When "B" becomes "A": the emerging threat of influenza B virus

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Influenza virus (flu) caused the worst disease mediated devastation in recorded human history in 1918, when global death was estimated to be between 50 and 100 million people [1]. Flu continues to kill more people every year with no apparent decrease in its pathogenicity despite advancement in our understanding of the disease and with the availability of vaccines and antiviral agents. Last year, the death toll of influenza was estimated to be 80 000 in the USA alone, making it the most lethal infectious disease [2]. One apparent change that occurred in the influenza virus is the emergence of influenza B strain as a significant contributor to the annual disease over the years. The origin of influenza B is unclear but was first isolated around 1940 and later separated into two clear lineages by 1983, the Yamagata-like and Victoria-like strains [3]. The scientific and healthcare community has been underplaying this important event and influenza B has been labelled as the "B" team compared to influenza A. Influenza B is believed to be a milder virus compared to some strains of influenza A, such as H3N2, but more potent than the influenza A strains like H1N1 [4]. In fact, multiple studies have suggested increased potency of influenza B virus in causing severe disease and mortality. Influenza B is the most prominent circulating strain of influenza every four to five years. Furthermore, influenza B infections carried higher risks of hospitalisations compared to influenza A infections in HIV patients [5]. Similarly, influenza B has been described to have significantly higher mortality rates compared to influenza A strains. For example, during the flu season in 2010–2011, influenza B was responsible for 38% of deaths in the paediatric population. National Respiratory and Enteric Virus Surveillance System collaborating laboratories indicated that only 26% of circulating strains of flu were influenza B viruses during this period [6]. Similarly, a Canadian study from 2004 to 2013 found significantly higher mortality rates due to influenza B compared to influenza A in children younger than 16 years of age [7]. These data strongly refute the claims that influenza B is the milder version of the flu. In this issue of the *European Respiratory Journal*, the study by BUI *et al.* [8] sheds light on influenza B interactions within the human respiratory tract and lung to demonstrate its pathogenicity and its potential to spread and cause severe lung infections.

Unlike influenza A, there is limited antigenic drift observed in influenza B virus, making the virus relatively stable. Another remarkable difference between the influenza A and B strains is the lack of animal reservoirs for influenza B, which is known to infect only humans, besides sporadic reports of infections in seals [9]. The lack of antigenic drift and animal reservoir deprives influenza B of two important

opportunities to continuously evolve. Both these phenomena provide important opportunities to the virus to modify its genome and increase its pathogenicity to emerge as a pandemic strain. The evolutionary mechanisms of influenza B remain largely unknown and are an important area of further investigation.

The threat of influenza B has been recently recognised and acknowledged by the introduction of the quadrivalent vaccine that includes both lineages of influenza B. These vaccines significantly decrease rates of infection; however, its effectiveness is disappointingly low in susceptible populations such as children within the age group of 9–17 years of age (28% effective) [10]. This indicates the limitation in our current vaccine strategies as well as the effectiveness of influenza B virus to spread in the susceptible school age population, where simple protective measures such as hand hygiene and or masking one's cough may not be as robust. In addition, multiple clinical studies have demonstrated increased risk factors for respiratory viral infections among children, such as day care attendance and presence of school age siblings in the same household. These data urge further studies in the pathogenesis of influenza B virus in order to discover new therapies that are needed to halt the continuous deaths caused by this virus. Furthermore, the expectations that therapies for influenza A will work similarly for influenza B may be a naïve assumption.

Antiviral resistance is another major obstacle in the treatment of influenza B. The main influenza antiviral therapies are oseltamivir and zanamivir. Both are neuraminidase inhibitors and act by inhibiting release of progeny virions. Mutations in neuraminidase can lead to antiviral resistance and potentially worse clinical outcomes in patients. Such mutation has been reported in the influenza B Yamagata lineage with a Gly407Ser neuraminidase substitution [11, 12]. Other mutations include Asp198Asn, Ile222Thr and Ser250Gly. This resulted in persistent viral shedding among children who tested positive for influenza B and who were managed with oseltamivir [13]. In addition, oseltamivir was shown to be less effective in influenza B patients compared to those with influenza A [14]. Antivirals are also prone to multiple adverse effects, mostly gastrointestinal, in both adults and children. Its main outcome is reduction in influenza symptoms and, per a Cochrane review, it is crucial to weigh the benefits and harms when making the decision to start these antiviral therapies [15]. These studies again emphasise the needs of influenza B specific antivirals to treat this virus.

Host response to the influenza B virus is largely similar to the influenza A virus and recently circulating strains of influenza B have shown comparable pathogenicity to influenza A in mouse models [16]. The study by BUI et al. [8] sheds important light on the tropism, replication ability and host immune response by a wide range of influenza B strains, including the strains obtained before the separation of influenza B into the two currently known lineages (Victoria-like and Yamagata-like strain). The authors used primary human bronchus, lung tissue and human airway organoids along with bronchial and alveolar epithelial cells to study these parameters. Influenza B infected acetyl α tubulin positive ciliated cells as well as CC10 positive secretory club cells in the upper respiratory tract, demonstrating its ability to initiate, spread and cause infection amongst humans. Similarly, influenza B effectively infected and replicated in human lung transplant, showing its ability to cause severe lower respiratory tract infections which are often associated with the lethal disease. Interestingly, one striking difference that was observed in this study was the dependency of viral replication on mucin, which selectively inhibited influenza B but not influenza A strains [8]. Cell surface mucin, specifically MUC-1, is upregulated in lung infections. Using human epithelial cell culture and mouse models, it has been demonstrated by others that MUC1 plays a key role in the inflammatory process and in host defence with influenza A [17, 18]. Overexpression of MUC1 led to reduced infection and MUC1 knockout mice had higher mortality due to influenza A [18]. Additional studies have demonstrated the anti-inflammatory role of MUC1 [19]; however, further studies are needed to define the role of MUC1 and other mucins in influenza B infection.

Consistent with the epidemiological data showing that influenza B contributes to a significant number of pathological events, most of the strains tested had comparable infectivity to influenza A strains. Further, the infecting potential was dependent on strain specificity, rather than lineage of influenza B, explaining the year-to-year variability in both percentage of cases and mortality rates between influenza A and B. The current study explains these findings, showing that different strains of influenza B have an infection potential that is even greater than those of influenza A strains, including highly pathogenic strains such as H3N2.

Although the studies indicate various similarities between influenza A and B, this may be caused by investigator bias where most of the parameters observed are those that are already known for influenza A. The influenza B-specific effects on the host are largely unknown. The current study also indicates many similar findings between influenza A and B in terms of infectivity, tropism and inflammatory response. However, many questions remain to be answered for influenza B. Why does influenza B show higher infectivity in children compared to adults? Does influenza B colonise in humans without causing disease symptoms? Why do the peaks of influenza B infection often come after influenza A infection peaks? Since

humans are the main reservoirs of this virus, is it possible that influenza A strains increase the susceptibility to influenza B? Further exploration of the evolutionary mechanisms of influenza B, which continues to change without animal reservoirs, will be important in order to understand its pathogenic potential and develop possible new antiviral therapies.

To answer these questions, more research is needed on influenza B strains. The current study provides important tools and techniques to answer many of the above questions. We would like to emphasise the need for further understanding of influenza B pathogenesis in a timely manner, so we can anticipate and be well prepared for the first influenza B mediated pandemic, which could be devastating with the current knowledge and therapeutic options available.

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