In the current issue of the Journal, van den Brand and colleagues [1] report on the pathogenicity of seasonal H1N1 influenza virus, highly pathogenic avian influenza (HPAI) H5N1 virus, and the new 2009 H1N1 influenza virus strains after intratracheal inoculation into ferrets. They determine that the pulmonary pathogenicity of the 2009 H1N1 pandemic strain is intermediate between that of HPAI H5N1, which is the most severe, and that of seasonal H1N1, which is the least severe. Indeed, the authors were able to distinguish cellular selectivity for viral replication by demonstrating more widespread replication of 2009 H1N1 throughout the lower respiratory tract. These studies were performed with the expectation of using the ferret model as a predictor of the behavior of 2009 H1N1 in the human population, because the influenza-infected ferrets are an outstanding model of human influenza infection [2, 3].

So, how do we interpret these findings in light of knowledge being gained about the natural history and outcome of the 2009 H1N1 virus infection? Detailed knowledge of the current pandemic is indeed limited, even at this juncture. However, in the United States, the first wave of the pandemic was experienced in the spring of 2009, and the second wave was experienced during the fall of 2009. It remains to be seen whether a third wave will occur early in 2010. As of early December 2009, a current estimate of the extent of disease reported that ∼1 of 6 Americans had experienced pandemic influenza, accounting for ∼50 million cases [4]. The report indicates that ∼200,000 individuals had been hospitalized, and there were 10,000 deaths due to 2009 H1N1 infection. Of those deaths from influenza, 7500 occurred in young adults. The morbidity and mortality of the current pandemic are in sharp contrast to the annual toll of influenza, which historically results in about 250,000 hospitalizations and 36,000 deaths but mainly in elderly individuals, rather than in young adults and children [5, 6].

Historically, risk factors for severe disease have included the extremes of age—namely, the very young and the elderly, as well as individuals with chronic underlying diseases, including immunosuppression. In the current pandemic, those individuals at greatest risk have tended to be previously healthy young adults, pregnant women, the obese, patients who have neurocognitive impairment or who are immunocompromised, and indigenous populations. Notably, the elderly have been spared from significant disease (as reviewed in [7]).

The severity of pneumonia, the primary focus of the van den Brand et al [1] article, has varied widely from available reports [8–10]. Notably, the true incidence of pneumonia awaits analysis of ongoing prospectively collected data. Nevertheless, pneumonia has been a leading cause of death during the current pandemic. Both primary viral infection of the lung, as well as secondary bacterial infections, caused predominantly by both Staphylococcus pneumoniae and Staphylococcus aureus (both methicillin-susceptible and methicillin-resistant Staphylococcus aureus), have been reported as important causes of death. Notably, secondary bacterial infection appears to be more common in children, occurring in nearly 50% of cases [11], than in adults, for whom it is reported in 30% of cases [12]. In many cases, the heroic use of advanced ventilatory strategies, including extracorporeal membrane oxygenation, appears to have reduced mortality [7]. Nevertheless, the overall mortality from 2009 H1N1 appears much lower than that either anticipated with seasonal influenza, being at least 3-fold less, or that currently reported for HPAI H5N1.

Thus, the current study would have anticipated an increase in the severity of pulmonary pathologic findings, as compared to seasonal H1N1 infection. The van den
Brand et al [1] findings are supported by the work of other investigators as well [13]. Utilizing one 2009 H1N1 strain (CA-04), sequence analysis failed to demonstrate markers of enhanced virulence in either avian or mammalian species. Replication in human bronchial epithelial cells was similar for pandemic and seasonal H1N1, but the median lethal dose for mice was much lower, and viral antigen could be detected for longer periods of time in the lung. In addition, as demonstrated in the current work, the CA-04 strain induces a proinflammatory cytokine response with resultant pneumonia in a ferret model.

As we compare human and ferret data, several thoughts warrant consideration. First, is the ferret an acceptable model of human disease? From existing data the answer would appear to be yes [2]. Second, does the virus inoculum utilized in this study parallel what would be encountered in humans? Third, does the 2009 H1N1 virus use alternative receptors for replication in the ferret model? If so, are these same receptors operational in humans? Fourth, it is unlikely that the strain selected for these studies has a unique property that would alter its pathogenicity, as noted in other studies. Lastly, the immune competence of the host surely contributes to morbidity, but such would not seem to be a factor in the ferret model. Regardless, although these questions remain to be answered, the circulating pandemic strain behaves differently in this experimental model than does either the seasonal or the HPAI H5N1 viruses.

In spite of the lower mortality attributed to 2009 H1N1, from a public health perspective the availability of a vaccine for disease prevention cannot be overemphasized. With nearly 100 million doses of vaccine available in the United States by the middle of December 2009, every effort should be made to immunize as many individuals as possible, but especially those at high risk. In so doing, a potential third wave of the pandemic can be mitigated.

References