Influenza

Influenza is fundamentally a respiratory illness, yet the involvement of organ systems beyond the lungs is often overlooked in discussions of influenza pathogenesis. Extrapulmonary complications associated with influenza infections include renal issues, neurological disorders, and cardiac problems. Furthermore, myocarditis, which is a rare but significant adverse effect linked to mRNA SARS-CoV-2 vaccinations and SARS-CoV-2 infections, can also manifest during influenza cases.[1,2]The repercussions of influenza on public health extend to considerable economic implications. To gauge the economic impact of influenza, it is essential to evaluate both direct and indirect costs. These costs encompass medical treatment expenses and lost income. In the United States, the estimated economic burden of influenza ranges from 6.3 to 25.3 billion US dollars annually, with the most pronounced effects observed in individuals aged 18 to 49.[3,4,5]

The implementation of effective treatments and preventive strategies, such as vaccines and antiviral medications, can alleviate both health and economic challenges posed by influenza. However, the considerable variability among influenza viruses complicates these efforts.[32,33] Influenza viruses are classified under the Orthomyxoviridae family and are divided into types A, B, C, and D. Types A and B are the primary seasonal strains that can infect humans, leading to mild to severe respiratory illnesses and other complications. Consequently, annual vaccine formulations typically include both types. Influenza viruses are further categorized into subtypes and lineages based on the antigenic properties and genetic sequences of the surface glycoproteins hemagglutinin (HA) and neuraminidase (NA). Currently, there are 18 HA and 11 NA subtypes identified in nature for the influenza A virus (IAV), which can be classified into group 1 and group 2 based on its HA.[6,7,8]

Influenza B viruses (IBVs) are distinct from other influenza types as they are not categorized into groups or subtypes; instead, they are divided into two primary lineages: B/Yamagata and B/Victoria.[9] The nomenclature used for influenza viruses reflects their inherent diversity. For example, the IAV labeled A/Tasmania/503/2020 represents an H3N2 component included in the Flucelvax quadrivalent vaccine for the 2021-2022 season in the United States. This designation indicates that it was the 503rd human isolate from Tasmania, Australia, featuring an H3 hemagglutinin (HA) and N2 neuraminidase (NA) subtype, isolated in the year 2020.[10]

The diversification of influenza viruses occurs through two primary mechanisms: antigenic shift and antigenic drift. Antigenic shift takes place when two distinct influenza viruses of the same type co-infect a host's cells, leading to the reassortment of viral genome segments. This process can result in alterations to the HA and NA antigenic properties.[11] A notable example is the 2009 pandemic virus, initially referred to as "swine" flu, which is classified as a triple-reassortant virus due to its genetic segments originating from avian, human, and swine IAVs. Historical pandemic strains, such as the 1918 Spanish flu A (H1N1), the 1957 Asian influenza A (H2N2), the 1968 Hong Kong influenza A (H3N2), and the 2009 pandemic influenza A (H1N1) pdm09, emerged as a result of antigenic shifts. In contrast, antigenic drift is a slower process characterized by the gradual accumulation of genetic mutations within the viral genome over time.[12,13] Both antigenic drift and shift play significant roles in the emergence of epidemics, pandemics, and drug-resistant strains of influenza. This ongoing viral diversity underscores the necessity for annual updates to influenza vaccines.[14]

Vaccination remains the most effective strategy for safeguarding against the morbidity and mortality associated with influenza infections. Nonetheless, the effectiveness of vaccines can fluctuate based on the year, the specific population being examined, and the circulating strain. From 2004 to 2021, the effectiveness of the influenza vaccine in the United States varied between 10% and 60%.[16] Several factors contribute to this variability, including vaccine mismatch, preexisting immunity to influenza, age, body weight, biological sex, and overall immune status. Addressing the challenge of enhancing vaccine efficacy is a pressing issue, as both host and viral characteristics significantly influence outcomes. In the meantime, there is a pressing need for alternative strategies to address the limitations posed by vaccine-related challenges in both preventive and therapeutic contexts.[17,18]

Antiviral medications have proven to be essential in the fight against influenza viruses. The Centers for Disease Control and Prevention (CDC) endorses four antiviral agents for the treatment of influenza: Oseltamivir phosphate, Zanamivir, Peramivir, and Baloxavir marboxil (BXM). Oseltamivir, Zanamivir, and Peramivir function as neuraminidase (NA) inhibitors,[34,35] obstructing NA activity and preventing the release of the virus from infected cells, while Baloxavir acts by inhibiting viral replication through the inhibition of the polymerase acidic protein (PA).[19,20,21] Although these medications do not provide a cure, they can significantly shorten the duration until clinical resolution is achieved. Additionally, NA inhibitors and Baloxavir are recommended for the treatment of individuals infected with avian influenza viruses, including A(H5N1), A(H7N9), and A(H5N6).[22,23]

The rise of drug-resistant strains of influenza can lead to the ineffectiveness of antiviral medications. M2 inhibitors, such as Amantadine, which have been utilized since the 1960s for seasonal influenza, are no longer advised for use.[24,25] The widespread occurrence of M2 mutations that confer resistance began with A(H3N2) viruses from 2003 to 2006 and continued with A(H1N1) viruses in 2009, leading to the cessation of M2 inhibitors in influenza treatment.[26,27,28] Furthermore, strains resistant to NA inhibitors and Baloxavir have also emerged, although their prevalence can fluctuate rapidly based on the specific antiviral agent and the background strain associated with the mutation.[29,30] Enhancing therapeutic options for influenza is essential to address the gaps in vaccine effectiveness that are expected to remain both in the near and distant future, given the unpredictable nature of seasonal and pandemic influenza outbreaks.[36]

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