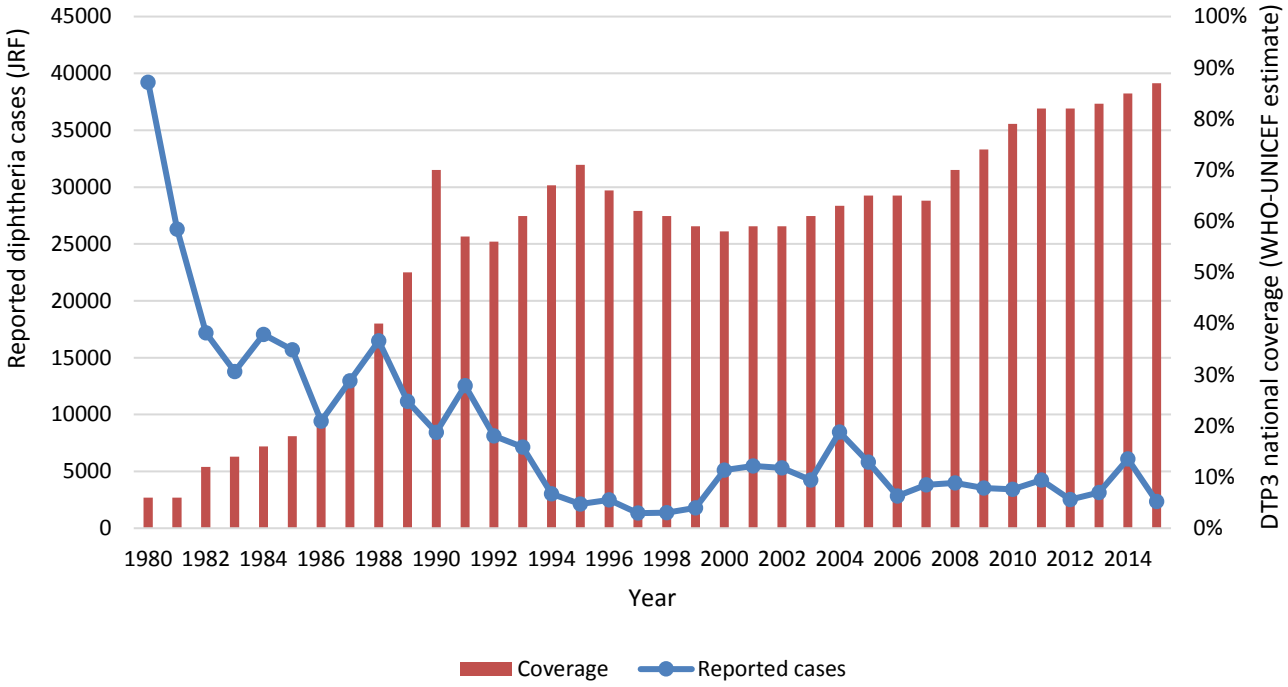


Figure 15: Diphtheria Incidence and DPT3 Coverage Trends - India, 1980-2015

recent years (Figure 14), India consistently reports the greatest number of cases, making this a key country to examine. In recent years, several articles and letters have been published noting the persistence or perceived resurgence of diphtheria in India and querying whether improved surveillance and additional booster doses should be recommended[14, 37, 40, 42, 77]. Fortunately, India has recently implemented a case-based surveillance system, and data from this system were included in this review[71]. To better understand coverage trends in India and subnationally, survey data were also examined from various sources[78-86].

The review dataset captured 8196 cases from India ranging from 1997-2016 from 12 sources, compared to 70,361 cases reported on the JRF from 2000-2015. Among those cases, 67% were unvaccinated but a substantial proportion (26%) were completely vaccinated. While most cases analyzed in India were over 5 years of age, percentages of cases below and above 15 years of age were 51% and 48%, respectively. When a sensitivity analysis was conducted using the "15 Year" dataset, 55% of cases were 15 or older as compared to 45% under 15 years of age. However, the question remains: are these cases susceptible because they were unvaccinated or due to waning immunity?

We approached this question in two ways; first, the incidence and coverage trends were assessed. Out of the population analyzed above, cases 15 years of age would have been born in 1982- 1998, a period when DTP3 coverage was still ramping up (Figure 14). Therefore it is likely many of these cases in adolescents and adults are in unvaccinated individuals. Because diphtheria incidence dropped sharply in the early 1980s, it is also likely that, even if vaccinated, immunity in this population may have waned due to lower exposure to disease in the community compared to previous generations. Secondly, a study was examined which showed linked vaccination and age data in a large population (n=2925 cases) in India from 2008-2012[35]. In this study, 41% of cases were reported to be completely vaccinated. Out of those unvaccinated and partially vaccinated (reported in aggregate), most cases were aged 15 years and older, while cases among completely vaccinated cases were predominantly amongst those 5-14 years old and those aged over 15 (Figure 16). Therefore, the data available show both a cohort effect of lower primary series coverage (DTP3 coverage was between 60%-70% when 15 year olds in this group were infants) and also a high percentage of cases among older vaccinated individuals which could indicate waning immunity.

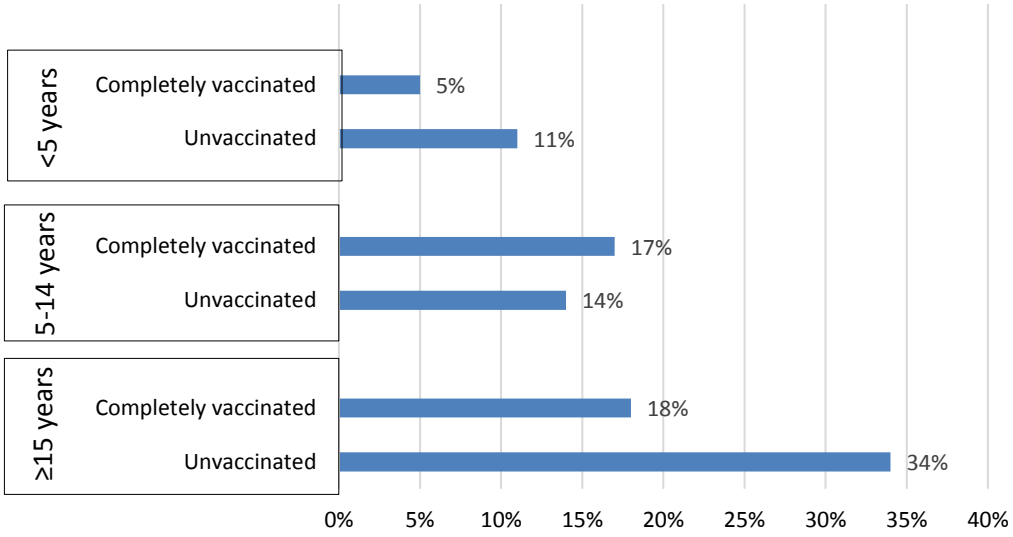


Figure 16: Distribution of age and vaccination status among cases in Andhra Pradesh, India – 2008-2012 (n=2925)

The 2016 surveillance data, which comes from the states of Bihar, Haryana, Kerala, and Uttar Pradesh (UP), shows the importance of examining subnational surveillance data and coverage. The age distribution of cases for these states is very different, with Bihar having the highest proportion of cases under 5, Kerala having the highest proportion of cases over 10, and Haryana and UP showing the highest proportion of cases between 5 and 10 years of age (Table 4). Survey data demonstrate that the coverage for both DTP3 and the fifth dose at 5 years of age is also highly variable among regions (Figure 17).

State	Total cases	Under 5	5-10 years	Over 10
Bihar	71	41%	34%	25%
Haryana	59	27%	53%	20%
Kerala	556	8%	18%	74%
Uttar Pradesh	844	25%	53%	22%
Total	1530	20%	39%	41%

Table 4: Age distribution of cases in states of India with case-based surveillance, 2016

Overall, the large proportion of cases under 5 in Bihar is probably explained by the very recent ramp up in DTP3 coverage along with the still very low coverage with the 5 year booster dose, yet it is surprising that UP shows a different age distribution, since vaccination coverage patterns are similar. In Kerala, the consistently higher coverage with both DTP3 and the 5 year booster explain the predominance of cases in the oldest age group. While the vaccination coverage in Haryana is substantially higher than in the two other states, DTP3 coverage is still approximately 10 absolute percentage points lower compared to Kerala, which could explain the differences in age distribution.

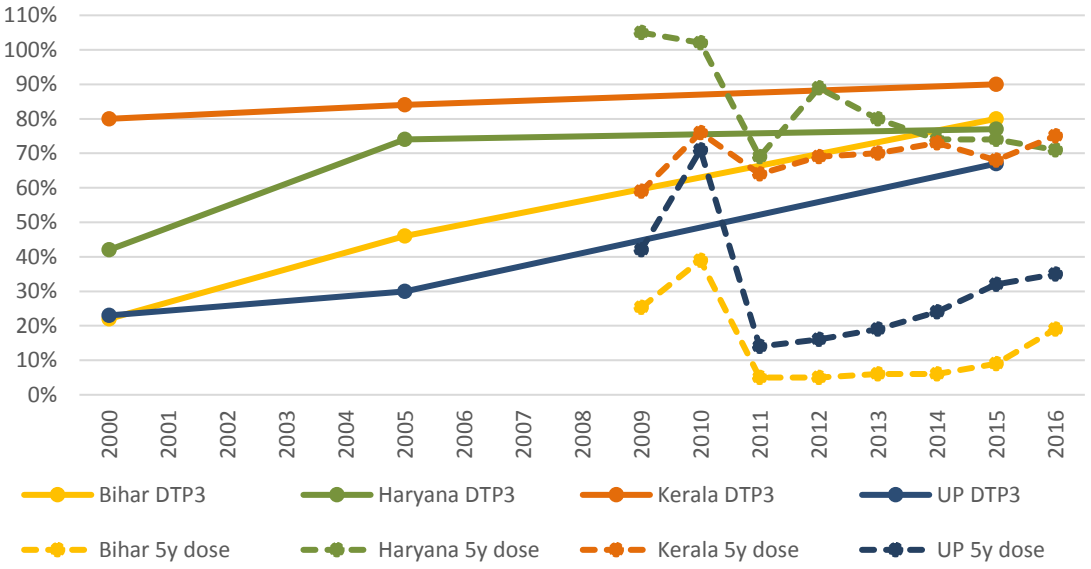


Figure 17: Trends in DTP3 and 5yr booster coverage in States with case-based diphtheria surveillance - India, 2000-2015

Latvia

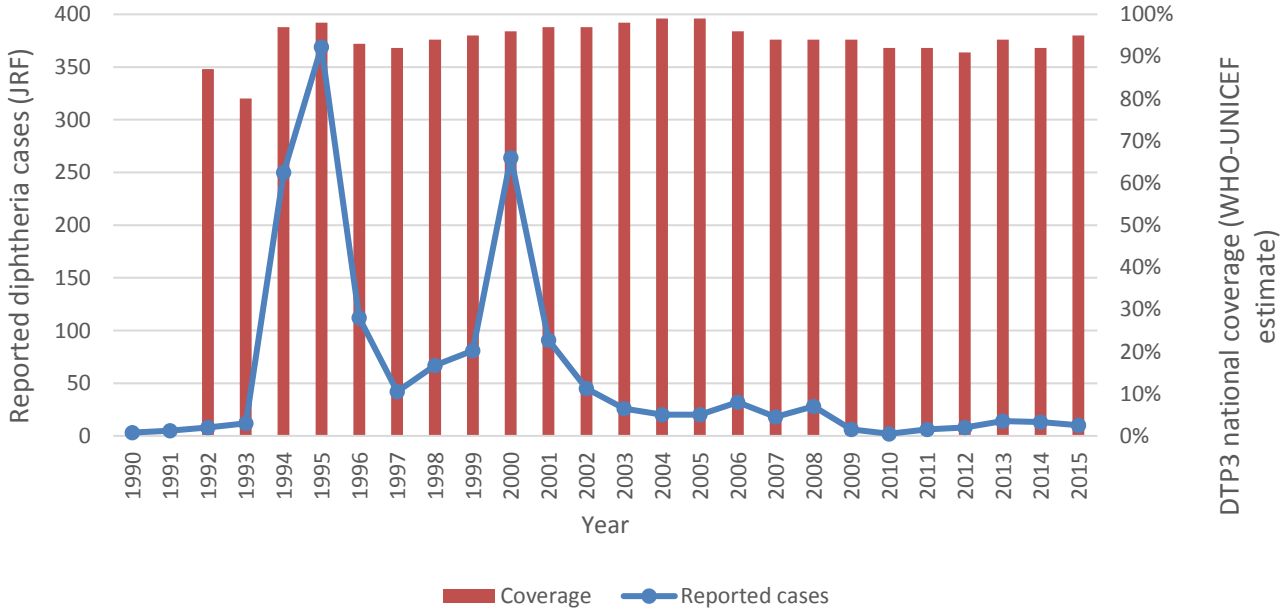


Figure 18: Diphtheria Incidence and DPT3 Coverage Trends - Latvia, 1990-2015

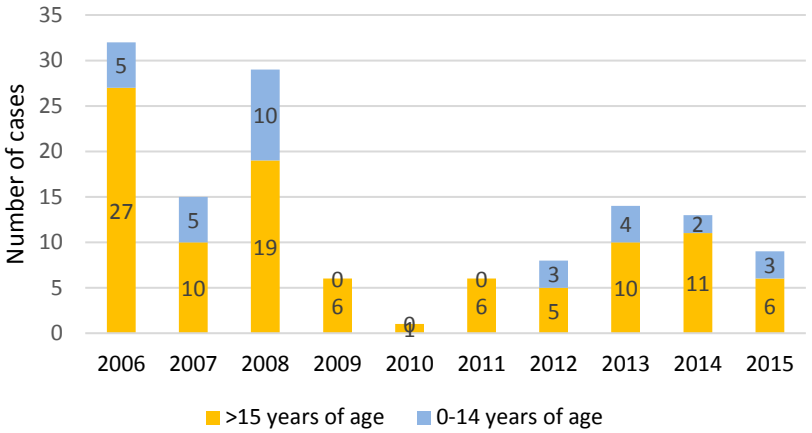


Figure 19: Age distribution of cases in Latvia, 2006-2015 (n=98)

DTP3 coverage has historically been high in Latvia, with a brief dip in the early 1990s followed by the well-documented outbreak in that country and several other post-Soviet republics (Figure 18). Routine adult boosters have been recommended since 1994. From 1994 to 2014, 43% of cases were in individuals 40 years of age or older, who were born near the time of the introduction of DTP vaccine in the former Soviet Union. Many in this group were both missed by vaccination as infants and not exposed to the disease in their environment due to rapidly declining incidence[87]. This is consistent with data available from 2006-2015, which shows that while diphtheria incidence has declined over this period, even in recent years the majority of cases are in those 15 years of age or older (Figure 19). When the age distribution of these cases is further broken down, many of these cases are in the same cohort shown to be most at risk in the 1994-2014 study, now aged 60 and above (Figure 20). Both age and vaccination status data are available for a subset of cases from Latvia in 2011-2015 (Figure 21). This shows quite a different distribution from other case studies, with most cases in unvaccinated adults; this is also consistent with the 1994-2014 data.

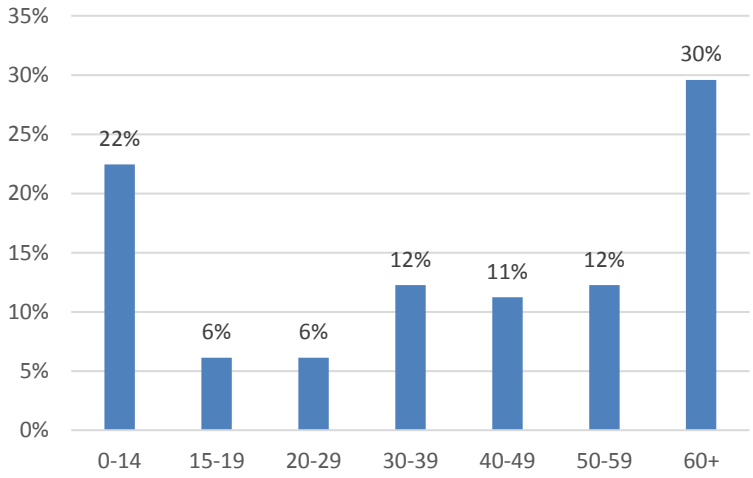


Figure 20: Age distribution of cases in Latvia by year, 2006-2015 (n=98)

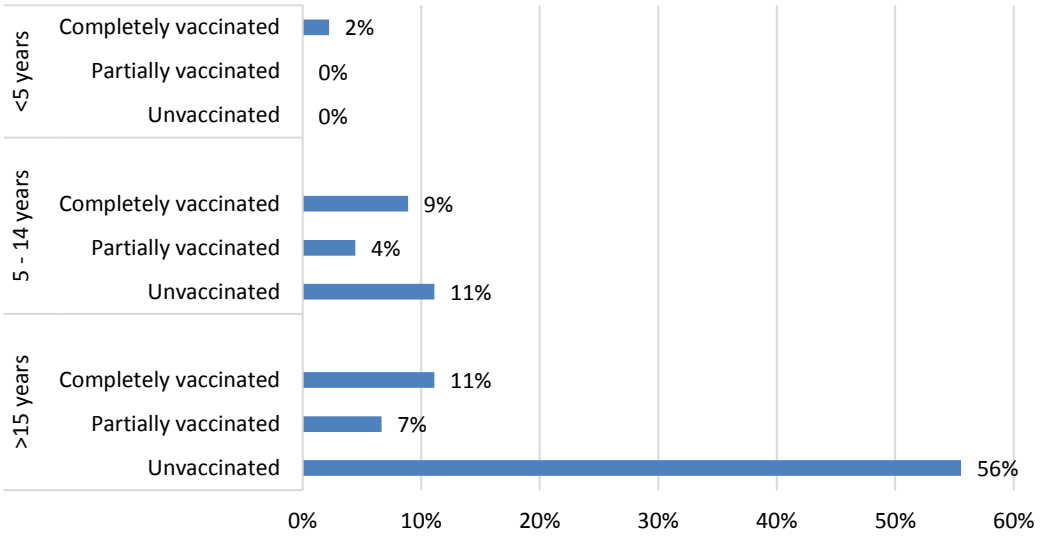


Figure 21: Vaccination status and age of cases in Latvia, 2011-2015 (n=45)

Philippines

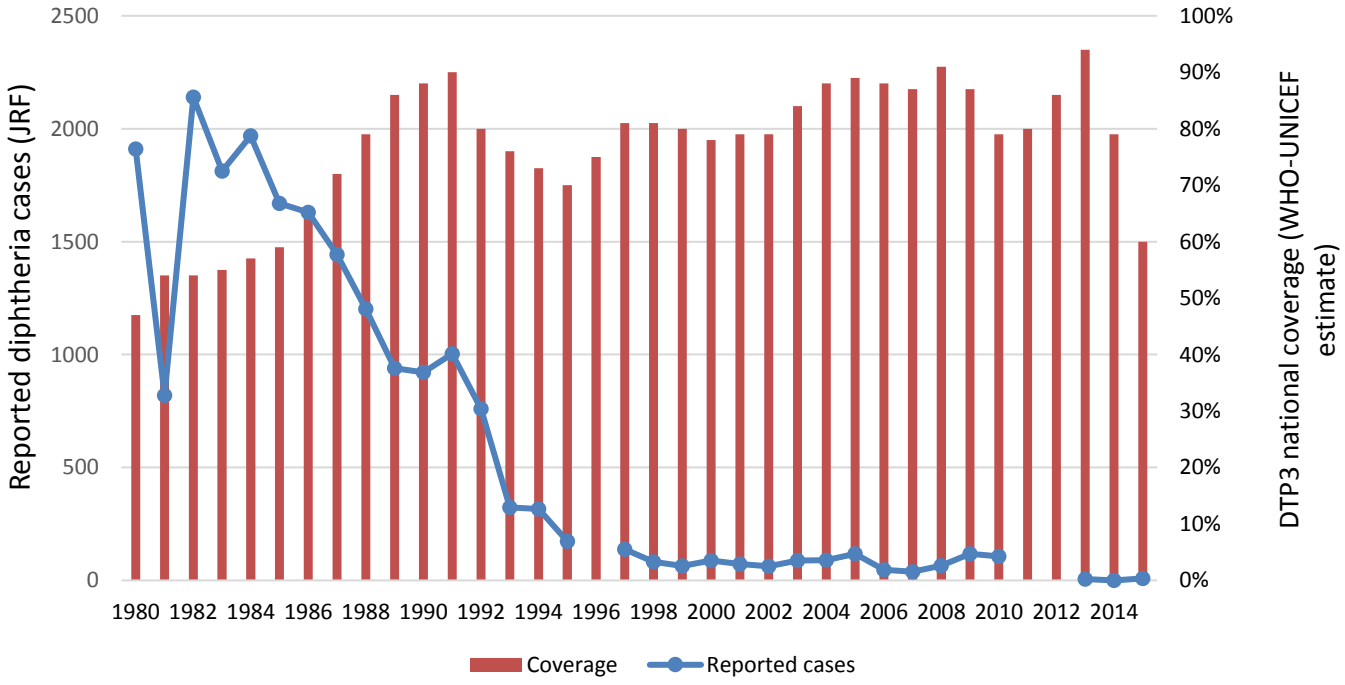


Figure 22: Diphtheria Incidence and DPT3 Coverage Trends - Philippines, 1980-2015

The 3 dose primary series is offered in the Philippines with no boosters, and DTP3 coverage has been over 80% since the late 1990s (Figure 21). National data reviewed spanned 2011-2016 (n=280 cases), and showed that 47% of cases were among completely vaccinated individuals. When linked age and vaccination data from 2016 were reviewed (n=37), 16% were among completely vaccinated individuals 5-14 years of age (Figure 22).

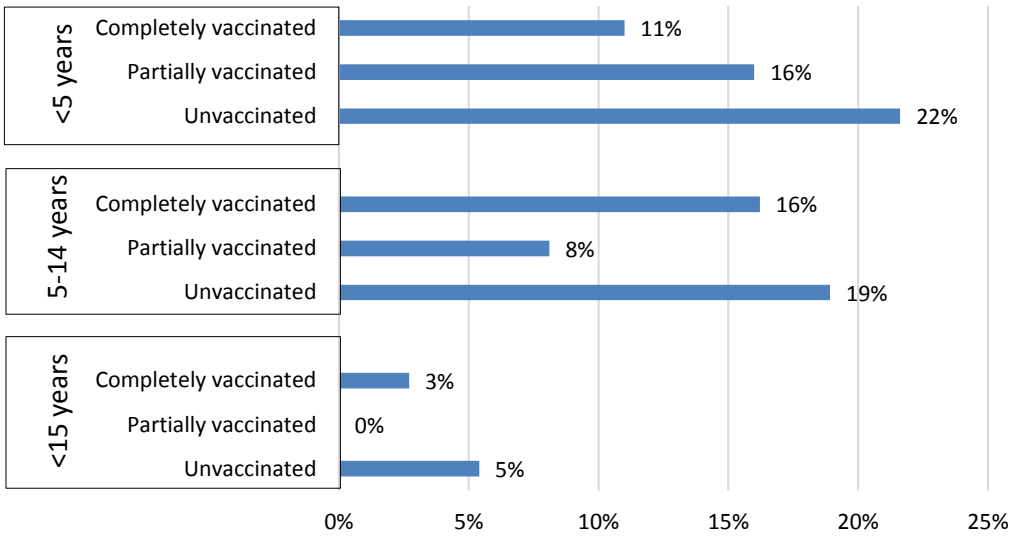


Figure 21: Vaccination status and age of cases in the Philippines, 2016 (n=37)

This shows the possibility of cases due to waning immunity; immunity is expected to wane during the school-age years if the last dose was given during the first year of life[8]. Only 3% of cases overall were among those aged 15 and over with a completed primary series. This could indicate past boosters from natural exposure, since incidence dropped sharply in the Philippines in the early 1990s. However, these data are limited by a small sample size and must be interpreted with caution.

Main Findings:

1. Progress in decreasing diphtheria incidence worldwide has stalled over the past 10 years.
2. The South-East Asia Region, particularly India, is the major driver of global diphtheria incidence trends.
3. A wide variety of diphtheria vaccination schedules are used globally.
4. There are frequent discrepancies between diphtheria incidence reported to WHO compared to data published in the medical literature, making comparisons of published data with JRF data challenging.
5. Diphtheria incidence data are underreported by countries on the JRF, particularly in the African and Eastern Mediterranean regions.
6. Diphtheria data with information on age and/or vaccination status are incomplete and not equally representative across all regions.
7. Information on age and/or vaccination status of diphtheria cases is inconsistently reported and therefore difficult to aggregate and compare.
8. Most diphtheria cases occur in unvaccinated individuals, particularly in countries with higher case counts.
9. Age distributions of cases in counties with sporadic cases and countries with adult boosters reflect age shifts to the adolescent and adult populations. Countries with higher case counts or using different vaccination schedules have either not yet made this shift or may be in the process of doing so.
10. Countries with higher vaccination coverage had an increased percentage of cases over age 15 years compared to countries with lower vaccination coverage.

11. In countries in the dataset using the primary schedule only, the highest proportion of cases are in children 5-14 years of age among both unvaccinated and completely vaccinated individuals. This could be due to low vaccination rates and concentrated populations of children in a school setting, combined with potentially waning immunity after the primary series.

12. In analysis of vaccination status data across age groups, along with case studies of individual countries, there appears to be some evidence for cases in older vaccinated individuals due to waning immunity, especially in countries with higher current vaccination coverage.

13. Subnational coverage rates and age distributions, when available, can be important factors in explaining national incidence trends.

Disclaimers

The findings and conclusions in this report are those of the author and do not necessarily represent the official position of the US Centers for Disease Control and Prevention.

The views and opinions of the authors expressed herein do not necessarily state or reflect those of ECDC. The accuracy of the authors' statistical analysis and the findings they report are not the responsibility of ECDC. ECDC is not responsible for conclusions or opinions drawn from the data provided. ECDC is not responsible for the correctness of the data and for data management, data merging and data collation after provision of the data. ECDC shall not be held liable for improper or incorrect use of the data.

Acknowledgements

Dr. Colleen Scott, Dr. Nita Patel, and Dr. Tejpratrap Tiwari reviewed abstracts and articles as part of the CDC Literature review workgroup; their contributions were critical to compiling the case data analyzed and interpreted in this report.

Dr. Eric Mast, Dr. Peter Bloland, Dr. Adam MacNeil, Dr. Stephen Hadler, Dr. Nita Patel, Dr. Colleen Scott, Dr. Tejpratrap Tiwari, Dr. Kathleen Dooling, and Dr. Lina Nerlander of the US Centers for Disease Prevention and Control assisted by providing feedback and guidance on early drafts or sections of this report. Dr. Steve Cochi provided advice and guidance at the early stages of this analysis.

Dr. Thomas Cherian and Dr. Melanie Marti of WHO provided feedback and guidance on an early draft of this report.

Dr. Howard Gary provided statistical support and methodological guidance for the analysis.

The author would like to recognize international organizations and colleagues for sharing data from outbreak reports and surveillance systems for use in this analysis, particularly colleagues at the European CDC and Dr. Sudhir Joshi and Dr. Lucky Sangal of WHO-India.

References

1. Zakikhany K, Efstratiou A. Diphtheria in Europe: current problems and new challenges. *Future Microbiology* 2012; **7**(5)**:** 595-607.

2. Diphtheria Reported Cases. In: Organization WH, (ed), 1980-2015.

3. Markina SS, Maksimova NM, Vitek CR, Bogatyreva EY, Monisov AA. Diphtheria in the Russian Federation in the 1990s. *Journal of Infectious Diseases* 2000; **181**(SUPPL. 1)**:** S27-S34.

4. Galazka A. The Changing Epidemiology of Diphtheria in the Vaccine Era. *Journal of Infectious Diseases* 2000; **181**(Suppl 1)**:** 52-59.

5. Galazka A. Implications of the diphtheria epidemic in the Former Soviet Union for immunization programs. *Journal of Infectious Diseases* 2000; **181 Suppl 1:** S244-248.

6. Galazka A, Robertson SE. Immunization against diphtheria with special emphasis on immunization of adults. *Vaccine* 1996; **14**(9)**:** 845-857.

7. Golaz A, Hardy IR, Strebel P, Bisgard KM, Vitek C, Popovic T *et al.* Epidemic diphtheria in the newly independent states of the former Soviet Union: Implications for diphtheria control in the United States. *Journal of Infectious Diseases* 2000; **181**(SUPPL. 1)**:** S237-S243.

8. Tiwari T, Wharton M. Diphtheria Toxoid. In: Plotkin SA, Orenstein WA, Offit PA (eds). *Vaccines*, 6th edn. Elsevier Saunders: Edinburgh, 2013, pp 153-166.

9. Golaz A, Vitek C, Popovic T, Wharton M. Epidemiology of diphtheria in the 1990s. *Clinical Microbiology Newsletter* 2001; **23**(5)**:** 33-37.

10. Scheifele DW, Ochnio JJ. *Diphtheria Update*. World Health Organization: Geneva, 2009.

11. Organization WH. WHO–recommended standards for surveillance of selected vaccine-preventable diseases. In. Geneva, 2014. pp 10-12.

12. Wagner KS, White JM, Lucenko I, Mercer D, Crowcroft NS, Neal S *et al.* Diphtheria in the postepidemic period, Europe, 2000-2009. *Emerging Infectious Diseases* 2012; **18**(2)**:** 217-225.

13. Sutter RW, Stikas RA, Hadler SC, Fedson DS, Katz SL. Tetanus Immunization: Concerns about the Elderly and about Diphtheria Reemergence. *Journal of General Internal Medicine* 1994; **9:** 117-118.

14. Dravid MN, Joshi SA. Resurgence of diphtheria in Malegaon & Dhule regions of north Maharashtra. *Indian Journal of Medical Research* 2008; **127**(6)**:** 616-617.

15. Sadoh AE, Oladokun RE. Re-emergence of diphtheria and pertussis: Implications for Nigeria. *Vaccine* 2012; **30**(50)**:** 7221-7228. doi: http://dx.doi.org/10.1016/j.vaccine.2012.10.014

16. Mattos-Guaraldi AL, Moreira LO, Damasco PV, Hirata Junior R. Diphtheria remains a threat to health in the developing world--an overview. *Memorias do Instituto Oswaldo Cruz* 2003; **98**(8)**:** 987-993.

17. Landazabal Garcia N, Burgos Rodriguez MM, Pastor D. Diphtheria outbreak in Cali, Colombia, August-October 2000. *Epidemiological bulletin* 2001; **22**(3)**:** 13-15.

18. Quarterly communicable disease review January to March 2002. *Journal of Public Health Medicine* 2002; **24**(3)**:** 232-238.

19. Disease watch. *Expert Review of Anti-Infective Therapy* 2003; **1**(3)**:** 355.

20. Anima H, Malay M, Santanu H, Rajashree R, Sita C, Baran SA. A study on determinants of occurrence of complications and fatality among diphtheria cases admitted to ID & BG Hospital of Kolkata. *J Commun Dis* 2008; **40**(1)**:** 53-58. e-pub ahead of print 2009/01/09;

21. Bonmarin I, Guiso N, Le Fleche-Mateos A, Patey O, Grimont Patrick AD, Levy-Bruhl D. Diphtheria: A zoonotic disease in France? *Vaccine* 2009; **27**(31)**:** 4196-4200.

22. Nath B, Mahanta TG. Investigation of an outbreak of diphtheria in borborooah block of dibrugarh district, assam. *Indian Journal of Community Medicine* 2010; **35**(3)**:** 436-438.

23. Perkins S, Cordery R, Nixon G, Abrahams A, Andrews J, White J *et al.* Investigations and control measures following a non-travel-associated case of toxigenic Cornyebacterium diphtheriae, London, United Kingdom, December 2009-January 2010. *Euro Surveillance: Bulletin Europeen sur les Maladies Transmissibles = European Communicable Disease Bulletin* 2010; **15**(16)**:** 22.

24. Saikia L, Nath R, Saikia NJ, Choudhury G, Sarkar M. A diphtheria outbreak in Assam, India. *The Southeast Asian journal of tropical medicine and public health* 2010; **41**(3)**:** 647-652.

25. Chumachenko T, Podavalenko A, Glushkevich T. Spread of Corynebacterium diphtheriae in Ukraine during post-epidemic period. *Clinical Microbiology and Infection* 2011; **17:** S285.

26. Diphtheria Outbreak in an Urban City in Central Philippines, 2010. *EIS Conference International Night*; Atlanta, GA, 2011.

27. Niti T, Jignesh C, Himanshu N, Chintul S, Krunal M, Jaydeep D. Investigation of an outbreak of diphtheria in Dabela Village of Amirgagh Taluka and CHC, Banaskantha, Gujarat. *National Journal of Community Medicine* 2011; **2**(2)**:** 196-200.

28. Rasmussen I, Wallace S, Mengshoel AT, Hoiby EA, Brandtzaeg P. Diphtheria outbreak in Norway: Lessons learned. *Scandinavian Journal of Infectious Diseases* 2011; **43**(11-12)**:** 986-989.

29. Besa NC, Coldiron ME, Bakri A, Raji A, Nsuami MJ, Rousseau C *et al.* Diphtheria outbreak with high mortality in northeastern Nigeria. *Epidemiology and Infection* 2013; **142**(4)**:** 797-802.

30. Phalkey RK, Bhosale RV, Joshi AP, Wakchoure SS, Tambe MP, Awate P *et al.* Preventing the preventable through effective surveillance: the case of diphtheria in a rural district of Maharashtra, India. *BMC public health* 2013; **13:** 317.

31. Wanlapakorn N, Yoocharoen P, Tharmaphornpilas P, Theamboonlers A, Poovorawan Y. Diphtheria outbreak in Thailand, 2012; seroprevalence of diphtheria antibodies among Thai adults and its implications for immunization programs. *The Southeast Asian journal of tropical medicine and public health* 2014; **45**(5)**:** 1132-1141.

32. Rashid ZZ, Mohamed NA, Fong TS. A case of fatal diphtheria in a paediatric patient. *Internet Journal of Microbiology* 2015; **14**(1)**:** 1-5.

33. Santos LS, Sant'Anna LO, Ramos JN, Ladeira EM, Stavracakis-Peixoto R, Borges LLG *et al.* Diphtheria outbreak in Maranhão, Brazil: Microbiological, clinical and epidemiological aspects. *Epidemiology and Infection* 2015; **143**(4)**:** 791-798. doi: 10.1017/S0950268814001241

34. Doanh PV, Pham TD, Vu NL, Chu VT, Do THH, Nguyen TTH *et al.* An outbreak of diphtheria in K'Bang District, Gia Lai, Vietnam, October 2013 - July 2014. *International Journal of Infectious Diseases* 2016; **45:** 172.

35. Meera M, Rajarao M. Diphtheria in Andhra Pradesh-a clinical-epidemiological study. *International Journal of Infectious Diseases* 2014; **19:** 74-78.

36. Lumio J SP, Olander RM, Saxen H, Salo E. Fatal case of diphtheria in an unvaccinated infant in Finland. *Pediatric Infectious Disease Journal* 2003; **22**(9)**:** 844-846.

37. Nandi RD, Mriganka; Browning, Simon; Purkayastha, Prabhati; Bhattacharjee, A K. Diphtheria: the patch remains. *The Journal of Laryngology and Otology* 2003; **117**(10)**:** 807.

38. Krumina A, Logina I, Donaghy M, Rozentale B, Kravale I, Griskevica A *et al.* Diphtheria with polyneuropathy in a closed community despite receiving recent booster vaccination. *J Neurol Neurosurg Psychiatry* 2005; **76**(11)**:** 1555-1557. doi: 10.1136/jnnp.2004.056523

39. Prasad KC KV, Shenoy S, Prasad SC. Upper Respiratory Tract and Cutaneous Diphtheria. *Indian Journal of Otolaryngology and Head and Neck Surgery* 2005; **57**(3)**:** 250-252.

40. Sharma NCB, J N; Ranjan, Rajesh; Kumar, Rajnish. Bacteriological and epidemiological characteristics of diphtheria cases in and around Delhi- a retrospective study. *Indian Journal of Medical Research* 2007; **126**(6)**:** 545.

41. Communicable disease and health protection quarterly review: July to September 2008. *J Public Health (Oxf)* 2008; **30**(4)**:** 510-511. doi: 10.1093/pubmed/fdn090

42. Bitragunta S, Murhekar MV, Hutin YJ, Penumur PP, Gupte MD. Persistence of diphtheria, Hyderabad, India, 2003-2006. *Emerg Infect Dis* 2008; **14**(7)**:** 1144-1146. doi: 10.3201/eid1407.071167

43. Fajolu IB TE, Egre-Okwaji MTC. Sporadic Emergence of Probable Cases of Diphtheria. *Nigerian Journal of Paediatrics* 2009; **36:** 87-90.

44. Fredlund H NT, Lepp T, Morfeldt E, Henriques Normark B. A case of diphtheria in Sweden, October 2011 *Eurosurveillance* 2011; **16**(50).

45. Mattos-Guaraldi AL, Damasco PV, Gomes DL, Melendez MG, Santos LS, Marinelli RS *et al.* Concurrent diphtheria and infectious mononucleosis: difficulties for management, investigation and control of diphtheria in developing countries. *J Med Microbiol* 2011; **60**(Pt 11)**:** 1685-1688. doi: 10.1099/jmm.0.027870-0

46. Rousseau C BE, Broche B, Badell E, Guiso N, Laharie I, Patey O, Lévy-Bruhl D. Diphtheria in the south of France, March 2011. *Euro Surveill* 2011; **16**(19).

47. Lindhusen-Lindhé E DL, Berglund M. Imported laryngeal and cutaneous diphtheria in tourists returning from western Africa to Sweden, March 2012. *Euro Surveillance* 2012; **17**(23).

48. Paul NI UR. Diphtheria in a 13 year old adolescent girl: Management challenges. *Nigerian Journal of Paediatrics* 2014; **41**(3)**:** 247-250. doi: 10.4314/njp.v41i3,19

49. Garib Z, Danovaro-Holliday MC, Tavarez Y, Leal I, Pedreira C. Diphtheria in the Dominican Republic: reduction of cases following a large outbreak. *Revista Panamericana de Salud Pública* 2015; **38:** 292-299.

50. Sane J ST, Widerström* M, Kauma H, Kaukoniemi U, Tarkka E, Puumalainen T, Kuusi M, Salminen M, Lyytikäinen O. Respiratory diphtheria in an asylum seeker from Afghanistan arriving to Finland via Sweden, December 2015. *Euro Surveill* 2016; **21**(2). doi: 10.2807/1560-7917

51. Sein C, Tiwari T, Macneil A, Wannemuehler K, Soulaphy C, Souliphone P *et al.* Diphtheria outbreak in Lao People's Democratic Republic, 2012-2013. *Vaccine* 2016; **34**(36)**:** 4321-4326. doi: 10.1016/j.vaccine.2016.06.074

52. PAHO. Diphtheria Outbreak in Paraguay. *PAHO Immunization Newsletter* 2002; **24**(3)**:** 6.

53. PAHO. Diphtheria Outbreak in Paraguay – An Update. *PAHO Immunization Newsletter* 2002; **24**(5)**:** 7.

54. Lurie P SH, Tran P, Teacher C. Fatal Respiratory Diphtheria in a U.S. Traveler to Haiti. *MMWR* 2004; **52**(53)**:** 1285.

55. PAHO. Diphtheria Outbreak in the Dominican Republic. *PAHO Immunization Newsletter* 2004; **26**(3)**:** 1.

56. England PH. *Death in a child infected with toxigenic Corynebacterium diphtheriae in London*. Public Health England, 2008.

57. PAHO. Diphtheria Outbreak in Haiti, 2009. *PAHO Immunization Newsletter* 2009; **31**(6)**:** 1.

58. Group NARW. Australia's notifiable disease status, 2011: Annual report of the National Notifiable Diseases Surveillance System. *Communicable diseases intelligence* 2013; **37**(4)**:** E313-E393.

59. Control ECfDPa. *A case of diphtheria in Spain; Rapid Risk Assessment*. ECDC: Stockholm, 2015.

60. ECDC. A fatal case of diphtheria in Belgium. In: CDC E, (ed) *Rapid Risk Assessment*: ECDC, 2016. pp 1-10.

61. Flambées de diphtérie en Haiti-2004 et 2009. In: Haiti MSPP; PanAmerican Health Organization, 2010.

62. Tiwari T, Estivariz C, Lam E. Report on the Centers for Disease Control and Prevention mission to assist Indinesia's field epidemiology training program students to investigate and identify risk factors for the diphtheria outbreak in East Java during 2012. In, 2013.

63. Kaiser R. Diphtheria outbreak in KwaZulu-Natal, South Africa, March through June 2015. In: World Health Organization, 2015.

64. Informe de brote de Difteria en Venezuela. In: Panamerican Health Organization, 2016.

65. Report on Diphtheria Outbreak in Haiti. In: US Centers for Disease Control and Prevention, 2016.

66. Situation of Diphtheria in Punjab as on 12-11-2016. In: WHO Punjab, 2016.

67. Crucena JJD. Diphtheria in the Philippines. In: Republic of the Philippines, 2016.

68. Division EBotPHS. In: Republic of the Philippines, 2016.

69. Nguyen TD, Tran NVN, Vien QM, Do H, Nolen L. A diphtheria outbreak in a remote mountainous area of Quang Nam province, Viet Nam, 2015. In: World Health Organization, Vietnam; Pasteur Institute Nha Trong; US Centers for Disease Control and Prevention Vietnam, 2016.

70. Nihal A. Global and South-East Asia regional burden of diphtheria disease and strategies for control. In: WHO SEARO, 2016.

71. Sangal L, Joshi S. VPD Surveillance in India: A glance. In: WHO India, 2017.

72. The European Surveillance System (TESSy). In: Control ECfDPa, (ed), 2006-2016.

73. Organization WH. WHO-UNICEF estimates of DTP3 coverage In, 1980-2015.

74. Organization WH. Immunization schedule by disease In, 2016.

75. Control ECfDPa. Vaccine Schedule Search Tool. In. ECDC Network, 2016.

76. Vashishtha VM, Kumar P. 50 years of immunization in India: Progress and Future. *Indian Pediatrics* 2013; **50:** 111-118.

77. John TJ. Resurgence of diphtheria in India in the 21st century. *Indian Journal of Medical Research* 2008; **128**(5)**:** 669-670.

78. Ramesh BM AF, Roy TK, Kanitkar T, Govindasamy P, Retherford RD. *National Family Health Survey (MCH and Family Planning), India 1992-1993*: Mumbai, 1995.

79. Roy TK AF, Kulkarni S, Kishor S, Gupta K, Mishra V, Nangia P, Retherford RD, Pandey A, Kumar S. *National Family Health Survey (NFHS-2), 1998–99: India.* Government of India: Mumbai, 2000.

80. *Multiple Indicator Survey 2000 India Summary Report*. Government of India: New Delhi, 2001.

81. Bhat PNM AF, Gupta K, Kishor S, Parasuraman S, Arokiasamy P, Singh SK, Lhungdim H. *National Family Health Survey (NFHS-3), 2005–06: India*. Government of India, 2007.

82. Health Information Management System. In: Government of India MoHaFW, (ed): Digital India, 2008-2016.

83. Bhavan N. *State Fact Sheet Bihar*. Government of India Ministry of Health and Family Welfare: Mumbai, 2015-16.

84. Bhavan N. *State Fact Sheet Kerala*. Government of India Ministry of Health and Family Welfare: Mumbai, 2015-2016.

85. Bhavan N. *State Fact Sheet Uttar Pradesh*. Government of India Ministry of Health and Family Welfare: Mumbai, 2015-2016.

86. Bhavan N. *State Fact Sheet Haryana*. Government of India Ministry of Health and Family Welfare: Mumbai, 20015-16.

87. Kantsone I, Lucenko I, Perevoscikovs J. More than 20 years after re-emerging in the 1990s, diphtheria remains a public health problem in Latvia. *Euro Surveill* 2016; **21**(48). doi: 10.2807/1560-7917.ES.2016.21.48.30414

Appendix A: Full search terms from literature review

Search Strategy (First search):

Database	Strategy	Run Date
Medline (OVID)	(Diphtheria/ AND Disease Outbreaks/) OR (diphtheria.ti AND (outbreak* OR cluster* OR epidemic*).ti,ab.) OR (diphtheria ADJ3 (outbreak* OR cluster* OR epidemic*)).ab.	11/4/2015
Embase (OVID)	(Diphtheria/ AND Disease Outbreaks/) OR (diphtheria.ti AND (outbreak* OR cluster* OR epidemic*).ti,ab.) OR (diphtheria ADJ3 (outbreak* OR cluster* OR epidemic*)).ab.	11/4/2015
Scopus	TITLE-ABS-KEY(diphtheria W/2 outbreak*)	11/4/2015

Search Strategy (Second search):

Database	Strategy	Run Date
Medline (OVID) 1946-	*diphtheria/ or diphtheria.ti,ab. AND Epidemics/ OR Disease Outbreaks/ OR (outbreak* OR cluster* OR epidemic*).ti,ab. AND Limit 2000-	06/20/2016
Embase (OVID) 1996-	*diphtheria/ or diphtheria.ti,ab. AND Epidemic/ OR (outbreak* OR cluster* OR epidemic*).ti,ab. AND Limit 2000-	06/20/2016
Global Health (OVID) 1973-	diphtheria/ OR diphtheria.ti,ab,sh. AND Epidemics/ OR (outbreak* OR cluster* OR epidemic*).ti,ab,sh. AND Limit 2000-	06/20/2016
CINAHL (Ebsco) 1982-	(MJ diphtheria) or (TI diphtheria) OR (AB diphtheria) AND (MH "Disease Outbreaks") OR (MH Epidemics) OR (TI (outbreak* OR cluster* OR epidemic*)) OR (AB (outbreak* OR cluster* OR epidemic*)) AND Limit 2000- ; Exclude Medline records	06/20/2016

Cochrane Library 1800-	[mh diphtheria] or diphtheria:ti,ab AND [mh "Disease Outbreaks"] OR [mh Epidemics] OR (outbreak* OR cluster* OR epidemic*):ti,ab AND Limit 2000-	06/20/2016
LILACS 1982-	Diphtheria AND (outbreak* OR cluster* OR epidemic*)	06/20/2016
Scopus 1960-	INDEXTERMS(Diphtheria) AND INDEXTERMS("disease outbreak*" OR epidemic*) AND (LIMIT-TO(PUBYEAR,2015) OR LIMIT-TO(PUBYEAR,2014) OR LIMIT-TO(PUBYEAR,2013) OR LIMIT-TO(PUBYEAR,2012) OR LIMIT-TO(PUBYEAR,2011) OR LIMIT-TO(PUBYEAR,2010) OR LIMIT-TO(PUBYEAR,2009) OR LIMIT-TO(PUBYEAR,2008) OR LIMIT-TO(PUBYEAR,2007) OR LIMIT-TO(PUBYEAR,2006) OR LIMIT-TO(PUBYEAR,2005) OR LIMIT-TO(PUBYEAR,2004) OR LIMIT-TO(PUBYEAR,2003) OR LIMIT-TO(PUBYEAR,2002) OR LIMIT-TO(PUBYEAR,2001) OR LIMIT-TO(PUBYEAR,2000)) AND (LIMIT-TO(DOCTYPE,"ar") OR LIMIT-TO(DOCTYPE,"re")) AND (LIMIT-TO(EXACTKEYWORD,"Diphtheria"))	06/20/2016

Appendix B: Definitions of variables and datasets in diphtheria epidemiology analysis	
Country type	
Higher case count	Countries reporting at least 10 diphtheria cases in at least 3 years of JRF incidence data between 2000 and 2015; Designation intended to be sensitive to include countries with possible endemic disease as well as those where imported cases lead to notable secondary transmission. (n= 225 cases; 19 countries in main review dataset)
Sporadic incidence	Countries who reported at least one diphtheria case between 2000 and 2015 but did not reach the threshold for higher case count countries; Designation intended to be specific for countries with occasional importations without wide secondary transmission and low likelihood of endemic disease. (n=10,694; 14 countries in main review dataset)
Vaccination schedule type	
Primary series only	3 doses of DTP or similar in infancy ("primary series") are the only diphtheria-containing vaccines included in the national immunization schedule. (n= 1283 cases; 5 countries in main review dataset)
Last dose at <6y	In addition to the primary series, at least one booster dose of diphtheria-containing vaccine is on the national schedule. The last booster dose on the schedule is administered prior to 6 years of age. (n= 10,931; 5 countries in main review dataset)
Last dose at 6-17y	In addition to the primary series, at least one booster dose of diphtheria-containing vaccine is on the national schedule. The last booster dose on the schedule is administered between 6 and 17 years of age. (n= 872; 11 countries in main review dataset)
Adult boosters	In addition to the primary series and boosters, at least one dose of diphtheria-containing vaccine given at or after age 18 (n= 231; 12 countries in main review dataset)
Datasets	
Main review dataset	Main compilation of age and vaccination status of diphtheria cases worldwide constructed by principal investigator; all other datasets include a subset of these data. (n=10,919 cases)
5 Year dataset	Includes all cases with clear case age data around the 5 year cut-off (±1 year). Excludes cases without age data. (n=10,385)
15 Year dataset	Includes all cases with clear case age data around the 15 year cut-off (±1 year). Excludes cases without age data. (n=5,544)
Vaccine dataset	Includes all cases with clear data around vaccination status (cases clearly categorized as unvaccinated, partially vaccinated, completely vaccinated, or unknown vaccination status). Excludes cases without vaccination data. (n=1360)
Age and Vaccination status dataset	Includes data from sources that reported the vaccination status of cases within each age group. Includes data with age and vaccination status limitations. (n=3719)