Diphtheria in the 21st Century: Trends in incidence and outbreaks

Kristie E. N. Clarke, MD MSCR FAAP
Medical Epidemiologist
Global Immunization Division
US Centers for Disease Control and Prevention

SAGE Meeting Presentation
27 April, 2017
Diphtheria

- Toxigenic *Corynebacterium diphtheriae*
  - *Corynebacteria* other than diphtheriae can produce exotoxin

- Toxoid vaccine

- Speed of administration of diphtheria anti-toxin (DAT) critical to reduce mortality and complications
  - 5-10% case fatality rate
  - Myocarditis
  - Neuropathies

Photo credit: CDC Public Health Image Library
Schematic of diphtheria immunity in the pre-and post-vaccine eras

Changing epidemiology of diphtheria

- **Pre-vaccine:**
  - ≥40% of cases in children under 5 years
  - ≥70% of cases in children under 15 years

- **Post-vaccine:**
  - **Stage one:** Cases predominantly in school-age children aged 5-15 years
  - **Stage two:** Cases predominantly in older adolescents/ adults aged >15 years
Reported cases of diphtheria worldwide- 1980 -2015

- >157,000 cases
- >5,000 deaths
- 64 - 76% >15 years of age

Nonimmune adults + poor childhood coverage = potential severe outbreaks
WHAT VACCINATION SCHEDULES ARE CURRENTLY RECOMMENDED BY COUNTRIES?
Median age at last childhood dose (and range) among countries recommending the same type of vaccination schedule

<table>
<thead>
<tr>
<th>Vaccination Schedule</th>
<th>Percentage of countries with each vaccination schedule</th>
<th>Median age (in years) at last scheduled childhood dose</th>
<th>Range of age at last scheduled childhood dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 dose primary series</td>
<td>25%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>3 dose + 1</td>
<td>9%</td>
<td>5</td>
<td>1-15</td>
</tr>
<tr>
<td>3 dose + 2</td>
<td>16%</td>
<td>6</td>
<td>&lt;1-16</td>
</tr>
<tr>
<td>3 dose + 3</td>
<td>25%</td>
<td>13</td>
<td>6-17</td>
</tr>
<tr>
<td>3 dose + 4</td>
<td>4%</td>
<td>14</td>
<td>7-17</td>
</tr>
<tr>
<td>3 dose + 2 + adult boosters</td>
<td>7%</td>
<td>12</td>
<td>5-15</td>
</tr>
<tr>
<td>3 dose + 3 + adult boosters</td>
<td>12%</td>
<td>14</td>
<td>10-16</td>
</tr>
<tr>
<td>3 dose + 4 + adult boosters</td>
<td>2%</td>
<td>16</td>
<td>14-17</td>
</tr>
</tbody>
</table>
Vaccination schedules and DTP3 coverage for the 10 countries reporting the most cases of diphtheria in 2011-2015

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>18350</td>
<td>3 dose + 2</td>
<td>5</td>
<td>84%</td>
</tr>
<tr>
<td>Indonesia</td>
<td>3203</td>
<td>3 dose + 4</td>
<td>8</td>
<td>82%</td>
</tr>
<tr>
<td>Madagascar</td>
<td>1633</td>
<td>3 dose</td>
<td>-</td>
<td>72%</td>
</tr>
<tr>
<td>Nepal</td>
<td>1440</td>
<td>3 dose</td>
<td>-</td>
<td>91%</td>
</tr>
<tr>
<td>Iran</td>
<td>513</td>
<td>3 dose + 2</td>
<td>6</td>
<td>99%</td>
</tr>
<tr>
<td>Lao PDR</td>
<td>344</td>
<td>3 dose</td>
<td>-</td>
<td>84%</td>
</tr>
<tr>
<td>Pakistan</td>
<td>321</td>
<td>3 dose</td>
<td>-</td>
<td>72%</td>
</tr>
<tr>
<td>Sudan</td>
<td>222</td>
<td>3 dose</td>
<td>-</td>
<td>93%</td>
</tr>
<tr>
<td>Myanmar</td>
<td>180</td>
<td>3 dose</td>
<td>-</td>
<td>79%</td>
</tr>
<tr>
<td>Thailand</td>
<td>157</td>
<td>3 dose + 2</td>
<td>4</td>
<td>99%</td>
</tr>
</tbody>
</table>
CURRENT TRENDS IN INCIDENCE DATA
Reported cases of diphtheria per year worldwide by 5 year average

![Graph showing the decrease in reported diphtheria cases over the years 2000-2015. The y-axis represents the number of cases, ranging from 0 to 12,000, and the x-axis represents the years 2000-2004, 2005-2009, and 2010-2015. The graph shows a consistent decrease in cases over the years.](attachment:image.png)
Cases of diphtheria by region by 5 year averages, 2000-2015
Reported diphtheria cases in the 10 highest case count countries by 5 year average - 2000-2015
Questions to answer

- How complete are available data on diphtheria incidence?
- Is there evidence for a shift in the age distribution of diphtheria cases?
- Does the vaccination status distribution of cases indicate waning immunity with existing schedules?
Flow chart of literature review and sources for data used in analysis

- 901 unique abstract results
  - 29 eliminated due to language
  - 779 not relevant on abstract review
  - 2 full text articles not retrievable

- 93 potentially relevant abstract results
  - 36 articles containing primarily pre-2000 data
  - 1 article on age-restricted population
  - 31 articles on diphtheria carriage or antibody serosurveys

- 91 retrievable results

- 54 results with dates and populations inside scope of review

- 23 articles on cases or trends of diphtheria 2000-2016

- 20 publications with case information relevant to the review
  - 17 additional publications found through reference lists
  - 9 sources from grey literature
  - 11 unpublished reports
  - ECDC’s TESSy database

58 sources; data on 10,919 cases in 33 countries
HOW COMPLETE ARE AVAILABLE DATA ON DIPHTHERIA INCIDENCE?
Completeness of review dataset, by case numbers - 2000-2015

<table>
<thead>
<tr>
<th>Region</th>
<th>Cases in review dataset</th>
<th>Cases reported from region, 2000-2015</th>
<th>Proportion of case number potentially captured in review</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFR</td>
<td>133</td>
<td>10182</td>
<td>1%</td>
</tr>
<tr>
<td>AMR</td>
<td>372</td>
<td>975</td>
<td>38%</td>
</tr>
<tr>
<td>EMR</td>
<td>456</td>
<td>3785</td>
<td>12%</td>
</tr>
<tr>
<td>EUR</td>
<td>239</td>
<td>7244</td>
<td>3%</td>
</tr>
<tr>
<td>SEAR</td>
<td>8981</td>
<td>80866</td>
<td>11%</td>
</tr>
<tr>
<td>WPR</td>
<td>738</td>
<td>3698</td>
<td>20%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>10919</td>
<td>106750</td>
<td>10%</td>
</tr>
</tbody>
</table>
Summary of completeness of JRF diphtheria data by country-year – 2000-2015

Percent of Country-years

Nonzero country-years
Zero reporting country-years
Missing data country-years

AFR (n=740)
AMR (n=560)
EMR (n=336)
EUR (n=848)
SEAR (n=176)
WPR (n=432)
TOTAL (n=3092)

9% 41% 1%
14% 86%
26% 21%
22% 10%
57% 38%
20% 19%
19% 18%
Concordance of cases captured in review and JRF reports

*for readability, depicts a subset of data with case counts under 150
Categorization of countries for analysis

Frequency of cases in country

- **Higher case count countries**
  - At least 10 diphtheria cases reported on JRF in at least 3 years during the period 2000-2016

- **Sporadic incidence countries**
Datasets created for sensitivity analyses

Age Distribution

- **5 year dataset**
  - All cases with clear case age data around the 5 year cut-off (±1 year). (n=10,385)

- **15 year dataset**
  - All cases with clear case age data around the 15 year cut-off (±1 year). (n=5,544)

Vaccination status

- **Vaccine dataset**
  - All cases clearly categorized as unvaccinated, partially vaccinated, completely vaccinated, or unknown vaccination status) (n=1360)
IS THERE EVIDENCE FOR A SHIFT IN AGE DISTRIBUTION OF DIPHTHERIA CASES?

- **Stage one**: Cases predominantly in school-age children aged 5-15 years

- **Stage two**: Cases predominantly in older adolescents/ adults aged >15 years
Sensitivity analysis of age distribution in higher case count versus sporadic incidence countries (using "5 Year" and "15 Year" datasets)

![Chart showing percent of diphtheria cases]

- **Higher case count countries**
  - <5: 18%, ≥5: 82%, n=10,253
  - <15: 60%, ≥15: 40%, n=5,413

- **Sporadic incidence countries**
  - <5: 8%, ≥5: 92%, n=132
  - <15: 34%, ≥15: 66%, n=131
Percentage of diphtheria cases reviewed aged 15+ by national DTP3 coverage

Note: Does not reflect the vaccination status of cases diagnosed or vaccination coverage in subnational areas where outbreaks occurred.
DOES THE VACCINATION STATUS DISTRIBUTION OF CASES INDICATE WANING IMMUNITY WITH EXISTING SCHEDULES?
Sensitivity analysis of vaccination status of cases in higher case count versus sporadic incidence countries (using "Vaccine" dataset)

![Bar chart showing the percent of diphtheria cases among vaccinated and unvaccinated individuals in higher case count and sporadic incidence countries.](chart.png)

- **Higher case count countries (n=1291)**
  - Unvaccinated: 76%
  - Partially vaccinated: 8%
  - Completely vaccinated: 17%

- **Sporadic incidence countries (n=69)**
  - Unvaccinated: 32%
  - Partially vaccinated: 38%
  - Completely vaccinated: 30%

(At least 3 doses)
Distribution of age and vaccination status among cases in countries offering the primary series only (n=127)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Completely vaccinated</th>
<th>Partially vaccinated</th>
<th>Unvaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 years</td>
<td>6%</td>
<td>6%</td>
<td>19%</td>
</tr>
<tr>
<td>5-14 years</td>
<td>17%</td>
<td>2%</td>
<td>37%</td>
</tr>
<tr>
<td>≥15 years</td>
<td>1%</td>
<td>0%</td>
<td>13%</td>
</tr>
</tbody>
</table>

Percent of diphtheria cases in dataset
CASE STUDY - INDIA
Age distribution of cases in states of India with case-based surveillance, 2016

<table>
<thead>
<tr>
<th>State</th>
<th>Total cases</th>
<th>Under 5</th>
<th>5-10 years</th>
<th>Over 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bihar</td>
<td>71</td>
<td>41%</td>
<td>34%</td>
<td>25%</td>
</tr>
<tr>
<td>Haryana</td>
<td>59</td>
<td>27%</td>
<td>53%</td>
<td>20%</td>
</tr>
<tr>
<td>Kerala</td>
<td>556</td>
<td>8%</td>
<td>18%</td>
<td>74%</td>
</tr>
<tr>
<td>Uttar Pradesh</td>
<td>844</td>
<td>25%</td>
<td>53%</td>
<td>22%</td>
</tr>
<tr>
<td>Total</td>
<td>1530</td>
<td>20%</td>
<td>39%</td>
<td>41%</td>
</tr>
</tbody>
</table>
Trends in DTP3 and 5yr booster coverage in States with case-based diphtheria surveillance - India, 2000-2015
CASE STUDY - LATVIA
Age distribution of cases in Latvia, 2006-2015 (n=98)
Age distribution of cases in Latvia by year, 2006-2015 (n=98)
### Vaccination status and age of cases in Latvia, 2011-2015 (n=45)

<table>
<thead>
<tr>
<th>Age</th>
<th>Completely vaccinated</th>
<th>Partially vaccinated</th>
<th>Unvaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 years</td>
<td>2%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>5-14 years</td>
<td>9%</td>
<td>4%</td>
<td>11%</td>
</tr>
<tr>
<td>&gt;15 years</td>
<td>11%</td>
<td>7%</td>
<td>56%</td>
</tr>
</tbody>
</table>

Percent of diphtheria cases
Limitations

- Data are not equally representative of all regions or countries.
- Due to heterogeneity of data, a valid meta-analysis could not be performed.
- Some findings based on data with limited sample size, especially in databases used for sensitivity analyses.
- Heterogeneity in many variables:
  - How vaccination status determined and classified
  - Level of confirmation of reported cases (probable, confirmed)
  - Whether lab data were available
Conclusions: General

- Progress in decreasing diphtheria incidence has stalled
- The South-East Asia Region, particularly India, is the major driver of global diphtheria incidence trends
- Most diphtheria cases occur in unvaccinated individuals
- Countries follow a wide variety of vaccination schedules
Conclusions: How complete are data on diphtheria incidence?

- Diphtheria incidence data are underreported on the JRF and are sometimes inconsistent with medical literature.
- There is poor availability and quality of diphtheria case data with information on age and/or vaccination status.
- Subnational data on vaccination coverage rates and the age distribution of diphtheria cases can be important factors in explaining national incidence trends.
Conclusions: Is there evidence for a shift in the age distribution of diphtheria cases?

- In this dataset, the age distributions of cases in counties with sporadic cases reflects an age shift to the adolescent and adult populations.

- In this dataset, countries with higher vaccination coverage tended to have an increased percentage of cases over age 15 years.
Conclusions: Does the vaccination status distribution of cases indicate waning immunity with existing schedules?

- In countries in the dataset using the primary schedule only, the highest proportion of cases were in children 5-14 years of age among both unvaccinated and completely vaccinated individuals. This could be due to low vaccination coverage combined with waning immunity after the primary series.
Acknowledgements

- CDC Literature Review WorkGroup: Dr. Colleen Scott, Dr. Nita Patel, Dr. Tejpratrap Tiwari

- CDC: Dr. Eric Mast, Dr. Peter Bloland, Dr. Adam MacNeil, Dr. Stephen Hadler, Dr. Kathleen Dooling, Dr. Lina Nerlander, Dr. Howard Gary, Dr. Jodi Vanden Eng and Dr. Steve Cochi

- WHO: Dr. Thomas Cherian, Dr. Melanie Marti, Dr. Philippe Duclos

- ECDC: Dr. Kari Johansen

- The author would like to recognize international organizations and colleagues for sharing data for use in this analysis, particularly colleagues at the European CDC and Dr. Sudhir Joshi and Dr. Lucky Sangal of WHO-India.
For more information please contact Kristie E. N. Clarke  kclarke2@cdc.gov
Visit: www.cdc.gov  |  Contact CDC at: 1-800-CDC-INFO or www.cdc.gov/info

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the 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.