Fatal Influenza B Infections: Time to Reexamine Influenza Research Priorities

Jonathan A. McCullers1 and Frederick G. Hayden2,3

1Department of Infectious Diseases, St. Jude Children’s Research Hospital, Memphis, Tennessee; 2Department of Medicine, Division of Infectious Diseases and International Health, University of Virginia School of Medicine, Charlottesville; and 3International Activities, Wellcome Trust, London, United Kingdom

(See the article by Paddock et al, on pages 895–905.)

Influenza A viruses (IAVs) are zoonotic pathogens that sometimes establish long-term lineages in humans and other mammalian hosts. New introductions of influenza genes or whole viruses from animal reservoirs can result in viruses with an exceptionally virulent phenotype. After a period of adaptation and development of population immunity, however, the descendents of pandemic viruses rarely cause severe illness and mortality through direct viral damage in immunocompetent hosts [1, 2]. Instead, exacerbation of a preexisting, chronic illness or virus-mediated impairment of host defenses facilitating bacterial superinfection account for most fatalities. Selwyn Collins of the US Public Health Service, who refined the terms by which we classify outcomes after influenza, expressed this view as, “In fact, influenza may well be thought of as not a killing disease except by the intervention of pneumonia or the presence of chronic disease in a patient” [3].

Influenza B viruses (IBVs) are stably adapted to humans, having diverged from IAVs at some point in the distant past. IBVs were first isolated from humans in 1940 and have caused seasonal epidemics since at least 1935 but likely have been endemic in humans for centuries. Although IBVs can establish lineages in seals, they are not known to have a stable animal reservoir from which new variants could emerge [4]. Over the last several decades, rates of hospitalization and mortality attributed to IBVs have been lower than those associated with H3N2 subtype IAVs but higher than those linked to the less virulent seasonal H1N1 strains. During the 2010–2011 season, 38% of all influenza-associated pediatric deaths were attributed to IBVs, despite only 26% of all circulating viruses being of this type [5]. Half (49%) of these children who died had no known high-risk medical condition, and only 50% received any antiviral therapy, pointing to missed opportunities for intervention and prevention of complications.

New research is starting to pinpoint some of the characteristics that predict virulence in novel influenza strains. The most important of these may be an ability to access and cause disease in the lower respiratory tract, a trait that appears to be governed largely by the surface glycoprotein hemagglutinin (HA). A combination of the correct receptor specificity and a lack of N-linked glycosylation at key sites on the globular head of the HA allows deep access to the lungs, manifest pathologically by diffuse alveolar damage, a hallmark of pandemic influenza [6, 7]. During adaptation in humans, there is improved recognition of receptors in the upper respiratory tract, and sequential addition of sites for attachment of glycoconjugates to the surface proteins. This latter adaptation serves to shield the virus from antibody neutralization but also shifts tropism from the lungs to the upper airways due to the presence of collagenous lectins in lung surfactant [8]. These “collectins” bind glycoconjugates on the HA and facilitate clearance. Recently circulating IBVs, like contemporary seasonal H1N1 and H3N2 strains, have been heavily glycosylated and thus relatively restricted from the distal airways and alveoli. The recent 2009 pandemic strain lacked this degree of glycosylation, likely accounting for its demonstrated ability to cause deep lung infections and acute lung injury in susceptible hosts [8].

In this issue of the Journal of Infectious Diseases, Paddock et al [9] characterize autopsy tissues from 45 patients with fatal IBV infections. IBV antigens and inflammatory changes accompanying the virus were found predominantly in the trachea and bronchi in a distribution...
common to seasonal IAVs, but distinct from the pattern of diffuse alveolar damage characteristic of pandemic viruses including the 1918 and 2009 H1N1 strains and of highly pathogenic H5N1 infections. Just over a third had bacterial superinfections, most frequently due to *Staphylococcus aureus*. The predominance of *S. aureus* in this fatal case series likely reflects the composition of the population from which it is drawn; pneumococcal vaccines are used widely in the United States, and the emergent USA300 clone of *S. aureus* has shown a propensity for necrotizing pneumonia in association with influenza both epidemiologically and in mouse models [10, 11]. *S. aureus* was also the predominant coinfecting organism in fatal cases during epidemics in the early 1940s, the 1957 pandemic, and the 2010–2011 season [5, 12].

Two features of the case patients in the autopsy series from Paddock et al [9] are striking and novel. First, cardiac injury was detected in about two-thirds of those for whom tissues were examined. Second, there was a clear dichotomy in age-associated disease patterns. Most deaths in persons ≥18 years were associated with bacterial superinfection (82% compared with 24% in those <18 years), whereas most deaths associated with cardiac injury were in children (90% of 20). Overall, consistent with the dogma that seasonal influenza rarely kills without a secondary cause, 40 of the 45 case patients had either a pre-existing high-risk chronic medical condition (>40%) or autopsy evidence of secondary bacterial pneumonia or acute cardiac injury. Notably, data on high risk conditions were not available for 1 of the remaining 5, and heart tissues were not available for the other 4, precluding an identifiable association with acute cardiac injury in these case-patients (C. D. Paddock, personal communication).

Cardiac complications have been frequently reported in clinical case series of severe influenza as far back as the 1889 pandemic, mostly on the basis of clinical symptomatology or electrocardiographic changes (reviewed in [13]). Indeed, abnormal electrocardiograms can be demonstrated in most young adults with acute influenza without any link to severe outcomes [14]. However, in most series of fatal cases specific pathologic changes in the heart are sepsis-related in the setting of bacterial superinfections. Isolated myocarditis, while described, is considered to be rare. During the 2009 H1N1 pandemic, myocarditis was a recognized but uncommon presentation, often seen in the setting of pneumonia [15, 16]. As in the current report, virus has been detected in the lungs in some well-documented cases, but evidence suggesting direct acute infection of the heart is unusual [13, 17]. Reports of specific cases attributable to IBV are also rare. Thus, the frequency of cardiac injury in this series is unexpected. Is this finding unique to this era and patient population? Are there contributing factors in these children that might predispose to cardiac-related death during influenza? Few clinical data were available on the patients in the study by Paddock et al [9], making even speculation difficult. More broadly, when considering pandemic strains capable of infecting the lower respiratory tract, what variables explain those progressing to severe viral pneumonia and acute respiratory distress syndrome, especially given the relative infrequency of severe phenotypes in pandemic 2009 infections? These questions reveal our fundamental lack of understanding of the host genetic factors that affect outcomes. Further study of these questions, including investigation of cardiac disease in children, is clearly necessary.

As the authors of the current report allude to with their prefacing quote, IBVs are understudied. This point extends to seasonal influenza in general. Concern over a devastating pandemic similar to that of 1918 has driven policy and public health funding decisions for many years, concentrating resources on study of highly pathogenic IAVs. With increasing recognition that the toll of seasonal influenza is large and that advances in understanding management of complications in common risk groups will benefit responses to novel strains, the time may be ripe to rebalance research priorities. Increased funding is urgently needed for basic research and enhanced clinical study of risk factors and complications of seasonal influenza caused by both type A and B viruses. The intersection between influenza and secondary bacterial infections, asthma, obesity, and heart disease needs to be explored at multiple levels, including pre-clinical studies in animals and large clinical studies in humans. Controlled clinical trials of antivirals, anti-inflammatory agents and their various combinations should target at-risk groups including both children and those with chronic medical conditions. Additional studies designed specifically for IBV are needed to understand differences in outcomes relative to IAV.

The 2009 pandemic revealed how unprepared we are to conduct rapid, high-quality, prospective research on influenza without significant lead time [18]. The dual goals of improving research on seasonal influenza and preparing for rigorous study of a suddenly emergent pandemic influenza strain or other novel respiratory threat could be accomplished by establishing clinical networks dedicated to this task. Such networks could develop common endpoint definitions, data collection and sharing tools, reporting standards, and draft templates and protocols for coordinated use. This strategy would allow accrual of sufficient patients to answer questions about infrequent outcomes, like cardiac injury, and host genomics while maintaining the infrastructure and intellectual resources necessary to rapidly collect data should a new antiviral or other therapeutic intervention merit investigation, or a novel pathogen emerge. Although an effort to link intensive care units was initiated during the 2009 pandemic [19], broader hospital-based networks are needed domestically and
across international boundaries. Agencies within the Federal Government of the United States should support and foster such initiatives and prioritize funding of clinical networks dedicated to influenza and severe acute respiratory infection (SARI)-related studies.

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