The Open Public Health Journal
DOI: 10.2174/0118749445428365251112070830, 2026, 19, e18749445428365
ISSN: 1874-9445
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REVIEW ARTICLE **OPEN ACCESS**

Global Diphtheria Trends and Regional Disparities: A Narrative Review on the Influence of Vaccine Hesitancy, Surveillance Gaps, and Public Health Interventions

Ali Reza Yusefi[1,2], Javad Moslemi Kia[3], Rasoul Raesi[4], Kiavash Hushmandi[5], Ahad Ashrafi Asgarabad[6], Elaheh Abiri[7] and Salman Daneshi[8,*]

[1]*Healthcare Services Management, School of Medical Sciences, Sirjan School of Medical Sciences, Sirjan, Iran*
[2]*Healthcare Services Management, School of Medical Sciences, kerman University of Medical Sciences, kerman, Iran*
[3]*Clinical Research Development Center of Imam Khomeini Hospital, Jiroft University of Medical Sciences, Jiroft, Iran*
[4]*Department of Public Health, School of Health, Torbat Jam Faculty of Medical Sciences, Torbat Jam, Iran*
[5]*Nephrology and Urology Research Center, Clinical Sciences Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran*
[6]*Department of Epidemiology and Biostatic, School of health, Bam University of Medical Sciences, Bam, Iran*
[7]*Department of Cellular and Molecular Biology, School of Biology and Institute of Biological Sciences, Damghan University, Damghan, Iran*
[8]*Department of Public Health, School of Health, Jiroft University of Medical Sciences, Jiroft, Iran*

Abstract:
Despite the availability of effective vaccines, diphtheria is still a major public health problem. The aim of this narrative review was to examine the global trend of diphtheria cases and their regional disparities, as well as the issues of vaccine hesitancy, diphtheria surveillance, and public health interventions. This narrative review aims to summarize current global trends in diphtheria surveillance and vaccination coverage based on reports from the World Health Organization (WHO), UNICEF, the European Centre for Disease Prevention and Control (ECDC), and peer-reviewed literature from PubMed and Scopus, published in English from 2000 to 2023. This narrative review shows that there are significant regional differences in diphtheria burden, with higher rates in Africa and Southeast Asia, where vaccination coverage is low, compared to Europe and North America, where strong immunization programs have been in place, resulting in the near-elimination of diphtheria. However, outbreaks are underreported, data is incomplete, and laboratory capacity is limited, which impairs the timely response to outbreaks, especially in low-resource countries. The global control efforts are complicated by vaccine hesitancy, geopolitical issues, and surveillance gaps. High vaccination coverage is important to reach herd immunity and to minimize disease rates. To improve outcomes, in addition to strengthening vaccination strategies, there is a need for community engagement and targeted vaccination campaigns, as well as for strengthening laboratory infrastructure and effective data collection. This narrative review highlights the importance of strengthening vaccination strategies, strengthening surveillance, and targeted interventions for the control of diphtheria and other vaccine-preventable diseases.

Keywords: Diphtheria, Vaccination coverage, Surveillance, Public health interventions, Global health, Outbreak control.

*Address correspondence to this author at the Department of Public Health, School of Health, Jiroft University of Medical Sciences, Jiroft, Iran; E-mail: salmandaneshi008@gmail.com

Cite as: Yusefi A, Kia J, Raesi R, Hushmandi K, Asgarabad A, Abiri E, Daneshi S. Global Diphtheria Trends and Regional Disparities: A Narrative Review on the Influence of Vaccine Hesitancy, Surveillance Gaps, and Public Health Interventions. Open Public Health J, 2026; 19: e18749445428365. http://dx.doi.org/10.2174/0118749445428365251112070830

Received: July 08, 2025
Revised: October 02, 2025
Accepted: October 10, 2025
Published: July 22, 2026

1. INTRODUCTION

Although effective vaccines are available, diphtheria is still a major public health problem, primarily due to *Corynebacterium diphtheriae* [1, 2]. The disease manifests in the form of a pseudo-membrane in the throat, which can block the airway and cause serious systemic complications like myocarditis, neuropathy, and death if not treated in a timely manner [3, 4]. The diphtheria vaccine was introduced in the mid-20th century and has significantly reduced the burden of diphtheria globally, but there are occasional outbreaks, especially in areas with low vaccination coverage or vaccine hesitancy [5, 6]. This review includes a summary of the global trends in diphtheria cases, regional differences, and how vaccine uptake, surveillance coverage, and public health interventions interact to influence diphtheria control and management, and offers some suggestions on how to improve it. The trends highlight the importance of specific interventions in high-risk areas to fill immunization and health service delivery gaps. Diphtheria is not evenly distributed throughout the world, and there are large regional differences. Africa and Southeast Asia are the most affected regions, and Europe and North America have been able to manage the disease through efficient immunization efforts. For instance, coverage for DTP3 (Diphtheria, Tetanus, and Pertussis) vaccine in Sub-Saharan Africa is as low as 50% in some regions, putting them at risk for continued transmission [7, 8]. In contrast, Western Europe and North America have DTP3 coverage rates > 90%, and the disease is nearly eliminated [5, 9]. These differences are further compounded by variations in health care facilities and surveillance. Underreporting and incomplete data are also common in low-resource countries, with about 63% of country-years reporting no cases, and 19% reporting no data at all [5]. For example, in Africa, 40% of country-years have incomplete diphtheria surveillance data, which indicates that there are large gaps in monitoring and response activities [5, 6]. Sustaining the disparities calls for reinforcing healthcare systems, enhancing data collection, and guaranteeing equal access to vaccines. Vaccine hesitancy has become a major hurdle to diphtheria control. Lacking trust in immunization programs, vaccine coverage rates have dropped in some areas due to misinformation about vaccines [10, 11]. The lack of surveillance makes it difficult to control diphtheria. There have been variations in reporting and in case definitions, which have resulted in inconsistencies between national surveillance data and local health records. To increase surveillance, there is a need for standardization of protocols, increased laboratory capacity, and better training of healthcare workers [12]. Public health interventions are key to reducing the effects of vaccine hesitancy and surveillance gaps. Community engagement campaigns to combat vaccine misinformation, mobile vaccination units to target hard-to-reach communities, and integrated surveillance systems that integrate case reporting with laboratory confirmation are among the strategies that have proven successful [13, 14]. Immunization drives and community-based organizations of local leaders can enhance immunization coverage in high-risk areas. Likewise, public health messaging about the safety and effectiveness of vaccines has helped to overcome vaccine hesitancy and keep coverage rates high [15, 16]. Diphtheria continues to be a public health problem, especially in areas with low immunization rates and poor surveillance. There is considerable progress in controlling the disease in developed areas, although there is still a significant gap in Africa and Southeast Asia, where outbreaks are still occurring. Solving these challenges will need a comprehensive strategy, such as enhancing surveillance systems, combating vaccine hesitancy, and targeted public health interventions. Through the experience gained from previous outbreaks and the implementation of best practices, countries can improve their ability to prevent and control diphtheria, and ultimately safeguard populations from this vaccine-preventable disease. Although diphtheria is preventable with vaccines, it continues to be a public health problem. This narrative review examines the trends in diphtheria cases worldwide, regional variations, and the role of vaccine hesitancy, underreporting, and public health measures. Diphtheria has been almost eradicated in developed countries like Europe and North America, which have high vaccination rates; however, in Africa and Southeast Asia, the disease can still cause outbreaks because vaccination rates are low and healthcare systems are fragile. Additionally, vaccine hesitancy is caused by misinformation and poor surveillance, further complicating control efforts. The review will consider these factors and offer insights for enhancing diphtheria prevention and control efforts worldwide.

2. MATERIALS AND METHODS

This narrative review aims to summaries the worldwide evidence regarding diphtheria trends, surveillance, and vaccination coverage. The review is based on studies and reports published in English between 2000 and 2023, and it includes information about the incidence of diphtheria, vaccination, and public health interventions. The secondary data were collected from published reports and peer-reviewed scientific articles. The data sources included four types: global reports (*e.g.*, the World Health Organization (WHO), the UNICEF Joint Reporting Form (JRF)); regional reports (*e.g.*, the European Centre for Disease Prevention and Control (ECDC) and the Pan American Health Organization (PAHO)); country-level reports from national public health authorities; and peer-reviewed literature from major scholarly databases (*e.g.*, PubMed, Scopus). Selected studies were used to extract relevant data such as diphtheria incidence, vaccination coverage rates (DPT3 coverage), case definitions, and reporting systems in various countries, laboratory confirmation systems used, and reporting trends. The extent to which cases were reported was evaluated by comparing the number of reported cases in the JRF with those reported in the published literature. This analysis was conducted to uncover any inconsistencies and omissions in the data gathering process. Several aspects were analyzed, including incidence rates, completeness of

data, vaccine coverage, and geographical distribution. The outcomes were summarized descriptively and comparatively. Incidence trends, vaccination coverage, and surveillance completeness data were presented in structured tables (Tables **1**-**4**) to enable easy comparison between years and regions. To show the temporal trend in global diphtheria cases and in annual incidence rates from 2000 to 2015, a line graph (Fig. **1**) was created. The tables gave specific numbers, and the graph gave a graphic representation of long-term patterns. The analysis concentrated on the following aspects: The evaluation of the diphtheria incidence trend was assessed globally between 2000 and 2017. Annual Incidence Rates (AIR) per 100,000 population were calculated for various regions to look for trends over time. Assessment of data completeness was done by calculating the percentage of country-years reporting no cases and those reporting cases for diphtheria. This comprised an assessment of the missingness of data at different geographic levels. Vaccination Coverage: DTP3 vaccination coverage was used as an important parameter affecting diphtheria incidence. Data was compared between regions to determine regions with low vaccination coverage that may be at greater risk of outbreaks. Geographical Distribution: Geographic Information Systems (GIS) tools were used to map diphtheria cases and provide visual trends and possible outbreak hotspots. We created country/region maps using ArcGIS (version 10.8, ESRI, Redlands, CA, USA) and QGIS (version 3.22, OSGeo).

3. RESULTS

Global analysis of diphtheria surveillance systems provided important information on trends, completeness, coverage, and regional differences. The results are presented in the following main categories: 1. Incidence Trends, Global Incidence Rates. The number of cases of diphtheria in the world has risen and fallen significantly between 2000 and 2017. The analysis revealed: From 2000 to 2015, there were about 106,750 reported cases of diphtheria in 97 countries. This data suggests that the disease is a problem in many areas [6, 17]. The overall AIR for diphtheria for this period was about 0.29 cases per 100,000 population, but there were large regional differences and inter-year fluctuations [18]. Incidence Trends Global Incidence Rates of Total Reported Cases: 106,750 cases from 2000 to 2015 across 97 countries. o Annual Incidence Rate (AIR): ~0.29 cases per 100,000 people. Table **1** shows the number of cases of disease and the annual incidence rate of disease cases worldwide, 2000–2015.

3.1. Regional Variations

The African region had the highest incidence rates, with outbreaks reported in Nigeria and the Democratic Republic of the Congo (DRC). Outbreaks occurred in some areas with AIRs as high as 3.5 per 100,000 population [19, 20]. Southeast Asia: In countries with low vaccination rates, such as Indonesia and Myanmar, sporadic outbreaks have occurred with varying numbers of cases in different years, including more than 1,000 cases in some years [21]. In contrast, Europe and North America have reported virtually no cases of diphtheria, due to high vaccine coverage, but there are occasional outbreaks, mainly in unvaccinated populations or communities with vaccine hesitancy [22]. Regional Variations of Africa: 3.5 cases per 100,000 in some areas. Of Southeast Asia: Localized outbreaks; considerable variations. Of Asia and Africa: Low incidence, with high vaccination rates. The average annual incidence rates and significant disease outbreaks are shown in Table **2**.

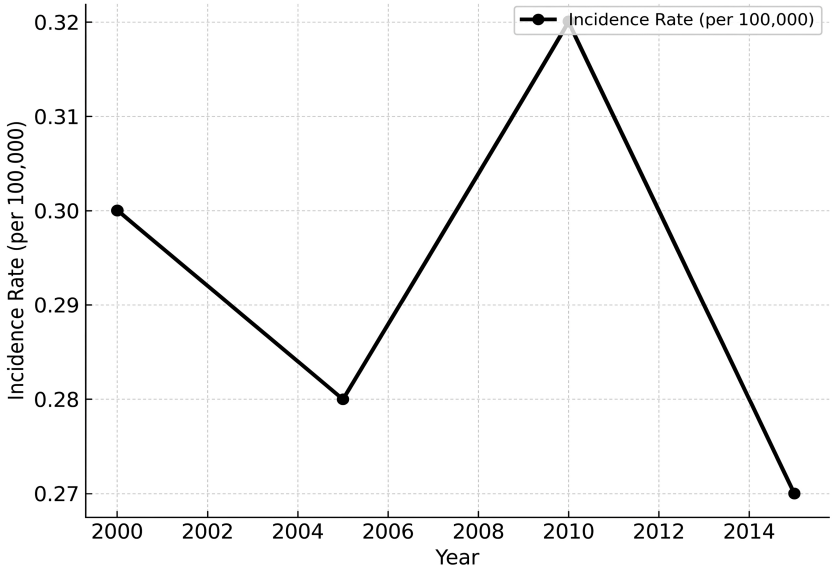

Fig. (1). The global incidence trends and annual incidence rates of disease cases from 2000 to 2015.

Table 1. The global incidence trends and annual incidence rates of disease cases from 2000 to 2015.

Year	Total Cases	AIR (per 100,000)
2000	5,000	0.30
2005	4,800	0.28
2010	6,200	0.32
2015	5,750	0.27

Table 2. The average annual incidence rates and notable disease outbreaks in different regions.

Region	Average AIR	Notable Outbreaks
Africa	1.5	Nigeria, DRC
Southeast Asia	0.5	Indonesia, Myanmar
Europe and N. America	0.01	Isolated cases

Table 3. The data completeness: zero reporting and missing data by region.

Region	% Zero Reporting	% Missing Data
Global	63%	19%
Africa	50%	40%
Other Regions	70%	10%

Table 4. The vaccination coverage: global and regional DTP3 rates.

Region	DTP3 Coverage (%)
Global	86%
Sub-Saharan Africa	65%
Southeast Asia	70%
Western Europe	95%
North America	92%

3.2. Data Completeness

3.2.1. Reporting Gaps

Diphtheria surveillance data were not completely uniform across regions: Zero Reporting- during the study period, there were 63% country-years with zero reported cases, which may represent the absence of active surveillance or underreporting in many areas [18]. Globally, about 19% of country-years were missing diphtheria cases, and in Africa, about 40% of country-years were missing, reflecting significant gaps in diphtheria surveillance [17]. Inconsistencies in Reporting Using the same data from the JRF, cross-referenced with published literature, discrepancies were identified: In some cases, published studies reported higher numbers of cases than cases reported in JRFs, such as in India, where local health authorities reported much higher numbers of cases than were reported to WHO [23]. These discrepancies indicate gaps within national reporting systems and stress the importance of a standardized case definition and reporting procedure. Data Completeness of Zero Reporting: 63% of country-years reported no cases. Globally, 19% of the data is missing, and 40% of the data is missing in Africa. The data completeness figures, including zero reporting and Missing Data by Region are shown in Table **3**.

3.3. Vaccination Coverage

Vaccination coverage is an important factor to consider in diphtheria incidence: DTP3 Coverage Rates Global Coverage: In 2020, global DTP3 vaccination coverage was estimated at around 86%, with significant regional variation [24]. Herd immunity is necessary and depends on high coverage. Regional Disparities: DTP3 coverage was less than 70% in Sub-Saharan Africa and parts of Southeast Asia, while in Nigeria, DTP3 coverage was as low as 50% in some states, contributing to ongoing transmission risks. On the other hand, high coverage rates for DTP3 (above 90%) in Western Europe and North America were associated with low diphtheria incidence [25]. Vaccination Coverage of Global DTP3 Coverage: 86% as of 2020. The regional disparities were less than 70% in o Sub-Saharan Africa and parts of Southeast Asia. Table **4** shows the Vaccination Coverage: Global and Regional DTP3 Rates.

3.4. Impact of Vaccine Hesitancy

Vaccine hesitancy has become a major obstacle: Misinformation about vaccines is shown to play a significant role in parents' vaccine hesitancy, especially in the COVID-19 pandemic, when parents' trust in health systems declined [26]. Recent outbreaks have been associated with low vaccination coverage, especially because of people's reluctance. For instance, Romania experienced an outbreak in 2016 due to a drop in vaccination rates in the unvaccinated population [27, 28].

3.5. Summary of Findings

Overall results show that some areas have efficient surveillance systems, while others still have significant problems, with higher completeness and timeliness rates in developed countries, and lower rates in low-resource countries, and effective identification management systems during recent outbreaks, emphasizing the importance of effective monitoring in controlling outbreaks in the future. Results highlight the importance of ongoing investments in strengthening infrastructure, training health workers, and community engagement strategies to boost vaccine uptake and overall results in the prevention and control of diphtheria and other diseases worldwide.

4. DISCUSSION

This narrative review underscores the ongoing problem of diphtheria in areas of low coverage and poor surveillance. In developed regions, the disease is well controlled, but in Africa and Southeast Asia, it continues to erupt because of poor immunization and health care facilities. Misinformation and vaccine hesitancy are still a huge challenge, as evidenced by recent outbreaks.

Community engagement and mobile vaccination units are important public health interventions to overcome these challenges. Strengthening surveillance, laboratory capacity, and trust in vaccines is essential for global diphtheria control. What works well in current surveillance systems? What is effective about current surveillance? Case-based Surveillance: Countries like India and Brazil have implemented case-based approaches, improving the quality and response, to better track individual cases and ensure timely interventions during outbreaks [29]. Countries can use the WHO/UNICEF Joint Reporting Form to report aggregate data for each year, compare the data across regions, and identify areas for targeted interventions to effectively combat disease spread over time [30]. Enhanced Awareness Response Capacity: Governments and health organizations have been quick to focus their monitoring and response capacities following recent outbreaks, with more funding available for disease control, such as diphtheria. Conflict has brought Yemen back into the news, and international support has been provided to strengthen the vaccination campaigns and improve overall monitoring [31]. What are some of the issues facing surveillance systems? One of the main challenges identified is underreporting, especially in low-resource countries where access to healthcare is limited, with about sixty-three percent of country-years reporting no cases, meaning that there is no active monitoring and limited mechanisms in place, which makes it difficult to implement effective responses to potential threats from diseases such as Diphtheria [32]. Laboratory capacity varies: Laboratory facilities are not equally available to confirm diagnosis in different countries, and many low-income countries have limited access to laboratories. This, in turn, affects the overall quality and effectiveness of monitoring as suspected cases are not confirmed, resulting in lower percentages of suspected cases being confirmed [33]. Misinformation about vaccines, particularly on social media, is a key driver of declining trust in vaccination programs, which can lead to an increase in disease outbreaks and epidemics that are preventable by routine vaccination [34]. Effective communication strategies to address vaccine hesitancy require reaching communities, fostering confidence, and public health efforts that are effective at countering misinformation spread across populations [35]. Geopolitical Factors Affecting Healthcare Infrastructure: In some regions, the conflict and political instability have a significant effect on the provision of adequate services, which makes it difficult to perform routine activities necessary for the protection of vulnerable people from the threats of infectious agents such as Diphtheria [36]. Global health organizations should focus on supporting countries in conflict and political instability to ensure that service delivery continues even in the face of difficult situations, to maintain control of disease [37].

5. RECOMMENDATIONS

A number of recommendations can be made to reinforce diphtheria surveillance systems in the world: (1) Improving Data Collection Practices: To ensure that data is collected in a manner that allows for the comparability of data quality, nations need to standardize the reporting protocols used to collect data; training healthcare providers to understand the definitions and requirements that are necessary to ensure proper identification across all levels of healthcare delivery systems involved in the effective management of these infectious diseases [38]. Laboratory capacity building, laboratory training programs, resource allocation, and collaboration with regional laboratories can enhance the accuracy of laboratory diagnosis and the timeliness of laboratory results, ultimately increasing the effectiveness of monitoring activities within respective jurisdictions and in response to emerging situations requiring immediate attention. Mobile laboratories and telemedicine solutions can play a role in filling the gaps in rural areas and increasing access to key services needed to respond to new situations that require prompt action [39]. (2): Community Engagement Initiatives: Public health campaigns that raise awareness about the need for vaccination should be prioritized, with the involvement of community leaders, health workers, and community organizations to effectively address vaccine hesitancy and build trust in campaigns and activities that aim to protect populations at risk from diseases that are currently controlled using a vaccine [40]. Effective communication strategies designed to gain confidence and participation in programs to increase uptake among targeted populations most vulnerable to contracting diseases that can be prevented through routinely offered vaccines are essential at the local level. The use of Technology Surveillance: the integration of EHRs streamlines processes, supports real-time data, and ultimately improves efficiency and effectiveness of monitoring activities across jurisdictions involved in the management of infectious diseases such as diphtheria, with mobile applications allowing for community reporting of cases and ensuring timely responses when needed, improving overall coverage [41]. Strengthening Global Collaboration (3): Enhanced collaboration among nations facilitates sharing information regarding best practices management outbreaks, ensures uniformity standards are upheld globally, ultimately benefiting everyone involved in combating threats posed by infectious agents, effectively protecting vulnerable individuals and communities worldwide [42].

6. LIMITATIONS

There are some limitations to consider in this narrative review. First, there is inter-country variability in the quality of diphtheria surveillance data, due to differences in case definitions and data collection methods, which can limit comparability of data between regions. Secondly, there is a serious problem of underreporting, especially in low-resource areas with less-than-optimal surveillance systems and healthcare services. Third, there is limited published information on diphtheria surveillance in some areas, which may restrict this review. Last, the review includes a wide time frame (2000–2023), but emerging trends after 2020 may not be fully captured, as the

literature search was limited by the date of the publication of the literature, which could limit the representation of recent developments in diphtheria epidemiology and control.

CONCLUSION

This narrative review highlights the persistent problem of diphtheria in areas with low vaccination coverage and poor surveillance. Improving public health measures, tackling vaccine hesitancy, and enhancing health care systems are essential for diphtheria control worldwide. Countries can learn from best practices in successful areas to safeguard populations against this preventable disease.

AUTHORS' CONTRIBUTIONS

The authors confirm their contributions to this paper as follows: A.R.Y. and R.R.: The study conception and design were conducted; A.A.A.: Conceptualization was carried; E.A.: Methodology was developed; J.M.K.: Data collection was performed; K.H.: Analysis and interpretation of the results were conducted; and S.D.: The draft manuscript was prepared. All authors reviewed the results and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

AIR	=	Annual Incidence Rate
COVID-19	=	Coronavirus Disease 2019
DTP3	=	Diphtheria, Tetanus, Pertussis (three-dose primary vaccination series)
ECDC	=	European Centre for Disease Prevention and Control
GIS	=	Geographic Information System
JRF	=	Joint Reporting Form (WHO/UNICEF)
PAHO	=	Pan American Health Organization
UNICEF	=	United Nations International Children's Emergency Fund
WHO	=	World Health Organization

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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