

Original Research

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Abstract

Objectives: Diphtheria, a highly contagious disease that can be prevented through vaccination, is emerging in Khyber-Pakhtunkhwa, Pakistan, an area known for its instability, which presents a severe risk of becoming an epidemic. This is particularly concerning, as the Government of Pakistan intends to send (push back, actually) Afghan refugees back to Afghanistan. This research aims to study the outbreak from an epidemiological perspective and suggest ways to manage it.

Methods: The study uses data from the Khyber Pakhtunkhwa Department of Health Information System, which systematically collects data throughout the province.

Results: Data from the provincial District Health Information System showed 291 confirmed cases of diphtheria across 28 districts, highlighting the considerable public health challenge posed by the disease's capacity to spread widely. Among these, 16 cases were confirmed through laboratory tests, emphasizing the urgent need for better diagnostic services to identify diphtheria quickly and accurately. The research points out 4 specific outbreaks confirmed in laboratories in Batagram, Charsadda, Khyber, and Kohat, showcasing the broad geographic reach of the disease and the necessity for targeted public health initiatives in these areas.

Conclusions: By adopting a comprehensive and multi-faceted approach, there is a significant opportunity to reduce and ultimately eliminate the risk of diphtheria becoming an uncontrolled epidemic in the region.

Diphtheria is a vaccine-preventable disease¹ with a long and significant history. The recorded history of diphtheria can be traced back to the fifth century BCE,² in the writing of Hippocrates.³ While he did not specifically name the disease diphtheria, his descriptions of throat and respiratory symptoms in his writings, particularly in “Epidemics,” are thought to correspond to the clinical manifestations of diphtheria.³ Hippocrates' observations were crucial in the early understanding of the disease, although it was not formally identified and named until much later in history.³

The first notable descriptions of the diphtheria membrane, a characteristic feature of the disease, were not recorded until 1576 by the French physician Guillaume de Baillou.⁴ The disease became more clearly defined in the 19th century.⁵ In 1826, Pierre Bretonneau distinguished diphtheria from other diseases, such as scarlet fever.⁵

Bacterium Discovery

In 1883, Edwin Klebs identified the causative bacterium, and Friedrich Loeffler further confirmed this in 1884, isolating *Corynebacterium diphtheriae*.⁶ Emil von Behring developed the first effective treatment, the diphtheria antitoxin, in the 1890s, for which he received the first Nobel Prize in Physiology or Medicine in 1901.⁷ The introduction of the diphtheria vaccine in the early twentieth century, particularly the Diphtheria-tetanus-pertussis (DTP) vaccine, significantly reduced the incidence of the disease.⁸ This historical context underscores the longstanding challenge of diphtheria as a public health issue, evolving from ancient descriptions to more detailed understandings in later centuries.

Diphtheria's history reflects the profound impact of medical advancements in infectious diseases and immunology, transforming it from a feared disease into a preventable condition. Although controlled mainly in many parts of the world due to widespread vaccination, diphtheria still poses a threat, particularly in areas with inadequate vaccination coverage.⁹ Diphtheria is a highly contagious vaccine-preventable disease. The disease can be fatal in 5–10% of cases,¹⁰ with a higher mortality rate in young children. In areas with poor access to diphtheria antitoxin, the crude fatality rate (CFR) can be as high as 40%.¹¹

Despite the availability of vaccines for diphtheria, developing countries still face diphtheria outbreaks. The most recently communicated outbreak by the World Health Organization (WHO) was in October 2023 in Guinea.¹² According to a study¹² during the period extending from July 4 to October 13, 2023, the Kankan region in Guinea experienced a fatal outbreak of diphtheria. The total reported cases amounted to 538, encompassing 520 suspected and 18 laboratory-confirmed instances of the disease. This outbreak culminated in 58 fatalities, of which 13 were among the confirmed cases. Consequently, this led to an overall case fatality rate (CFR) of 11% across all reported cases. Notably, the demographic group most affected by this outbreak was 1-4 years, constituting the most significant proportion of the cases. Recently, an outbreak of diphtheria has prevailed in one of the most volatile regions of the world, Khyber-Pakhtunkhwa, Pakistan,¹³ and there is a risk of an epidemic, as the government of Pakistan is making all arrangements to send Afghan refugees back to Afghanistan. This risk is exacerbated by the ongoing efforts of the Pakistani government to repatriate Afghan refugees back to Afghanistan, which could further destabilize the already precarious public health situation. In this regard, this study aimed to epidemiologically assess the situation and put forward recommendations to tackle the issue. The assessment study covers various factors including the demographic and geographic distribution of cases, the rate of infection, and the effectiveness of current public health measures. Additionally, it analyzes the impact of refugee movements on the spread of the disease and identifies high-risk populations that require immediate attention.

The findings of this study are crucial for informing public health strategies and interventions. Recommendations are put forward to tackle the issue effectively, focusing on both short-term emergency responses and long-term preventative measures. Furthermore, the study explores the potential for international cooperation and assistance, as the outbreak has implications that transcend national borders. The role of international organizations, non-governmental organizations, and neighboring countries is considered in forming a coordinated response to the diphtheria outbreak. By addressing both the immediate and underlying causes of the outbreak, this study aims to contribute to the broader goal of improving health outcomes and resilience in one of the world's most vulnerable regions.

Methodology

Study Area

Located in Pakistan's northwest, Khyber Pakhtunkhwa is one of the nation's 4 administrative provinces despite being the smallest in geography. It comprises 7 divisions and 26 districts. From 1998 to 2017, the population of this province grew from 17.7 million to 30.5 million, as per the latest census figures, surpassing the national growth rate with a 2.89% increase compared to Pakistan's overall rate of 2.40%.¹⁴ Predominantly rural, 81% of its inhabitants live in the countryside,¹⁴ although there are several densely populated cities, such as Peshawar, home to 2.1 million people. Additionally, it is estimated that over 3 million Afghan refugees have settled in the province.¹⁵ Khyber Pakhtunkhwa has experienced years of conflict and political turmoil, leading to significant economic and social development challenges. The region's economy has suffered due to refugee inflow, ongoing violence, and persistent insecurity.¹⁶

Generally, the health outcomes within South Asia and East Asia, Pakistan, notably its Khyber Pakhtunkhwa province, having a long border with Afghanistan, exhibit suboptimal performance.¹⁷ The existing health care system in this region demonstrates several critical deficiencies: inadequate accessibility and utilization of health services, compromised quality and efficacy of medical care, limited managerial competencies coupled with frail accountability mechanisms across various levels, systemic underinvestment in public health infrastructure, inefficient and inequitable distribution of health care resources, diminished financial safeguards for health care expenditures, and a pattern of fragmented and sporadic health care reforms.¹⁷ These factors contribute to the province's daunting challenge in realizing the Sustainable Development Goals. According to the Khyber Pakhtunkhwa Health Survey 2017, while 67.5% of childbirths occur in medical facilities, merely 26.8% of these cases involve postnatal stays exceeding 12 hours. Furthermore, the province exhibits alarming mortality statistics: a neonatal mortality rate of 41 per 1000 live births, an infant mortality rate of 58 per 1000 live births, and a maternal mortality ratio of 206 per 100 000 live births.

Pediatric immunization coverage in children aged 12-23 months is 55.5%, ascertained through medical records and maternal recollections, yet 17.3% of children aged 0-23 months remain unvaccinated. Additionally, over 40% of women in the province face nutritional health challenges, indicating a significant public health concern in maternal and child health domains. In children under 5 years of age, the prevalence of malnutrition is markedly high: 24% are underweight, 48% exhibit stunted growth, and 17% are categorized as wasted. These figures underscore significant public health challenges, highlighting the urgent need for targeted interventions.

Case Definition

This study uses data from the Government of Khyber Pakhtunkhwa Department of Health Information System (KP DHIS) and, therefore, needs to follow their standard case definition of Diphtheria. Details of all suspected measles cases reported to the national measles case-based surveillance system managed by the Department of Health were analyzed. A suspected measles case was defined as per the case definition of Diphtheria enacted by the Government of Khyber Pakhtunkhwa on the September 6 2017, under Notification Number SOH (E&A) 2-65/Vol II/2017, by the authority vested by subsection (n) of Section 2 of the Khyber Pakhtunkhwa Public Health (Surveillance and Response) Ordinance, 2017, the following definition of "Diphtheria" is at this moment decreed:

"Diphtheria Case Definition: Any individual exhibiting symptoms of an upper respiratory tract illness, distinctly characterized by the presence of an adherent membrane located on the tonsils, pharynx, and nose, accompanied by at least 1 of the following clinical manifestations: laryngitis, pharyngitis, or tonsillitis."

The DHIS functions as a pivotal data aggregation and analysis system within the KPK health care system, methodically curating data from Basic Health Units (BHUs), Rural Health Centres (RHS), Tehsil Headquarters Hospitals (THQs), and District Headquarter Hospitals (DHQs), which span the entirety of Khyber Pakhtunkhwa province. With a robust mechanism and human resource system, the DHIS rigorously scrutinizes incoming data to ensure the triad of quality, relevance, and timeliness.

Ethical Statement

The data used in this study didn't have any identifying information of the patients and hence it does not require a full review by the ethical board. All necessary permissions and consents were obtained from the data holders before the commencement of the study.

Study Design

This study adopted a retrospective design to estimate both the prevalence and the incidence rate of diphtheria in Khyber-Pakhtunkhwa (KPK), Pakistan. By analyzing historical data collected from medical records, health surveys, and regional health department reports, the study aimed to provide a comprehensive overview of the disease's impact over a specified period. The retrospective study approach involved systematically reviewing patient records from hospitals and clinics across KPK, identifying confirmed cases of diphtheria, and extracting relevant information such as patient demographics, clinical characteristics, and outcomes. This methodology enabled the researchers to calculate the prevalence rate, which indicates the proportion of the population affected by diphtheria at a specific point in time, as well as the incidence rate, which measures the number of new cases occurring within a given time frame.

In addition to prevalence and incidence rates, the study also sought to identify potential risk factors associated with diphtheria infection. This included examining variables such as age, gender, socioeconomic status, vaccination history, and geographic location. Understanding these risk factors is crucial for developing targeted public health interventions and improving disease prevention strategies. Furthermore, the retrospective study design allowed for the assessment of temporal trends in diphtheria cases, providing insights into how the disease has evolved in KPK. This information

is vital for evaluating the effectiveness of past and current public health measures and identifying areas where additional efforts are needed. By accurately estimating the prevalence and incidence rates, the study aims to highlight the burden of diphtheria in the region and underscore the urgent need for enhanced surveillance, vaccination campaigns, and health care infrastructure improvements to mitigate the impact of this potentially deadly disease.

Results and Discussion

This study uses the District Health Information System platform to investigate the spread of diphtheria in Khyber Pakhtunkhwa, Pakistan, up to the forty-fourth week of 2023. Data collected from the entire province through the District Health Information System recorded 291 confirmed cases spanning 28 districts. The extensive distribution of cases across the region signals a significant health concern, underscoring the disease's capacity for widespread transmission within the province. Of these cases, 16 have been verified through laboratory testing, highlighting the urgent need to enhance diagnostic capabilities for the swift and accurate identification of diphtheria. The research pinpointed 4 specific outbreaks, confirmed by lab tests, in Batagram, Charsadda, Khyber, and Kohat districts. These occurrences illustrate the disease's diverse geographical spread and underscore the necessity for targeted public health initiatives across various parts of the province. Further details are presented in Figure 1.

While Peshawar reports a higher absolute number of cases (68), an analysis based on the incidence rate reveals that Kohat (21.3/million) and Battagram (14.7/million) have the highest number of cases when adjusted for population size. This discrepancy arises because Peshawar, a metropolitan city, boasts the highest population density compared to other districts in the province. Additionally, Peshawar's proximity to the Torkham

Geographical Distribution -Diphtheria Cases 2023 in Khyber Pakhtunkhwa

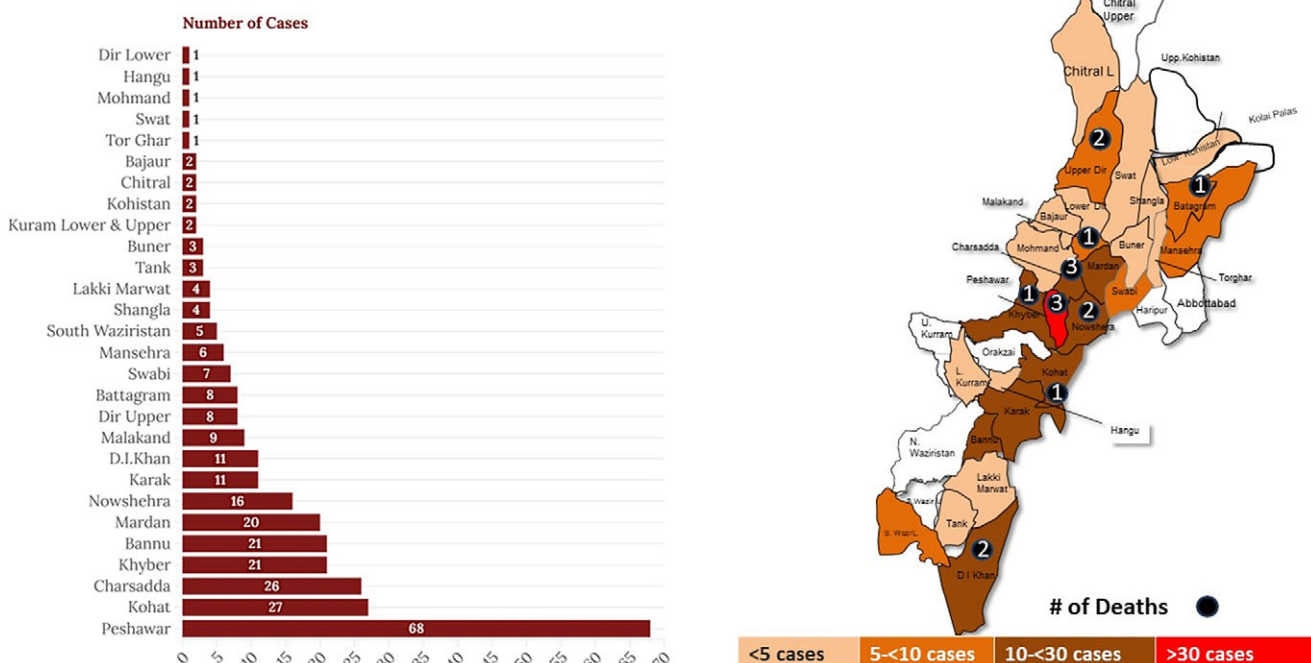


Figure 1. The Number of Cases Reported from Each District in KPK-Pakistan.

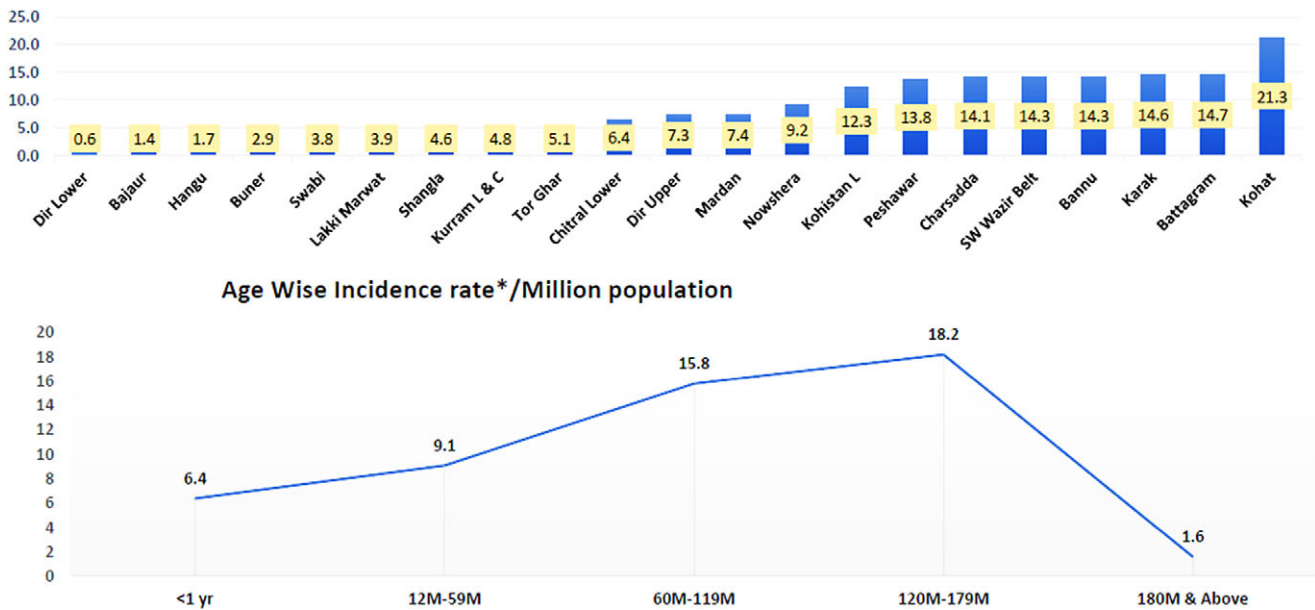


Figure 2. Diphtheria Incidence Rate in Each KPK's District (per million).

border crossing, a mere 45 km away, significantly influences disease transmission dynamics. This major border crossing between the Pakistani city of Torkham and Afghanistan, situated along the Grand Trunk Road, connects Afghanistan's Nangarhar province with Pakistan's Khyber Pakhtunkhwa province. As the busiest port of entry between the 2 countries, it is a critical hub for transport, shipping, and receiving. However, geopolitical complexities render the actual control of the border less effective than desired. Consequently, monitoring and regulating the movement of people across the border is challenging, complicating efforts to achieve 100% vaccination coverage in the area. This lack of effective border control and vaccination coverage contributes to not only the persistence of diphtheria but also the recurrence of polio cases in the region. The incidence rates per million in each district are detailed in Figure 2, offering a clearer understanding of the disease's distribution and highlighting the need for targeted public health strategies in these areas.

The study also reveals a concerning trend of a lack of Diphtheria-Pertussis-Tetanus (DPT) vaccination history in 89% of the cases, spanning all age groups. This underscores a widespread shortfall in the local vaccination program, missing a crucial chance for preventive health measures. The primary age group affected comprises individuals aged 5 years and older, constituting 81% of the cases. Ages span from 7 months to 68 years. The predominance of diphtheria cases in individuals aged 5 years and older challenges the common perception that diphtheria predominantly affects children. This finding necessitates a re-evaluation of target groups for vaccination campaigns, emphasizing the importance of community-wide immunity to protect individuals of all ages. The broad age range of affected individuals, from infants to the elderly, further underscores the universal susceptibility to diphtheria in the absence of vaccination, necessitating efforts to boost coverage universally rather than focusing solely on children.

With a case fatality rate (CFR) of 5%, translating to 16 deaths, the severity and potential fatality of the disease are highlighted. The case fatality rate of 5% is a stark reminder of the lethality of diphtheria, an illness that is preventable with adequate vaccination.

The loss of 16 lives to a preventable disease is a tragic outcome that highlights the urgent need for enhanced public health measures. Strategies such as improving vaccine supply chains, increasing awareness about the importance of vaccinations, and implementing more effective outreach programs to reach underserved communities could significantly mitigate the risk of further outbreaks.

The glaring lack of Diphtheria-Pertussis-Tetanus (DPT) vaccination coverage not only puts individuals at risk of contracting these potentially fatal diseases but also reflects a more significant systemic failure in public health infrastructure and outreach. The high percentage of unvaccinated individuals across all age groups signals a considerable lapse in vaccination efforts, which could be attributed to various factors such as accessibility, awareness, and vaccine hesitancy among the population. Moreover, these findings suggest the need for continuous surveillance and research to understand the dynamics of vaccine-preventable diseases in different populations and regions. Such efforts can help identify gaps in immunity, understand disease transmission patterns, and tailor interventions to the specific needs of communities. Public health authorities must also combat misinformation about vaccines, which can contribute to vaccine hesitancy and lower vaccination rates.

The shortcomings identified in the initial analysis have far-reaching consequences for public health management, particularly in controlling infectious diseases like diphtheria. The delay in accessing specialized health care services jeopardizes patient outcomes and increases the likelihood of disease transmission. The inadequate implementation of Infection Prevention and Control (IPC) measures in medical settings poses a significant risk, turning hospitals into potential hotspots for diphtheria spread. Furthermore, the slow pace of on-the-ground investigations and response rollouts hampers timely intervention, allowing the disease to gain a stronger foothold in affected communities. Lastly, neglecting to provide prophylactic antibiotics to close contacts of confirmed cases overlooks a critical preventive strategy, thereby missing an opportunity to break the chain of transmission effectively.

Discussion

Existing literature highlights a general issue in low-resource settings,¹⁸ such as Khyber Pakhtunkhwa, Pakistan, with delayed case identification for infectious and non-infectious diseases.¹⁹ Individuals with symptoms resembling tonsillitis often seek medical assistance too late, increasing the likelihood of misdiagnosis.¹⁸ This delay contributes to a higher transmission rate and a lower rate of laboratory confirmations and leads to more complicated disease progressions, underlining the importance of timely and accurate diagnoses.^{18–20} The typical response to investigating diseases like diphtheria is often inadequate, with health care efforts usually concentrated on immediate or nearby areas, failing to halt the disease's spread effectively.

One specific concern is vaccination coverage among children who have not received any doses. Second-dose vaccinations are frequently not. Face challenges in compliance among adults. The age group most affected by this outbreak was school-going children, highlighting how the disease can spread across areas. Furthermore, vaccinated children who have not received diphtheria booster doses are still susceptible to the disease. Accessing anti-diphtheria serum (ADS) remains challenging, as it is primarily available at points. Another challenge arises regarding providing antibiotics. Communities sometimes resist using them unless symptoms are present, and cost is also a concern. Additionally, at the district level, resources may not be enough to offer antibiotics for free, leading to periods of infectiousness.

Lastly, ensuring the availability of prophylactic antibiotics for close contacts of confirmed cases is essential in controlling the spread of diphtheria.²¹ This strategy helps to prevent asymptomatic carriers from transmitting the disease to susceptible individuals, cutting off the chain of transmission.⁹ Implementing these recommendations requires coordinating efforts among public health authorities, health care providers, and the community. Public awareness campaigns should complement these measures, emphasizing the importance of vaccination and early treatment-seeking behaviour. Additionally, collaboration with international health organizations can provide the necessary technical and financial support to bolster the region's diphtheria control efforts.²² The situation in Khyber Pakhtunkhwa serves as a reminder of the ongoing threat posed by vaccine-preventable diseases and the continuous need for vigilance and proactive public health measures.

Conclusion

The imperative need for a comprehensive strategy to combat the resurgence of diphtheria in Khyber Pakhtunkhwa is evident from the findings. A multi-faceted approach, as recommended, is essential to strengthen the region's capacity to effectively prevent and control diphtheria outbreaks. Each proposed recommendation plays a critical role in a holistic diphtheria control strategy. Enhancing immunization coverage is paramount. Integrating booster doses into the Expanded Programme on Immunization (EPI) schedule addresses a critical gap in the current vaccination strategy. This move would help maintain immunity among the population and protect against the potential waning of immunity over time. Targeting all age groups, focusing on the most affected demographics, is essential to ensure comprehensive coverage. Strengthening diagnostic and laboratory capacities is another critical recommendation. Quickly and accurately identifying diphtheria cases is

fundamental to controlling an outbreak. Enhanced laboratory capacities ensure timely diagnosis, enabling health authorities to implement targeted interventions swiftly. This also involves training health care workers in recognizing the symptoms of diphtheria and managing cases effectively, which is vital for early detection and containment.

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Author contribution. Junaid Ahmad: Conceptualization, Methodology, Writing- Original draft preparation.

Abdul Latif, Muhammad Sulaiman, Kamran Khan: Data collection and curation.

Muhammad Yasar Shah: Writing- Reviewing and Editing.

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