International Journal of Research in MEDICAL SCIENCE

ISSN Print: 2664-8733
ISSN Online: 2664-8741
IJRMS 2024; 6(2): 01-06
www.medicalpaper.net
Received: 03-05-2024
Accepted: 05-06-2024

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The inevitable menace of influenza: A looming global threat

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DOI: https://doi.org/10.33545/26648733.2024.v6.i2a.64

Abstract
Influenza remains a persistent global threat, with pandemic potential posing substantial health risks. Ongoing global surveillance of emerging influenza strains is crucial to pre-empting future crises. This exploration emphasizes the necessity for preparedness, focusing on surveillance, vaccine development, and international collaboration to mitigate influenza transmission. While vaccination is pivotal in pandemic control, ensuring rapid vaccine availability during outbreaks remains challenging. Advances in novel vaccine technologies offer promising solutions for scalable production under pandemic conditions. This review consolidates influenza's historical impact and ongoing evolution, presenting complex challenges from seasonal epidemics to potential pandemic outbreaks. Vigilant surveillance of evolving strains, including avian influenza variants like H5N1, H7, and H9, is essential for effective preparedness. The World Health Organization plays a central role in coordinating global influenza surveillance, guiding vaccine strategies, and facilitating rapid response efforts worldwide. Collaborative efforts across national and international health sectors are critical to enhancing global readiness against influenza pandemics through proactive vaccine development, surveillance capabilities, and robust public health preparedness initiatives.

Keywords: Influenza, global health emergency, surveillance, vaccine development, international collaboration, vaccine availability, novel influenza vaccines, public health cooperation

Introduction
Influenza, or the flu, is a highly contagious respiratory illness caused by the influenza virus, an RNA virus in the Orthomyxoviridae family [1]. It annually leads to 3–5 million severe cases and up to 300,000 deaths, primarily impacting vulnerable populations worldwide [2]. Although influenza pandemics are rare, they are significant global events occurring approximately every 10 to 50 years, with notable outbreaks in 1918, 1957, and 1968, the deadliest being the 1918 Spanish flu with 50 to 100 million deaths. Influenza viruses evolve rapidly due to mutations, resulting in new viral strains each year [3]. This mutation complicates vaccine development, necessitating regular updates to match circulating strains. Public health measures, ongoing research, and global surveillance are critical for monitoring influenza patterns, sharing viral strain data, and coordinating outbreak responses [4]. Historically, influenza epidemics have been documented since the 12th century, often named after their presumed origin [5]. The first use of maps to track influenza spread occurred during the 1889-1890 pandemic, highlighting the virus's global impact and the need for coordinated responses [6]. Global cooperation through organizations like the World Health Organization and its influenza surveillance network plays a vital role in monitoring influenza worldwide, facilitating annual exchanges of isolated strains to support vaccine development. Influenza's dynamic nature is underscored by its high mutation rate, leading to antigenic drift with minor changes over time and antigenic shift involving major changes from re-assortment, potentially causing pandemics when novel strains emerge. Understanding influenza's history, evolution, and ongoing surveillance is crucial for effective public health strategies. Preparedness efforts such as vaccination campaigns and rapid response capabilities are essential to mitigate the impact of future outbreaks [7]. The 1968 pandemic, caused by the H3N2 virus (A/Hong Kong influenza), exhibited significant antigenic shift with a major change in the H surface protein while retaining the N2 neuraminidase [8].

Compared to the 1957 pandemic, the spread of H3N2 was less severe, partly due to cross-immunity from antibodies against the shared N2 neuraminidase with the earlier H2N2 strain [9]. Serological studies indicate connections between pandemic strains, with H proteins of the 1957-1958 (H2) and 1968-1969 (H3) outbreaks resembling those from earlier occurrences [10]. Influenza's interaction with animals, such as horses in 1889-1890 and pigs in 1918, underscores the potential for cross-species transmission and the importance of monitoring both human and animal strains [11]. Avian influenza is particularly concerning due to its ability to cross species barriers and infect humans, necessitating ongoing surveillance and collaboration to effectively monitor and respond to influenza threats [12]. Research highlights genetic re-assortment involving animal and avian influenza viruses in the evolution of pandemic strains, highlighting the interconnected nature of influenza across species and the potential for the emergence of novel viruses [13]. Understanding these dynamics is crucial for global health preparedness against future influenza outbreaks and pandemics. It has been proposed that this adaptation may have occurred with pigs serving as an intermediary host. Nonetheless, there is still limited direct evidence of avian viruses infecting humans. The presence of an antibody response implies some replication of the virus in humans, even though this may be limited and inadequate for further transmission. As most of these subtypes have yet to be detected in pigs, it seems probable that birds are infecting humans directly, implying that there would be an opportunity for reassortment to occur directly in humans with existing human strains. This has been further substantiated by the recent H5N1 and H9N2 infections in humans in Hong Kong. Additionally, beyond the reassortment and direct transfer theories, there exists the possibility that only specific H subtypes (such as H1, H2, H3) have the potential to cause epidemics in humans, as demonstrated by the reappearance of these subtypes over the past century. This hypothesis is supported by studies of antibodies found in the blood of individuals World Health Organization lived through previous pandemics [14]. Serological data suggests that the pandemic viruses in 1889 and 1900 had H2 and H3 hemagglutinins, respectively, akin to those in the 1957 and 1968 pandemic viruses. Similarly, the 1977 resurgence of type A(H1N1) featured hemagglutinin and neuraminidase genes identical to those from the 1950 virus, suggesting these subtypes may persist in animals or via other mechanisms between pandemics [15]. It is indeed challenging to explain the striking similarity between the 1977 and 1950 type A(H1N1) viruses without considering the concept of "dormancy," which theoretically suggests a third possible mechanism for the emergence of pandemic influenza viruses, despite uncertainties about how influenza viruses could remain dormant for extended periods. However, it is important to acknowledge the potential for a major antigenic drift to cause a pandemic, as observed to a limited extent in 1947 with the A (H1N1) strains [16].

Discussion

Regarding prevention and control of influenza, vaccination has been pivotal. By the end of the last century, the concept of inducing resistance to communicable diseases through vaccination with attenuated live germs or extracts from dead organisms had gained traction following Pasteur's success with the rabies vaccine [17]. During the 1918 influenza pandemic, numerous flu vaccines were developed, though initially lacking significant immunological efficacy. Valid immunization results began emerging after the discovery of the influenza virus in 1933, particularly with Macfarlane Burnet's 1937 demonstration of immunogenic live vaccine [18]. The urgency for an influenza vaccine escalated during World War II, spurred by the devastating impact of the 1918 pandemic on military forces [19]. Burnet in Australia focused on developing a live vaccine, while the U.S. military pursued an inactivated vaccine approach, achieving promising results by 1943 [20]. Methods for large-scale production of killed vaccines were subsequently developed, supported by the establishment of a central reference laboratory in the United States to study and compare virus strains. Influenza vaccines operate by triggering the production of antibodies against the virus's surface H and N antigens, which in turn lowers its ability to replicate. However, vaccine-induced antibodies are specific to the antigens used in the vaccine, offering protection only against viruses with similar antigens. Even natural antibodies acquired from previous flu exposures wane over time [21]. Experience with vaccines has shown high levels of protection, typically ranging from 70% to over 90% in healthy individuals, reducing mortality and serious illness while contributing to herd immunity [22]. The ongoing challenge remains to update vaccines to match circulating virus strains due to antigenic drift, ensuring efficacy against evolving influenza viruses. Determining the optimal vaccine composition to combat influenza has long been a challenging endeavor in public health. While including as many strains as possible in vaccines would provide broader protection, practical considerations such as ensuring adequate viral antigen mass for effectiveness must be weighed [23]. In 1966, it was recommended not to exceed two strains of influenza A and two strains of influenza B in the vaccine [24]. Alternatively, composite vaccines containing strains from previous epidemics and pandemics were also considered, some containing up to seven strains. World Health Organization plays a pivotal role in selecting influenza vaccine strains annually, gathering representatives from its Collaborating Centers for Influenza Reference and Research, as well as regulatory bodies like the United States Food and drug administration, Australian Therapeutic Goods Administration, and British National Institute for Biological Standards and Control. This selection process, initiated in February each year since 1973, aims to identify viruses with epidemic potential.

For instance, for the 2000–2001 northern hemisphere influenza seasons, World Health Organization recommended a trivalent vaccine comprising strains such as A/Moscow/10/99 (H3N2), A/New Caledonia/20/99 (H1N1), and a B/Beijing/184/93-like strain [25]. Since 1998, World Health Organization has also made formal recommendations in September for the southern hemisphere, tailored to the influenza strains circulating there [26]. Vaccination timing varies by region due to differing influenza epidemiology: in the northern hemisphere, it's typically September–October, while in temperate southern hemisphere regions, March–April is recommended [27]. Tropical and subtropical areas may experience influenza activity throughout the year, with peaks around February–March and September–October. This strategic approach ensures that influenza vaccines are tailored annually to provide optimal protection against the

circulating strains in both hemispheres and different geographic regions. When the first Influenza Expert Committee met in 1950 it identified a series of measures for combating epidemics of influenza which included quarantine, restriction of public meetings, etc., and the provision of extended hospital services [28]. The 1918 experience no doubt contributed to the 1952 Expert Committee concluding, that the responsibility for mortality in influenza epidemics probably depends in part upon the character of the virus [29]. The exact measure of success to be expected with antibacterial agents in a virulent pandemic is therefore to some extent unpredictable. The tendency for the 1957 pandemic to first appear in camps, army units, schools and other communities where contact between individuals was particularly close, suggested that avoidance of crowding may be important in reducing the peak incidence of an epidemic. Other measures, such as wearing masks, adequate ventilation and disinfection of the air in selected buildings, were considered to have doubtful value [30].

The first Expert Committee on Respiratory Virus Diseases, in 1958, agreed with the 1950 recommendations, while adding some points learned from the 1957 pandemic [31]. Quarantine measures, historically, have shown limited efficacy in preventing the spread of epidemics, often only delaying their onset. For instance, during the 1957 pandemic, Israel experienced the outbreak two months later than its neighboring states due to quarantine measures restricting international travel and trade. Effective quarantine strategies must be stringent enough to significantly disrupt international movement and commerce [32]. In 1958, an Expert Committee recommended comprehensive global coverage by the World Health Organization network, emphasizing faster and more efficient operations, simplified diagnostic methods, improved vaccines, and more effective treatment and control measures. Historically, diagnostic methods for influenza included the hemagglutination-inhibition test, embryonated egg techniques, and ferret infection studies. Modern advancements have introduced improved culture systems and direct antigen detection methods. However, there remains a need for sensitive, rapid, reliable, and cost-effective antigen detection methods capable of distinguishing between influenza A subtypes H1, H3, and non-H1–H3 [33]. Treatment progress has been significant with the development of antiviral drugs like amantadine and rimantadine in 1979, which are effective prophylactically against influenza a viruses, reducing illness incidence by 70–90% when administered preventatively during epidemics [34]. Antibiotics play a crucial role in managing secondary bacterial infections associated with influenza, which contribute significantly to influenza-related mortality. Bacterial infections can exacerbate viral virulence and lead to severe complications such as viral pneumonia and tissue damage, as seen in historical pandemics like the 1918 Spanish flu and the 1997 H5N1 "chicken flu" in Hong Kong. While quarantine measures can delay the spread of epidemics, their effectiveness relies on strict implementation that disrupts global mobility. Advances in diagnostics, vaccines, antivirals, and antibiotics have improved treatment outcomes.

Ongoing research is crucial for developing more precise diagnostic tools and comprehensive prevention strategies against influenza and other viral outbreaks [35]. New antiviral drugs like zanamivir and oseltamivir, which inhibit neuraminidase in influenza A and B viruses have been licensed. They are effective against influenza B and can reduce the severity and duration of influenza a symptoms when administered within 48 hours of illness onset [36]. However, their application is limited due to the narrow window of effective treatment timing. Pandemic surveillance underscores the inevitability of another influenza pandemic among humans, supported by historical records, sero-archaeology, and molecular epidemiology. Influenza viruses circulating in wild birds, with minimal genetic changes, indicate that the next pandemic strain may emerge from these reservoirs [37]. The H2 subtype, absent from human infections for nearly three decades, poses a potential pandemic risk due to continued circulation in birds and a susceptible human population. Globalization has accelerated the spread of infectious diseases like influenza, necessitating vigilant monitoring and rapid response capabilities. As travel becomes faster and more accessible, the global community must remain vigilant to detect and contain potential outbreaks promptly. Influenza's association with deteriorating living conditions and the natural environment underscores the need for adequate surveillance and early warning systems in the poorest areas of the world [38]. Historical outbreaks, such as the 1889-1890 pandemic, illustrate how quickly influenza can spread globally through transportation networks [39]. Efforts in global surveillance have indeed expanded significantly over the decades, with the World Health Organization coordinating a network of national and collaborating centers dedicated to influenza reference and research.

This network plays a pivotal role in monitoring global influenza activity, providing viral isolates crucial for vaccine production, and issuing timely alerts during pandemics. However, several challenges persist. Funding shortages remain a significant hurdle, contributing to deficiencies in early warning systems particularly in developing countries. This disparity underscores the need for improved communication and resource sharing among surveillance centers worldwide. Public and political awareness of the ongoing threat posed by influenza pandemics requires continuous strengthening. Research priorities include early identification of emerging viral threats and advancements in vaccine production methods to meet the demands of potential pandemics. International collaboration remains essential in devising effective response strategies against potential influenza outbreaks, integrating efforts across both human and animal health sectors to mitigate future risks [40]. In a case example from Papua New Guinea, an influenza-like outbreak in a remote region underscored the challenges of monitoring and confirming outbreaks in isolated areas with limited healthcare and diagnostic resources [41]. This situation reflects similar regional surveillance variability observed in China, where improvements have been made in some areas but significant gaps persist in others, particularly in regions lacking national surveillance centers despite high population density and extensive trade. The significance of global surveillance cannot be overstated, as it provides crucial early warnings and insights into influenza epidemiology [42]. Despite advancements; weaknesses in surveillance systems endure, especially in resource-limited settings where infrastructure for timely outbreak warnings remains inadequate. Influenza outbreaks, such as the recent "chicken flu" in Hong Kong, initially receive substantial media

attention, especially when associated with high mortality rates [43]. However, sustained public and political attention often diminishes after the initial reports, emphasizing the ongoing need for awareness and preparedness efforts.

Future efforts should prioritize the development of effective methods to prevent influenza spread, protect vulnerable populations, and improve rapid vaccine production capabilities. Strengthening global surveillance and collaboration will be pivotal in enhancing early warning systems and response strategies, ensuring preparedness against potential influenza outbreaks worldwide. Public and political awareness of the persistent threat of global pandemics, particularly influenza, requires continual reinforcement. Despite historical pandemics throughout this century, influenza remains insufficiently understood and underappreciated as a global health challenge. Identifying potential pandemic candidates early through critical early warning systems is essential [44]. In the context of the global response to influenza pandemics, the establishment and expansion of the World Health Organization's influenza surveillance network have played a crucial role. Since its inception in 1958, this network has evolved significantly, integrating national influenza laboratories with public health authorities worldwide [45]. By 1979, there were 101 national centers in 72 countries, a number that has since grown to 110 centers across 82 countries by today. The primary objective of this network is consistent: to enhance global preparedness against influenza outbreaks by swiftly identifying and disseminating new pandemic strains to vaccine manufacturers [46]. This collaborative effort involves close coordination between national centers and World Health Organization Collaborating Centers for Influenza Reference and Research, located in Atlanta (United States of America), London (United Kingdom), Melbourne (Australia), and Tokyo (Japan). These centers are pivotal in detecting major new influenza viruses and providing critical data for vaccine development. Annually, World Health Organization analyzes data on isolated viral strains from the previous 12 months to determine the composition of influenza vaccines for the upcoming season [47].

This information is crucial in adapting vaccine formulations to effectively combat the prevailing strains of influenza. During pandemics, the World Health Organization Task Force activates to ensure rapid response: issuing pre-alerts to vaccine manufacturers, initiating vaccine production based on identified strains, enhancing surveillance through national centers, facilitating safe shipment of viral isolates, and updating pandemic plans across national authorities. The complexity of influenza demands continuous global collaboration and vigilance. World Health Organization's efforts focus on strengthening the network of national centers, particularly in developing countries, and ensuring seamless electronic communication and data exchange. This network not only supports real-time updates through platforms like FluNet but also publishes detailed epidemiological records to inform global disease management strategies [48]. In essence, the World Health Organization influenza surveillance network stands as a testament to the importance of international cooperation in confronting the ongoing and future threats posed by influenza pandemics. Viral genes represent the riddle, their variable surface antigens the mystery they code for, and the course and cause of epidemics the ultimate enigma. Over the past half-century, significant progress has been made in understanding influenza, a virus that has been a major contributor to illness and death since the devastating pandemic of 1918. While commonly circulating strains of influenza typically cause seasonal epidemics with varying severity, the rapid mutation rate of these viruses raises concerns about the emergence of more virulent strains capable of causing future pandemics. In addition to human-adapted strains like H1N1 and H3N2, avian influenza strains such as H5N1, H7, and H9 have sporadically crossed into human populations, posing further risks. Influenza viruses are categorized into types A, B, C, and D, with types A and B causing seasonal epidemics in humans. Notable subtypes of influenza A include A(H1N1)pdm09 and A(H3N2) [49].

The virus spreads easily through respiratory droplets and contaminated surfaces, leading to symptoms such as sudden fever, dry cough, sore throat, body aches, and fatigue. Complications, especially pneumonia, can occur, particularly in high-risk individuals such as the elderly, young children, pregnant women, those with chronic illnesses, and healthcare workers. Prevention strategies include vaccination, which remains the most effective method to prevent influenza and its complications. Vaccines are updated annually to match circulating strains and are recommended particularly for high-risk groups. Other preventive measures include hand hygiene, covering mouth and nose when coughing or sneezing, staying home when sick, and avoiding close contact with infected individuals. The World Health Organization plays a critical role in global influenza surveillance, monitoring influenza activity worldwide, recommending vaccine compositions biannually, and coordinating efforts to strengthen global influenza preparedness and response. The WHO Global Influenza Surveillance and Response System (GISRS) monitors antiviral resistance and facilitates timely response to influenza outbreaks, including those caused by avian influenza viruses like H5N1, H7, and H9, which have potential for severe outbreaks if they adapt to efficient human-to-human transmission. International collaboration among multiple agencies in both human and animal health sectors is essential for enhancing global readiness against potential influenza pandemics. This unified approach supports coordinated efforts in vaccine development, surveillance, and response strategies to mitigate the impact of influenza on global health security [50].

Conclusion

The ongoing risk posed by influenza pandemics, despite advancements in antiviral treatments and surveillance. It might emphasize the persistent danger of genetic re-assortment between human and animal influenza viruses, highlighting historical precedents such as the 1957 and 1968 pandemics. Furthermore, the conclusion could stress the importance of global cooperation in early detection, rapid response, and vaccine development to mitigate future pandemics. Ultimately, it would underscore the need for continual vigilance and preparedness in the face of this ever-present global health threat.

Financial support and sponsorship
Nil

Conflicts of interest
There are no conflicts of interest

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How to Cite This Article
Shrivastava A, Sarmah B, Kujur D, Garg M, Wadhawan R. The inevitable menace of influenza: A looming global threat. International Journal of Research in Medical Science 2024; 6(2): 01-06.