

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

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SAGE Meeting Presentation

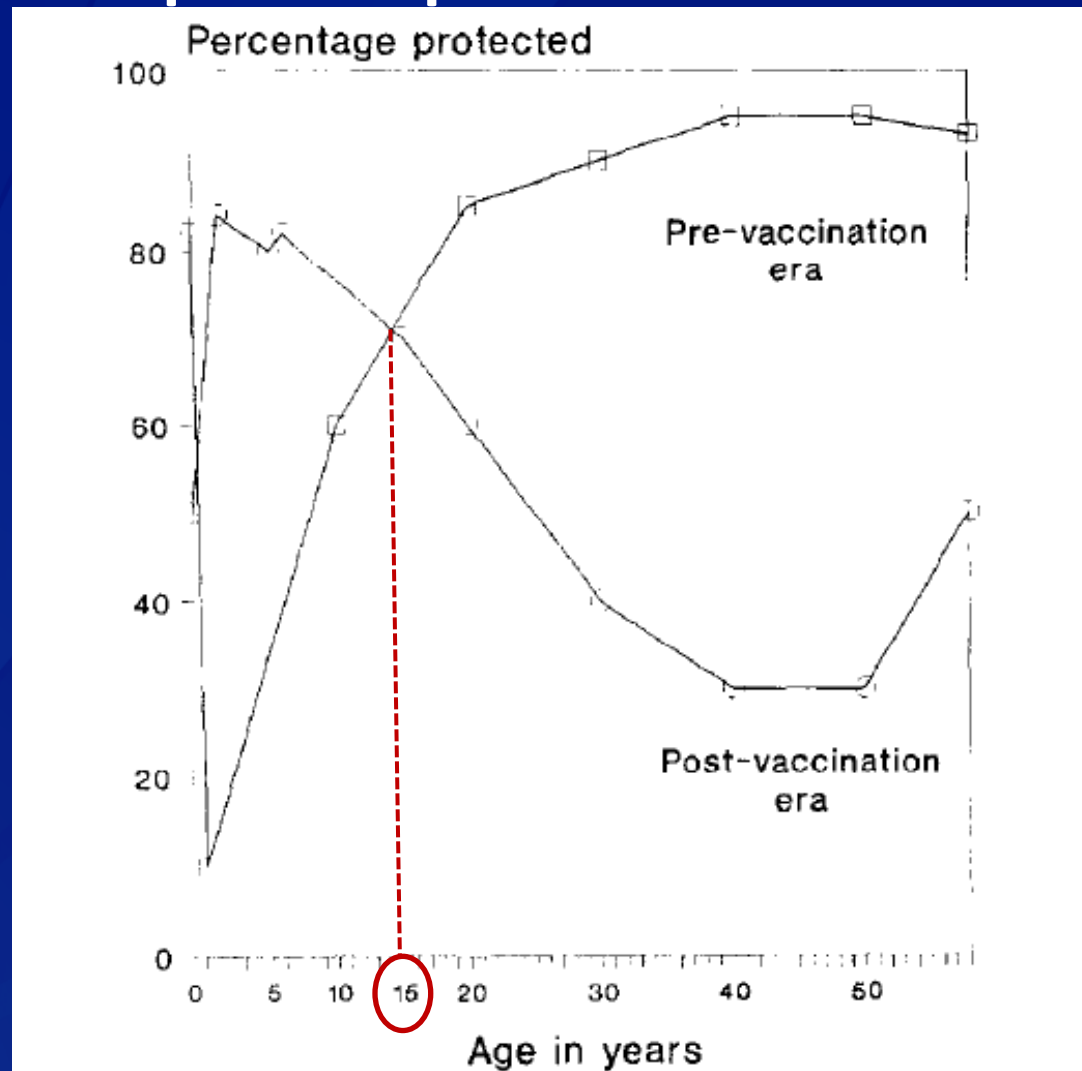
27 April, 2017

# 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



# Schematic of diphtheria immunity in the pre-and post-vaccine eras



Galazka, A. and S. E. Robertson (1996).  
"Immunization against diphtheria with special emphasis on immunization of adults."  
Vaccine 14(9): 845-857.

# Changing epidemiology of diphtheria

## ■ Pre-vaccine:

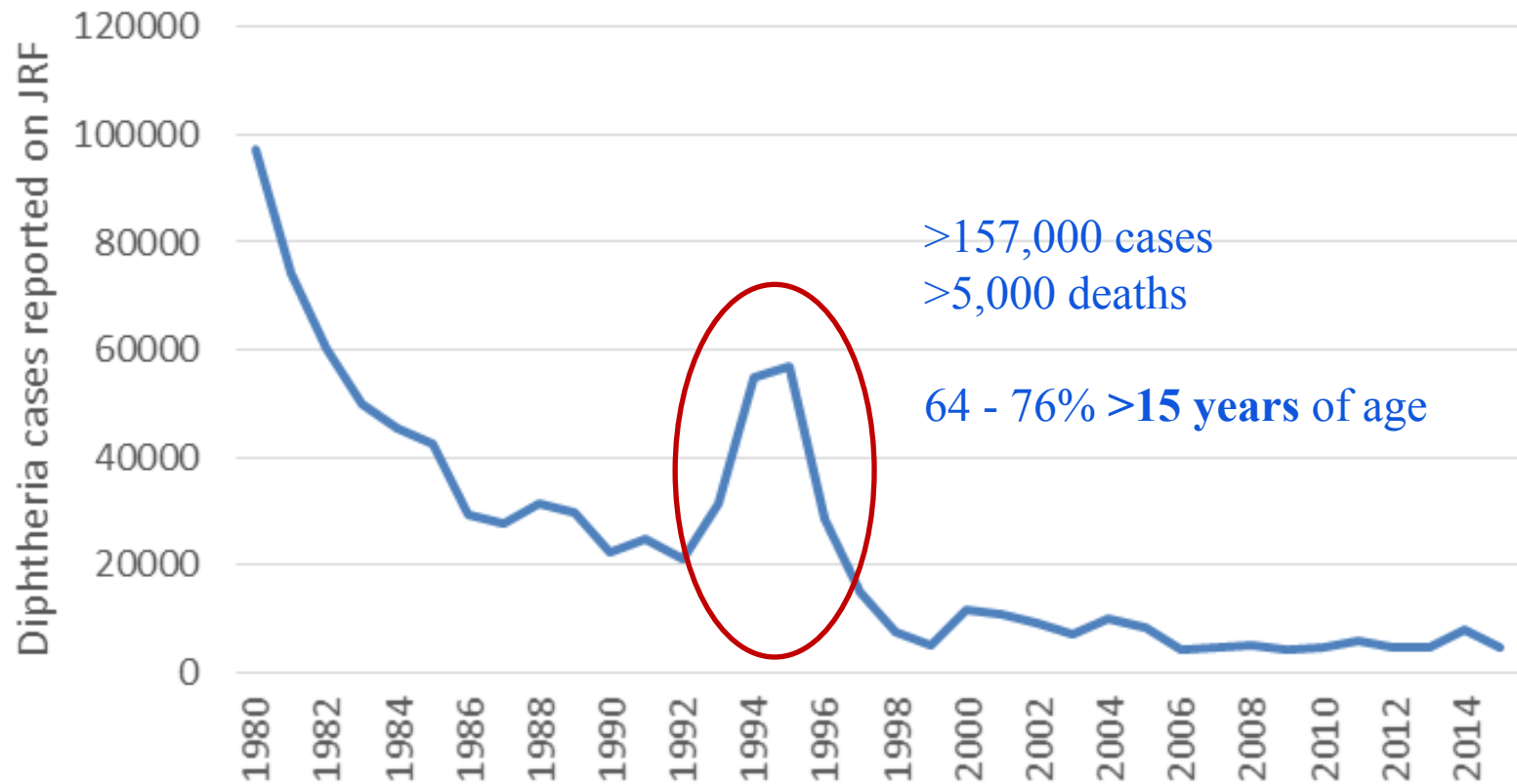
- $\geq 40\%$  of cases in children under 5 years
- $\geq 70\%$  of cases in children under 15 years

## ■ 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



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

Vaccination Schedule	Percentage of countries with each vaccination schedule	Median age (in years) at last scheduled childhood dose	Range of age at last scheduled childhood dose
3 dose primary series	25%	N/A	N/A
3 dose + 1	9%	5	1-15
3 dose + 2	16%	6	<1-16
3 dose + 3	25%	13	6-17
3 dose + 4	4%	14	7-17
3 dose + 2 + adult boosters	7%	12	5-15
3 dose + 3 + adult boosters	12%	14	10-16
3 dose + 4 + adult boosters	2%	16	14-17

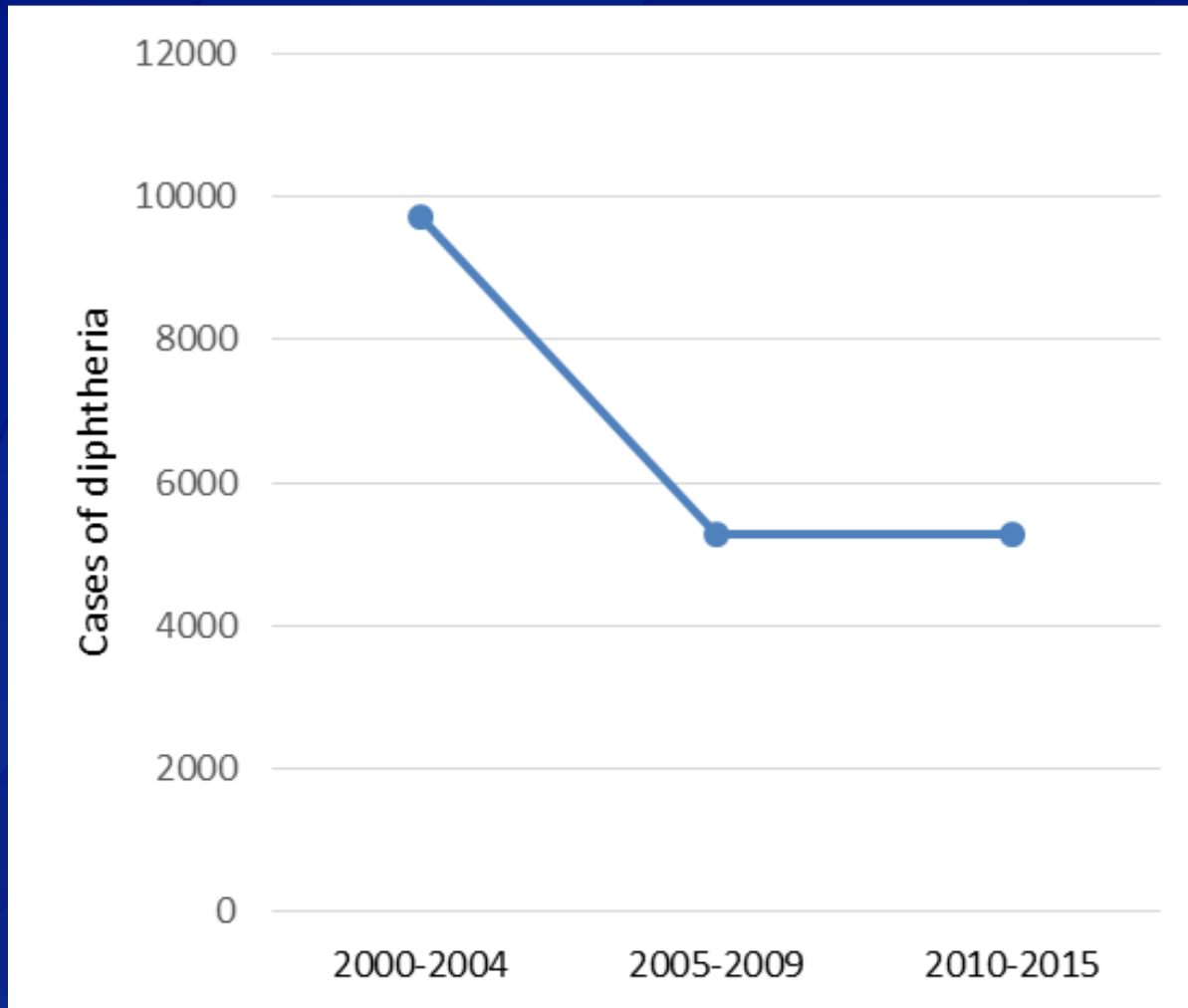
21%

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

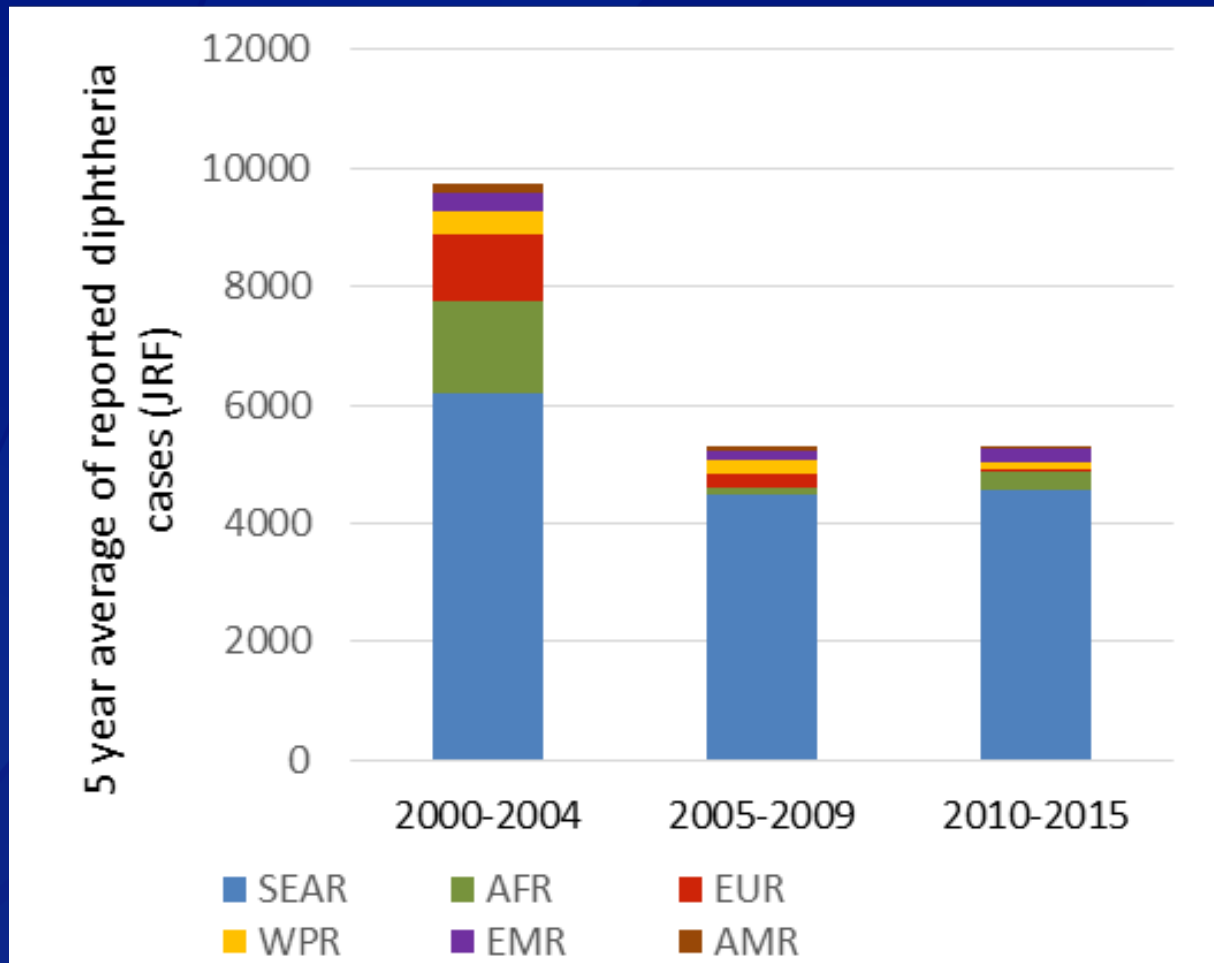
Country	Reported diphtheria cases (2011-2015)	Vaccination schedule	Age at last booster dose	Mean DTP3 coverage (2011-2015)
India	18350	3 dose + 2	5	84%
Indonesia	3203	3 dose + 4	8	82%
Madagascar	1633	3 dose	-	72%
Nepal	1440	3 dose	-	91%
Iran	513	3 dose + 2	6	99%
Lao PDR	344	3 dose	-	84%
Pakistan	321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

# **CURRENT TRENDS IN INCIDENCE DATA**

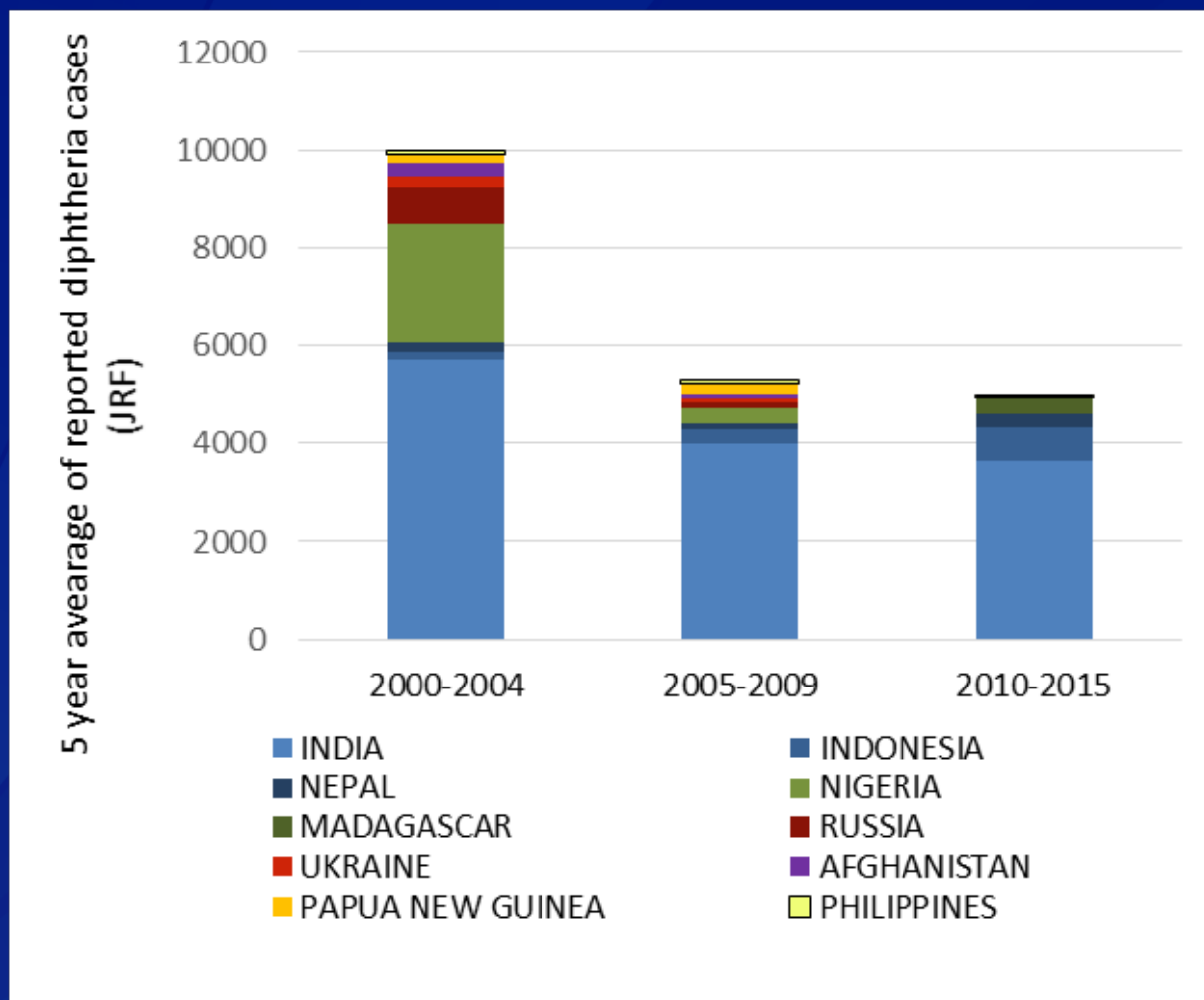
## Reported cases of diphtheria per year worldwide by 5 year average



# 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

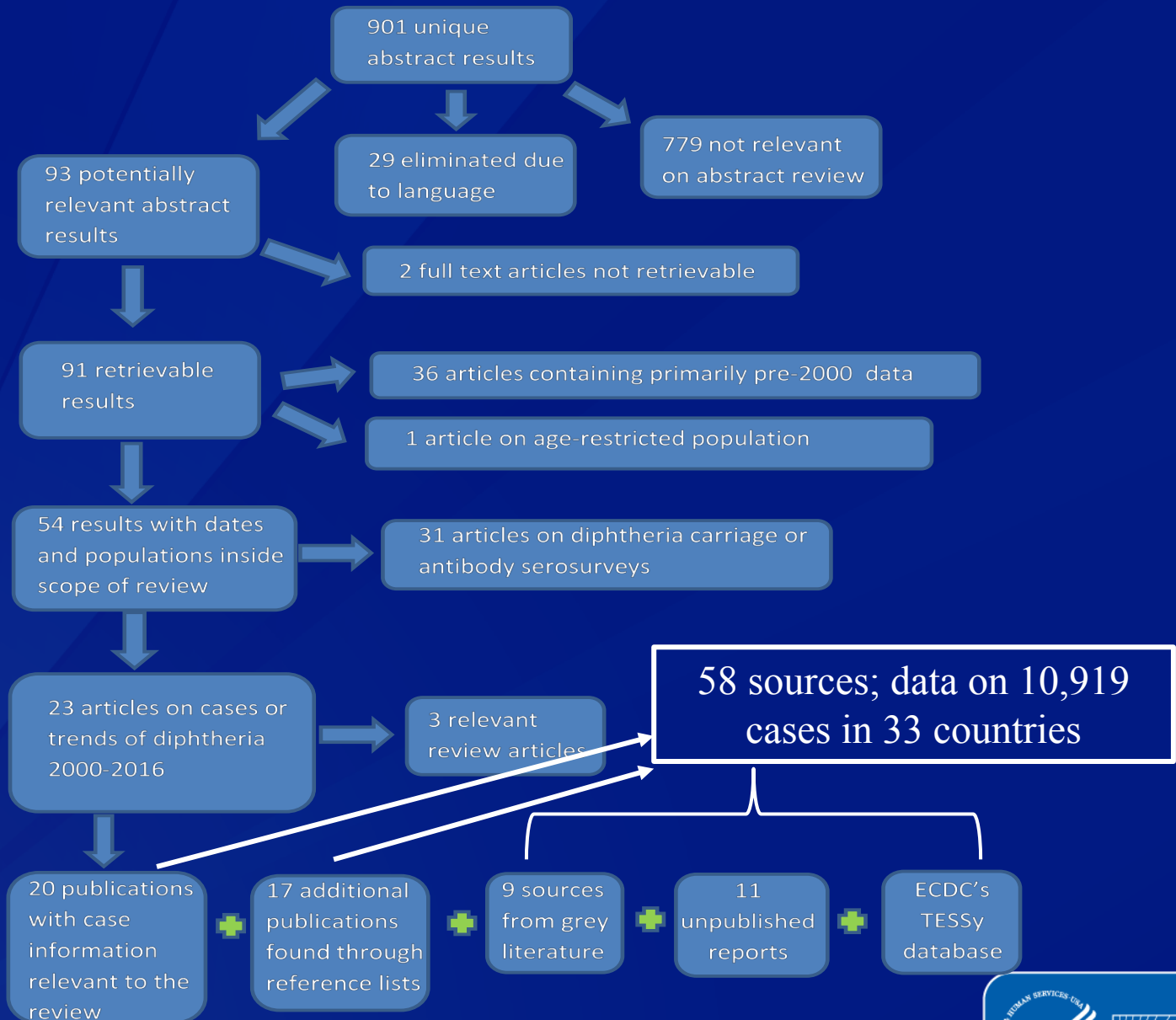




## Questions to answer

- **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

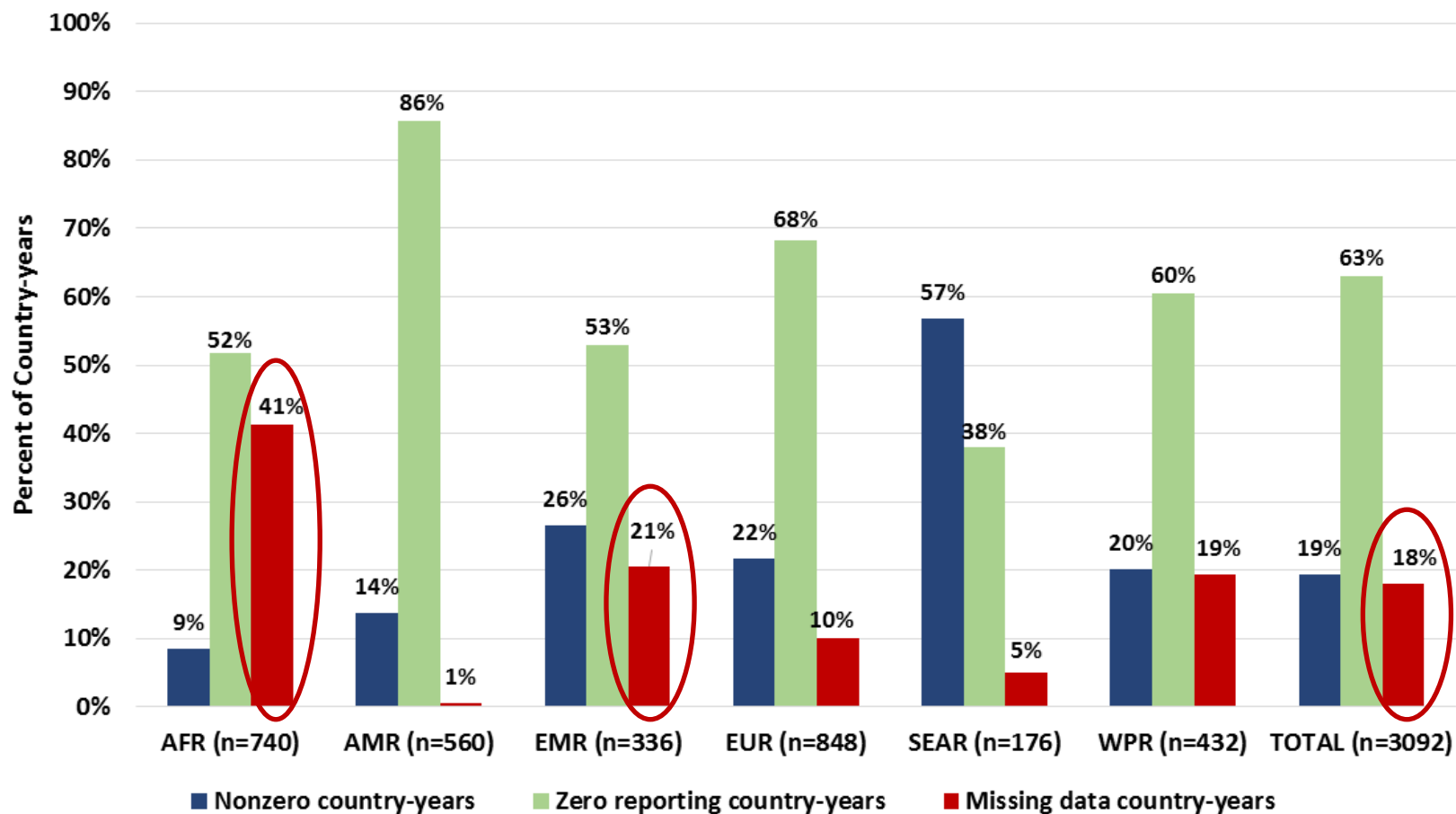


**HOW COMPLETE ARE AVAILABLE DATA  
ON DIPHTHERIA INCIDENCE?**

## Completeness of review dataset, by case numbers - 2000-2015

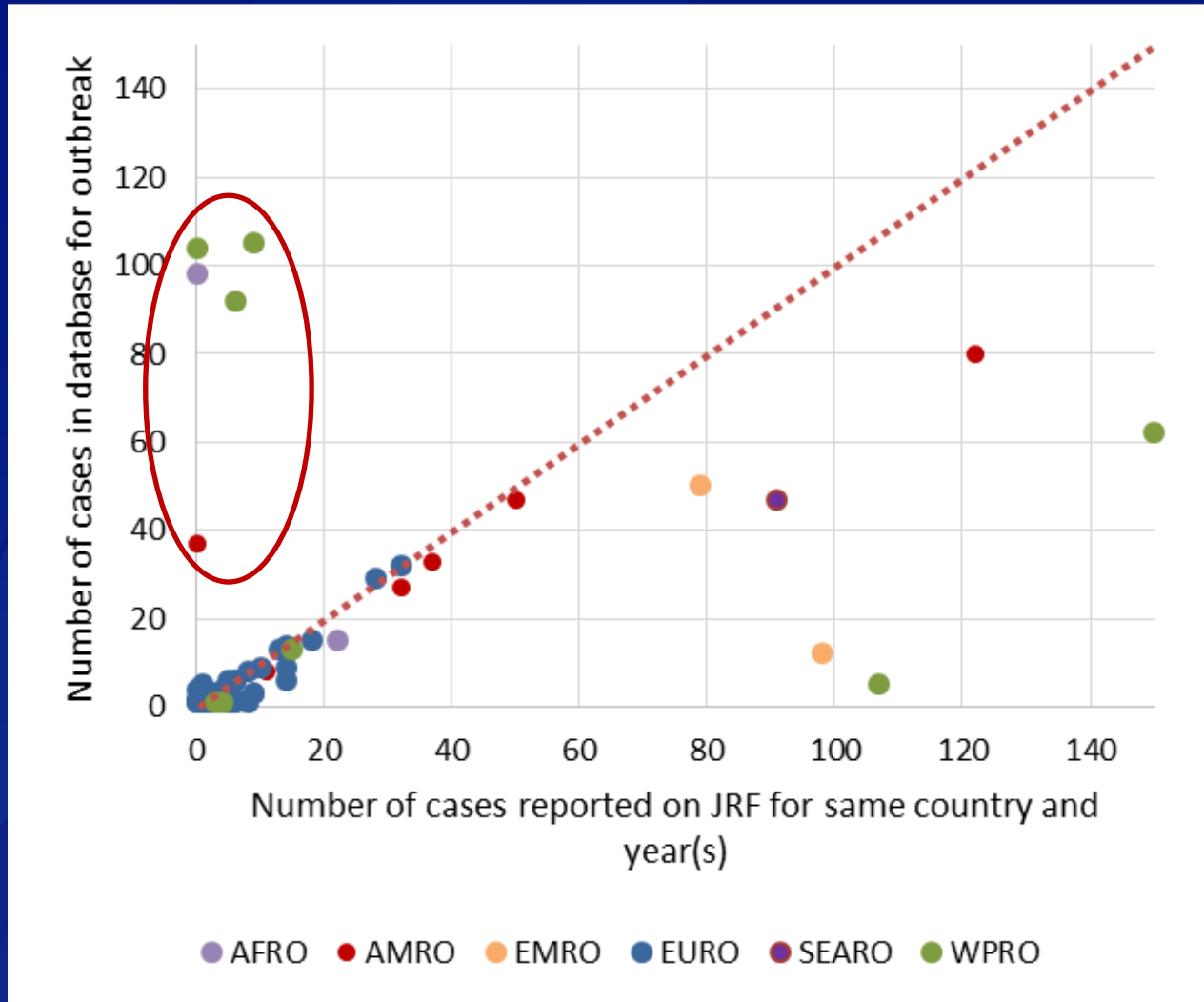
Region	Cases in review dataset	Cases reported from region, 2000-2015	Proportion of case number potentially captured in review
AFR	133	10182	1%
AMR	372	975	38%
EMR	456	3785	12%
EUR	239	7244	3%
SEAR	8981	80866	11%
WPR	738	3698	20%
<b>TOTAL</b>	<b>10919</b>	<b>106750</b>	<b>10%</b>

# Summary of completeness of JRF diphtheria data by country-year – 2000-2015



# 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 ( $\pm 1$  year). (n=10,385)
- **15 year dataset**
  - All cases with clear case age data around the 15 year cut-off ( $\pm 1$  year). (n=5,544)

## Vaccination status

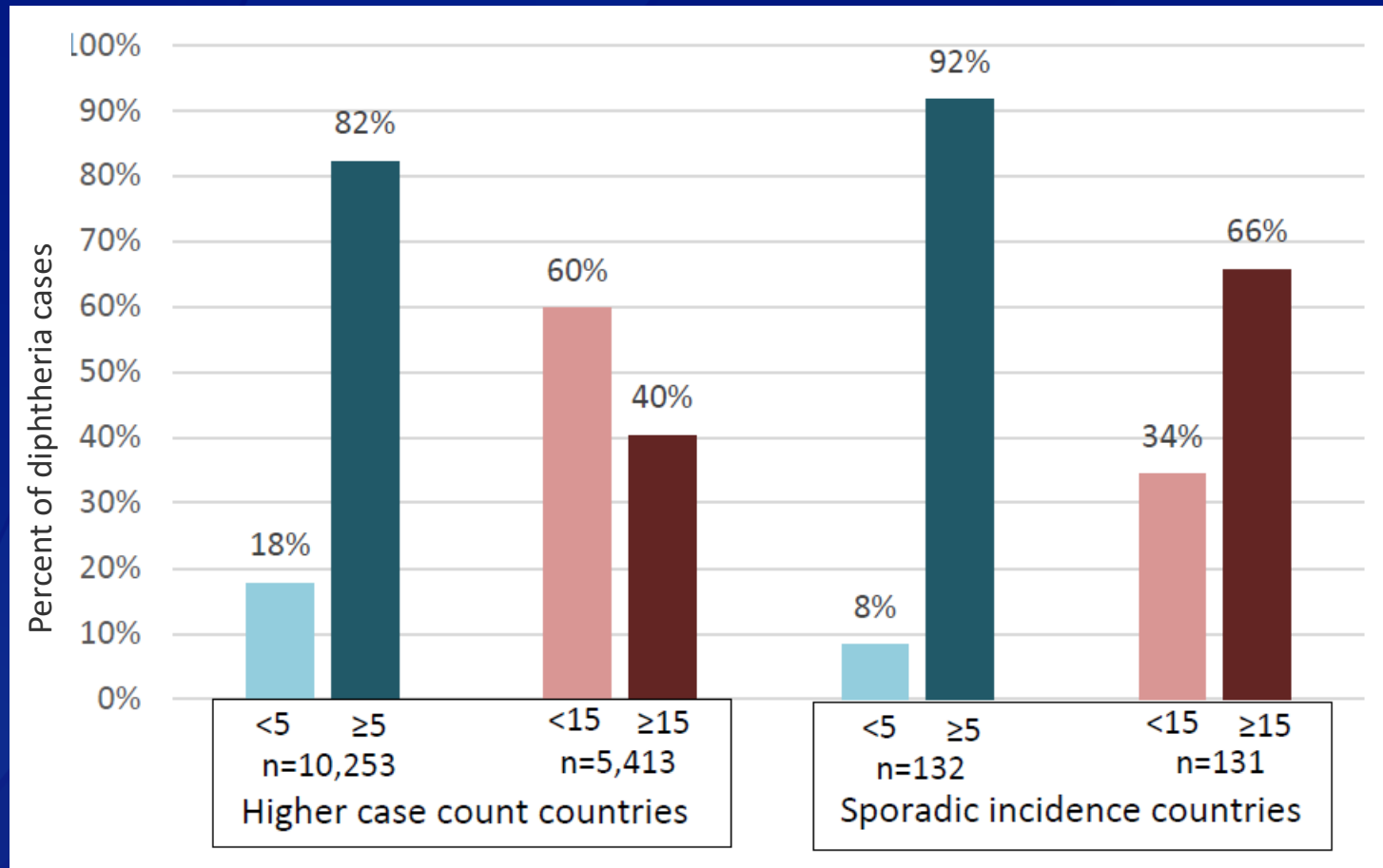
- **Vaccine dataset**
  - All cases clearly categorized as unvaccinated, partially vaccinated, completely vaccinated, or unknown vaccination status) (n=1360)



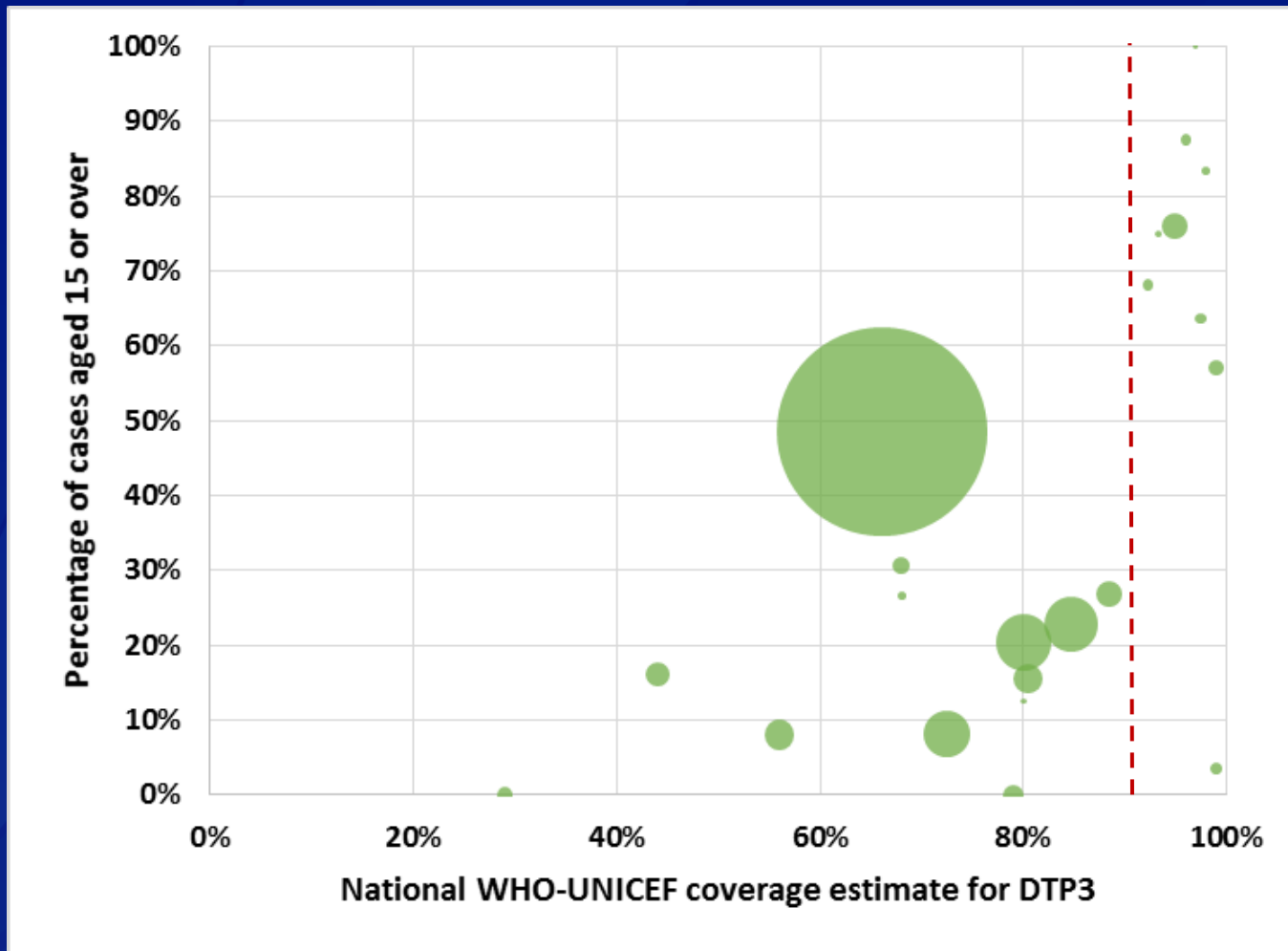
# IS THERE EVIDENCE FOR A SHIFT IN AGE DISTRIBUTION OF DIPHTHERIA CASES?

- 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)



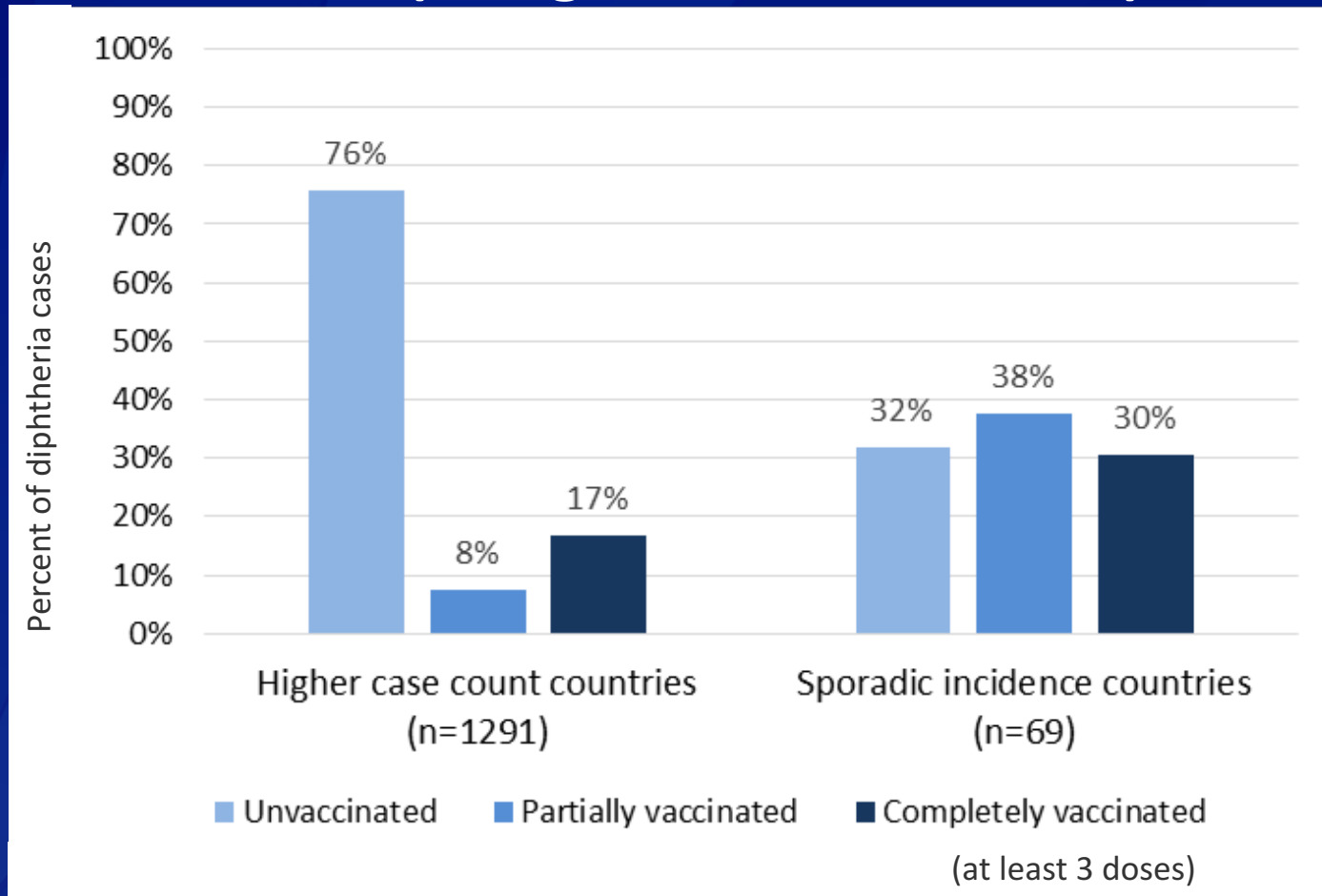
# Percentage of diphtheria cases reviewed aged 15+ by national DTP3 coverage



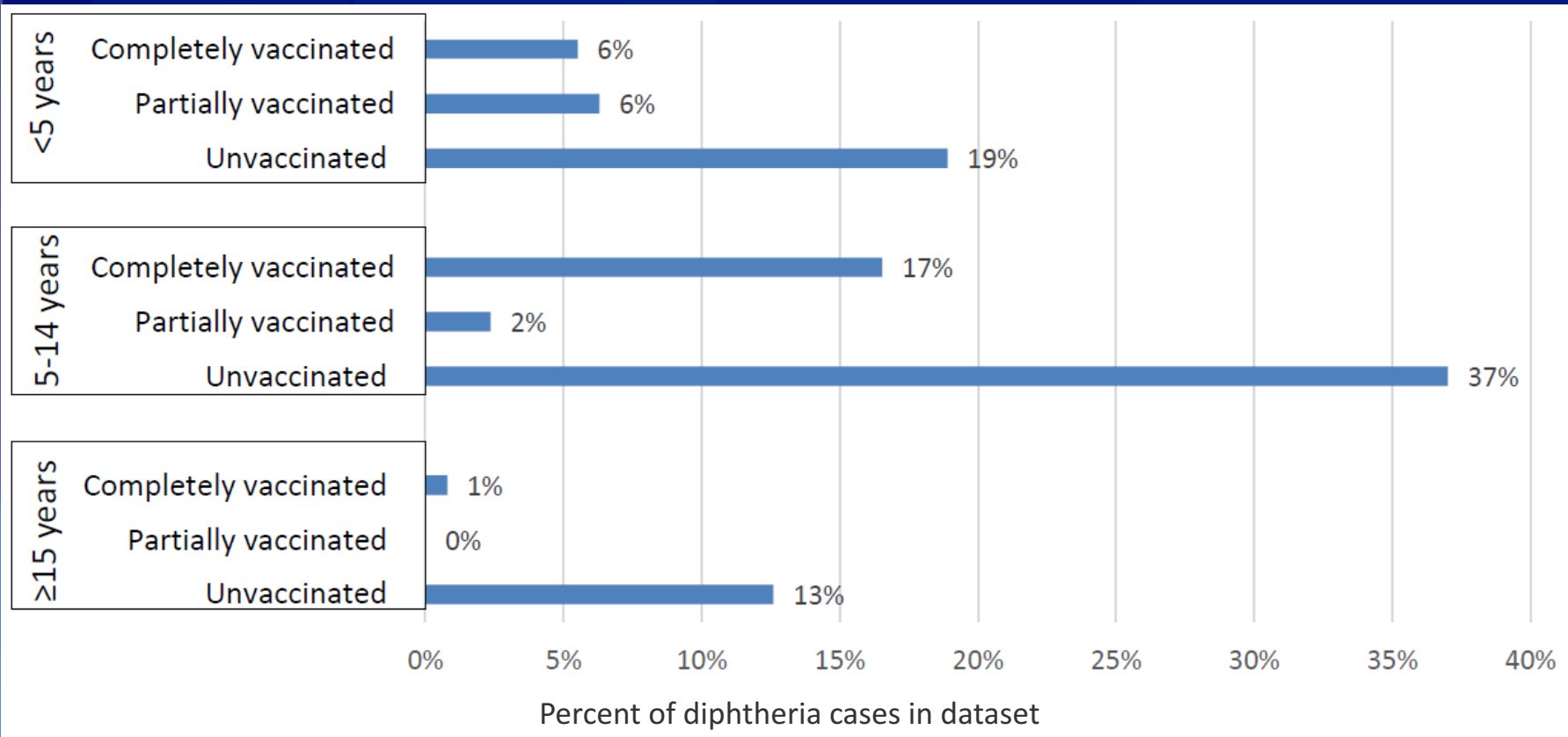
Note: Does not reflect the vaccination status of cases diagnosed or vaccination coverage in subnational areas where outbreaks occurred.

**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)



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



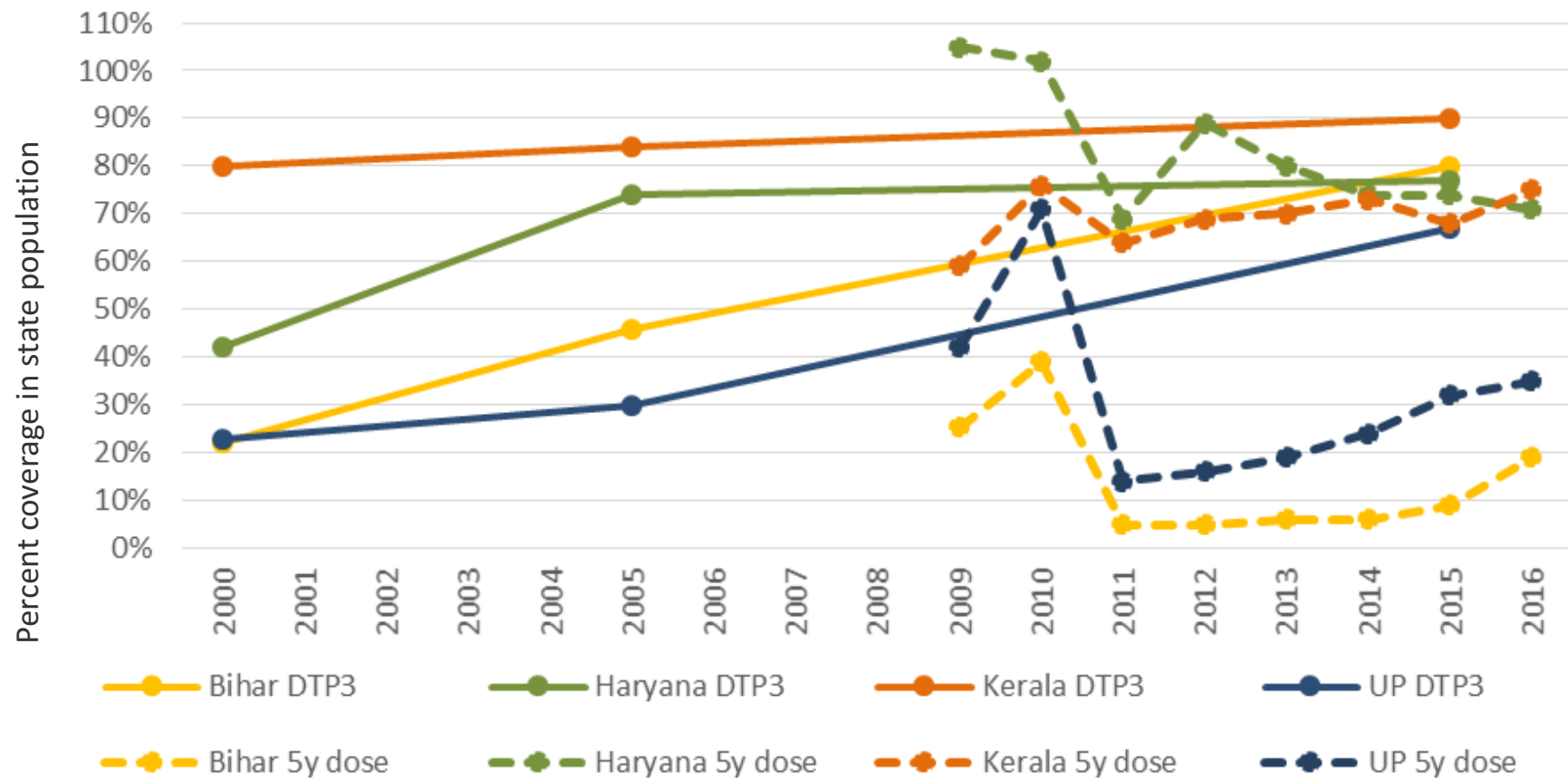
# **CASE STUDY- INDIA**

## Age distribution of cases in states of India with case-based surveillance, 2016

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%

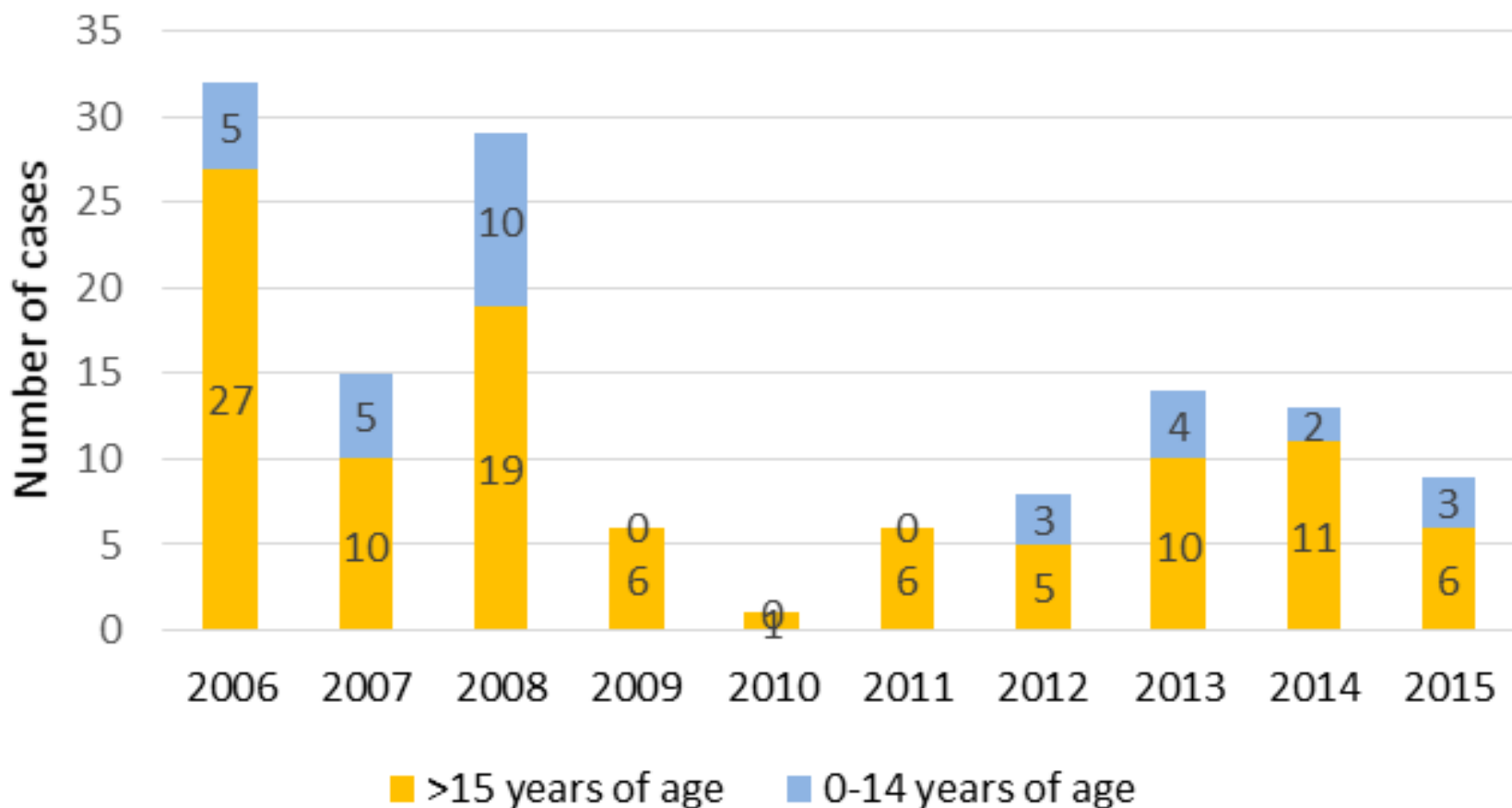


# Trends in DTP3 and 5yr booster coverage in States with case-based diphtheria surveillance - India, 2000-2015

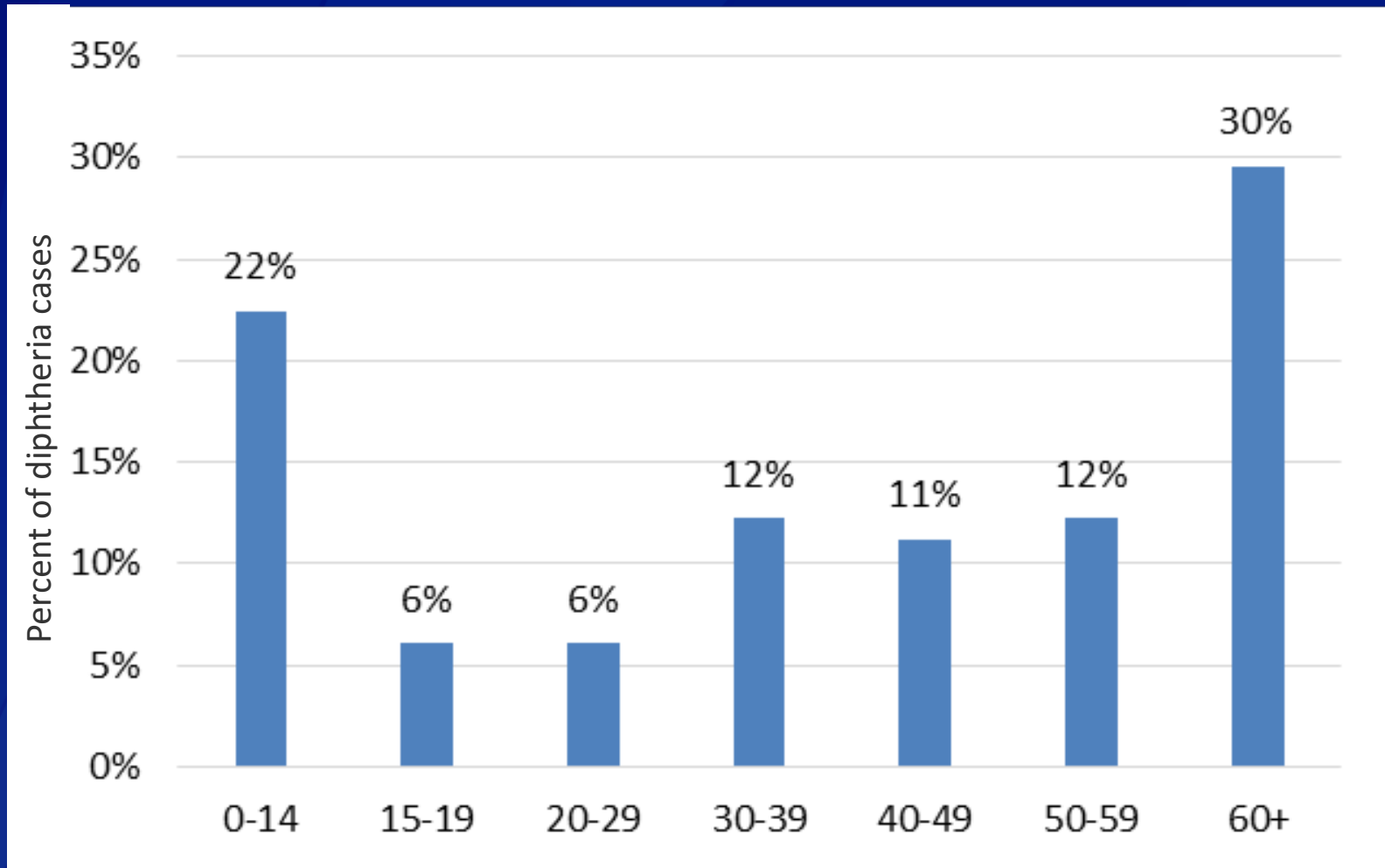


# **CASE STUDY - LATVIA**

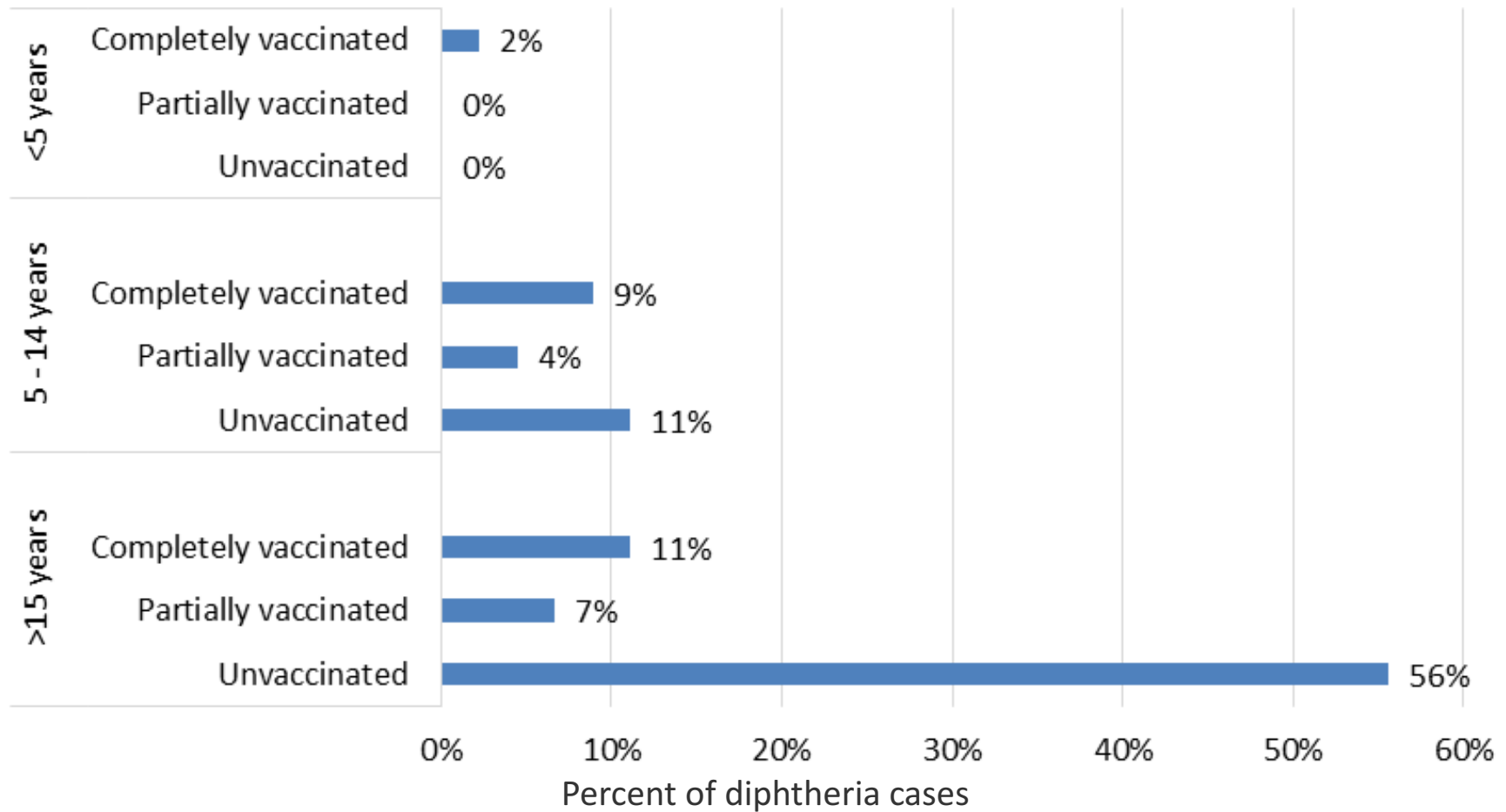
## Age distribution of cases in Latvia, 2006-2015 (n=98)



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



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



## 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

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