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Smallpox Re-Emergence Risk and Global Preparedness: A Comprehensive Review

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Abstract— Smallpox, once a highly lethal infectious disease, was successfully eradicated in 1980 through global vaccination efforts. However, concerns regarding its potential re-emergence persist due to bioterrorism threats, declining population immunity, and advances in synthetic biology. This study reviews the historical significance, epidemiology, transmission dynamics, and current prevention strategies associated with smallpox. It also highlights the role of vaccination, ring vaccination, and case isolation in outbreak control, along with recent advancements in antiviral therapies such as tecovirimat. Despite these developments, several research gaps remain, including limited data on long-term immunity, vaccine safety, and real-world effectiveness of antiviral treatments. The study emphasizes the need for improved surveillance systems, safer vaccines, and strengthened global preparedness to mitigate future risks associated with smallpox and related orthopoxvirus infections.

Keywords: Smallpox, Variola virus, Epidemiology, Vaccination, Antiviral therapy, Biosecurity, Orthopoxvirus, Public health preparedness.

I. INTRODUCTION

Smallpox, caused by the variola virus, was one of the most severe infectious diseases in human history, responsible for widespread morbidity and mortality across centuries. Characterized by high fever and a distinctive pustular rash, the disease had a fatality rate of up to 30% in its most severe form. The global eradication of smallpox in 1980, led by coordinated efforts of international health organizations and mass vaccination campaigns, remains one of the greatest achievements in public health [1]. This success demonstrated the effectiveness of vaccination, surveillance, and containment strategies in controlling infectious diseases on a global scale.

Despite its eradication, smallpox continues to be of significant concern in the modern era. The variola virus is still retained in high-security laboratories, and the possibility of its accidental or intentional release raises serious biosecurity issues [2]. Furthermore, advancements in synthetic biology have made it technically feasible to reconstruct viruses, increasing the potential risk of smallpox re-emergence. Another major concern is the declining immunity of the global population, as routine vaccination programs were discontinued following eradication, leaving a majority of individuals susceptible to infection [3].

In addition to these concerns, the emergence and spread of related orthopoxviruses, such as monkeypox, have highlighted the changing dynamics of infectious diseases in the post-smallpox era. Increased global travel, urbanization [4], and a growing number of immunocompromised individuals contribute to the potential for rapid disease transmission and outbreaks. These factors underscore the importance of maintaining preparedness against possible re-emergence [5].

Current research focuses on strengthening preventive and control measures, including the development of safer vaccines, antiviral therapies, and improved diagnostic tools [6]. Strategies such as ring vaccination, case isolation, and rapid response mechanisms remain central to outbreak management. Moreover, advancements in antiviral drugs, such as tecovirimat, provide additional options for treatment and containment [7].

This study aims to review the historical context, epidemiology, prevention strategies, and recent advancements related to smallpox, while identifying key research gaps and future directions. Understanding these aspects is essential for enhancing global preparedness and ensuring effective response to potential threats posed by smallpox and related infectious diseases in the future.

II. LITERATURE REVIEW

2.1 Smallpox: History, Eradication and Current Threat

Smallpox has historically been one of the most devastating infectious diseases, responsible for millions of deaths globally before its eradication in 1980 through coordinated international vaccination efforts. The disease, caused by the variola virus, exhibited high mortality rates, particularly with variola major strains, which had fatality rates of approximately 30% [8]. The global eradication program led by international health organizations demonstrated the effectiveness of mass vaccination and surveillance strategies in eliminating a disease

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that had persisted for centuries. Despite eradication, the virus remains preserved in high-security laboratories, and concerns persist regarding its potential misuse as a biological weapon or accidental release [9]. Additionally, advancements in synthetic biology have raised the possibility of reconstructing the virus artificially, thereby reintroducing risks associated with smallpox in the modern era .

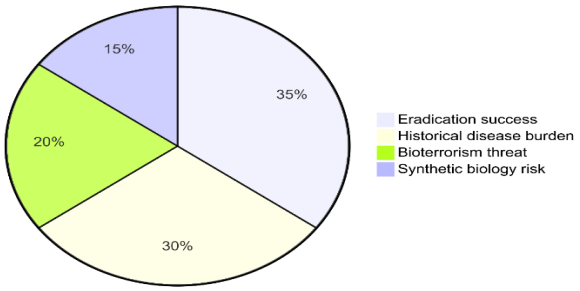

Figure 1. History, Eradication and Current Threat

Figure 1 illustrates the distribution of key themes related to the historical impact, eradication, and present-day risks of smallpox. The largest proportion is attributed to eradication success, highlighting the global achievement of eliminating the disease through coordinated vaccination programs. A significant portion also represents the historical disease burden, reflecting the widespread mortality and societal impact of smallpox before eradication. The chart further emphasizes ongoing concerns such as its potential use as a bioterrorism agent and the emerging risks associated with synthetic biology, which may enable reconstruction of the virus. Overall, the figure demonstrates that while smallpox has been eradicated, it continues to remain relevant due to modern technological and security concerns.

2.2 Epidemiology, Transmission and Re-emergence Risks

Although smallpox no longer occurs naturally, its epidemiological significance remains relevant due to the increasing susceptibility of the global population [10]. Following the cessation of routine vaccination, a large proportion of the population lacks immunity, making societies vulnerable to potential outbreaks. Transmission of the virus occurs primarily through respiratory droplets during close contact, with an incubation period of around 12 days followed by systemic symptoms and a characteristic rash [11]. Modern global conditions, including increased international travel and higher proportions of immunocompromised individuals, could facilitate rapid spread in the event of re-emergence. Furthermore, related orthopoxviruses such as monkeypox have shown increasing incidence and geographical spread, suggesting that ecological niches vacated by smallpox may be occupied by similar pathogens, thereby posing additional public health challenges [12].

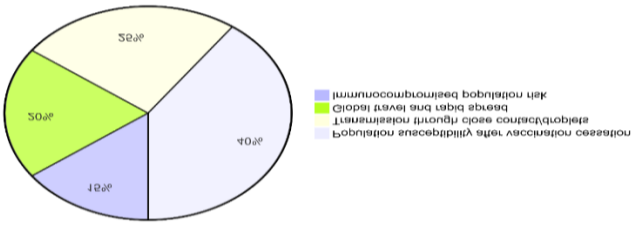

Figure 2. Epidemiology, Transmission and Re-emergence Risks

Figure 2 presents the major epidemiological factors contributing to the potential re-emergence of smallpox. The dominant segment reflects increased population susceptibility due to the discontinuation of routine vaccination programs, leaving a large proportion of individuals unprotected. Transmission through respiratory droplets during close contact is another important factor highlighted in the chart. Additionally, globalization and increased international travel contribute significantly to the rapid spread of infectious diseases. The figure also accounts for the growing number of immunocompromised individuals, which further elevates vulnerability. Collectively, these factors indicate that the risk of re-emergence, although theoretical, could have serious global health implications.

2.3 Prevention and Control Strategies

Vaccination remains the most effective strategy for preventing and controlling smallpox outbreaks. Historical evidence demonstrates that widespread immunization, combined with surveillance and containment measures such as case isolation and ring vaccination, can effectively interrupt transmission chains. Modeling studies indicate that early intervention, high rates of case detection, and rapid vaccination of contacts are critical in minimizing outbreak duration and healthcare burden. However, vaccination is not without risks, as adverse effects including dermatological and neurological complications have been reported. Current research efforts focus on developing safer vaccines and improving production techniques using modern cell culture methods. In addition to vaccines, public health preparedness plans emphasize rapid response mechanisms, healthcare system capacity strengthening, and strategic stockpiling of vaccines to mitigate the impact of any future outbreaks [13] .

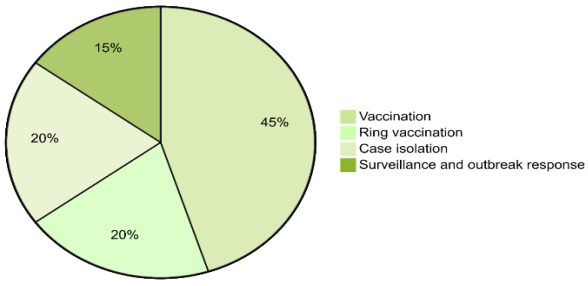

Figure 3. Prevention and Control Strategies

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Figure 3 depicts the relative importance of various prevention and control strategies for managing smallpox outbreaks. Vaccination constitutes the largest share, reaffirming its role as the most effective intervention in preventing disease transmission. Ring vaccination and case isolation are also prominently represented, as they are critical components of outbreak containment strategies. Surveillance and rapid response mechanisms are included as essential supportive measures to ensure early detection and timely intervention. The figure highlights that a combination of these strategies, rather than a single approach, is necessary for effective outbreak control and public health preparedness [14].

2.4 Advances in Treatment and Future Preparedness

Recent advancements in antiviral drug development have enhanced preparedness against potential smallpox outbreaks. The approval of antiviral agents such as tecovirimat and Brin cidofovir represents a significant milestone in biosecurity, providing therapeutic options in the absence of naturally occurring cases. These drugs have demonstrated efficacy against orthopoxviruses in both laboratory and animal studies, addressing challenges associated with clinical testing for eradicated diseases. Additionally, research into alternative antiviral compounds and bioavailability studies continues to expand treatment options. The development of diagnostic tools, improved surveillance systems, and integration of antiviral therapies into emergency response plans are essential components of future preparedness. Given the evolving landscape of infectious diseases and technological advancements, continuous research and global collaboration remain critical to effectively manage and mitigate the risks associated with smallpox and related pathogens [14].

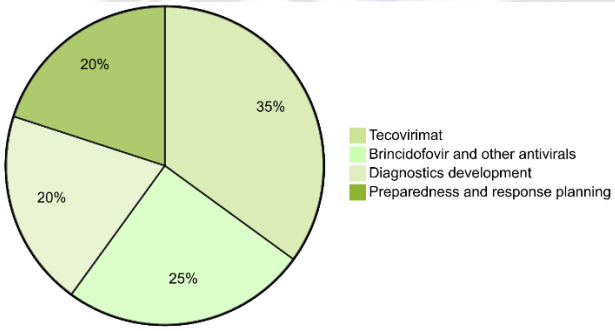

Figure 4. Advances in Treatment and Future Preparedness

Figure 4 illustrates the key areas of advancement in treatment and preparedness against smallpox. The largest segment represents the antiviral drug tecovirimat, reflecting its importance as a primary therapeutic option. Other antiviral agents, including Brin cidofovir, also contribute significantly to treatment strategies. The development of diagnostic tools is highlighted as a crucial component for early detection and response. Additionally, preparedness planning, including stockpiling of drugs and development of response frameworks, forms an essential part of future strategies. This figure emphasizes the shift from eradication-focused efforts to preparedness and response in the modern era.

III. RESEARCH GAP

Despite extensive research on smallpox eradication, epidemiology, and control strategies, several critical gaps remain that require further investigation. First, although smallpox has been eradicated globally, there is limited contemporary data on population immunity levels, especially in regions where vaccination ceased decades ago. The long-term immunity provided by earlier vaccinations and its effectiveness against potential re-emergence or related orthopoxviruses is still not fully understood.

Second, while modeling studies have explored outbreak scenarios, there is insufficient real-world validation of these models in diverse and resource-limited settings. Existing studies often focus on theoretical simulations, and there is a lack of region-specific preparedness assessments, particularly in densely populated countries where healthcare infrastructure may be challenged during outbreaks.

Third, although vaccination remains the primary preventive measure, concerns regarding vaccine safety and adverse effects persist. Current research has not fully addressed the development of safer, more effective vaccines with minimal side effects, especially for vulnerable populations such as immunocompromised individuals.

Fourth, advancements in antiviral therapies such as tecovirimat have shown promising results; however, clinical data in human populations are limited due to the absence of naturally occurring cases. This creates uncertainty regarding their real-world effectiveness, optimal dosing strategies, and long-term safety profiles.

Additionally, emerging risks associated with synthetic biology and the potential reconstruction of variola virus have not been adequately addressed in terms of global regulatory frameworks and biosecurity preparedness. There is also a lack of integrated surveillance systems that combine traditional epidemiological methods with modern technologies for early detection of outbreaks.

Finally, limited research has been conducted on the interaction between smallpox preparedness and other emerging infectious diseases, such as monkeypox, which may occupy similar ecological niches. Understanding these interactions is essential for developing comprehensive and adaptable public health strategies.

IV. CONCLUSION AND FUTURE WORK

Smallpox remains a significant subject of research despite its global eradication, primarily due to its potential re-emergence through bioterrorism or advances in synthetic biology. The literature highlights the importance of vaccination, surveillance, and rapid response strategies in controlling outbreaks.

Additionally, recent developments in antiviral therapies and diagnostic tools have strengthened preparedness against potential threats. However, gaps in immunity assessment, vaccine safety, and real-world validation of treatment strategies indicate the need for continued research.

Future work should focus on developing safer and more effective vaccines, improving global surveillance systems, and validating antiviral drugs through advanced experimental models. There is also a need to enhance biosecurity frameworks to address risks associated with synthetic reconstruction of viruses. Furthermore, integrating modern technologies such as artificial intelligence in outbreak prediction and response planning can improve preparedness. A multidisciplinary and globally coordinated approach will be essential to mitigate future risks associated with smallpox and related infectious diseases.

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