The Persistent Legacy of the 1918 Influenza Virus

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To understand what has been happening since 1918, it is helpful to think of influenza viruses not as distinct entities but as eight-member “gene teams” that work together and must sometimes trade away one or more team members to make way for new gene “players” with unique skills. In nature, avian influenza A viruses seem to exist as transient complexes of eight genes that assemble and reassemble promiscuously, if not randomly, in an enormous global avian reservoir. Within this reservoir, avian viruses remain stably adapted to the enteric tracts of hundreds of avian species, single members of which are often simultaneously infected by multiple viruses that engage in prolific gene reassortment. Because of this continual reassortment, a seemingly endless variety of new viruses with potentially new properties are continually being engineered. Indeed, thousands of unique gene
Mortality Associated with Influenza Pandemics and Selected Seasonal Epidemic Events, 1918–2009.*

<table>
<thead>
<tr>
<th>Years</th>
<th>Circulating Virus (Genetic Mechanism)</th>
<th>Excess Deaths from Any Cause no. per 100,000 persons/yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1918–1919</td>
<td>H1N1 (viral introduction), pandemic</td>
<td>598.0</td>
</tr>
<tr>
<td>1928–1929</td>
<td>H1N1 (drift)</td>
<td>96.7</td>
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<tr>
<td>1934–1936</td>
<td>H1N1 (drift)</td>
<td>52.0</td>
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<tr>
<td>1947–1948</td>
<td>H1N1 A' (intrasubtypic reassortment)</td>
<td>8.9</td>
</tr>
<tr>
<td>1951–1953</td>
<td>H1N1 (intrasubtypic reassortment)</td>
<td>34.1</td>
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<tr>
<td>1957–1958</td>
<td>H2N2 (antigenic shift), pandemic</td>
<td>40.6</td>
</tr>
<tr>
<td>1968–1969</td>
<td>H3N2 (antigenic shift), pandemic</td>
<td>16.9</td>
</tr>
<tr>
<td>1972–1973</td>
<td>H3N2 A Port Chalmers (drift)</td>
<td>11.8</td>
</tr>
<tr>
<td>1975–1976</td>
<td>H3N2 (drift) and H1N1 (&quot;swine flu&quot; outbreak)</td>
<td>12.4</td>
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<td>1977–1978</td>
<td>H3N2 (drift) and H1N1 (viral return)</td>
<td>21.0</td>
</tr>
<tr>
<td>1997–1999</td>
<td>H3N2 A Sydney (intrasubtypic reassortment) and H1N1 (drift)</td>
<td>49.5</td>
</tr>
<tr>
<td>2003–2004</td>
<td>H3N2 A Fujian (intrasubtypic reassortment) and H1N1 (drift)</td>
<td>17.1</td>
</tr>
<tr>
<td>2009</td>
<td>H3N2 and H1N1 (drift) and swine-origin H1N1 (viral introduction), pandemic</td>
<td>?</td>
</tr>
</tbody>
</table>

* Mortality data include deaths associated with all influenza A and B viruses combined. Many of these data have been calculated with the use of differing methods and may not be strictly comparable.1,2 The 1934, 1951, and 1997 data span 2 years.

constellations making up avian influenza viruses have already been identified; as research continues, the number will undoubtedly grow. The mechanisms by which avian viruses cross species barriers to infect humans or other mammals, either causing dead-end infections or leading to subsequent human-to-human transmission, are unknown. Moreover, the properties of influenza viruses that have the greatest medical and public health relevance, such as human infectivity, transmissibility, and pathogenicity, appear to be complex and polygenic and are poorly understood. Every influenza A virus has a gene coding for 1 of 16 possible hemagglutinin (HA) surface proteins and another gene coding for 1 of 9 possible neuraminidase (NA) surface proteins. These two proteins (facilitating viral attachment and release, respectively) not only are critical for the infection of susceptible cells of a host but also elicit immune responses that prevent infection or independently reduce viral replication, respectively. Of the 144 total combinatorial possibilities, only three HAs and two NAs, in only 3 combinations (H1N1, H2N2, and H3N2), have ever been found in truly human-adapted viruses — a fact that suggests inherent limitations in host adaptation. In addition to possible constraints related to HA or NA, viruses adapted to humans or other mammals may be constrained by a need for all their genes to be coadapted both to the host and to each other — a requirement that seems to be particularly difficult to fulfill. Chimeric viruses containing fewer than all eight genes of the 1918 virus, for example, are not as pathogenic in animal models as the fully reconstructed 1918 virus.

Once new human influenza viruses appear and cause pandemics, population immunity to their HA and NA proteins increases quickly. The powerful counterforce of population immunity is met by the remarkable ability of influenza virus to evolve by means of mutation (drift) or acquisition through reassortment either of different HA subtypes (shift) or through intrasubtypic reassortment with variant HAs of the same subtype or of other genes of cocirculating viruses.3 Direct descendants of the 1918 virus caused “shift pandemics” in 1957 (H2N2) and 1968 (H3N2); they also caused “pandemic-like events” associated with intrasubtypic reassortment in 1947 (H1N1), 1951 (H1N1), 1997 (H3N2), and 2003 (H3N2). By convention, the term “pandemic” influenza has been reserved for global influenza pandemics caused by viruses with new HA subtypes; it has not been consistently applied to widespread or even global epidemics resulting from other viral genetic changes. But the long-held belief that shifts always cause severe pandemics, whereas drifts lead to more modest increases in seasonal mortality, has been called into question. The effects on mortality of new influenza viruses created by the several genetic mechanisms mentioned above are not easily characterized (see table).1,2 In this regard, it is noteworthy that although the precise viruses that circulated before 1918 and the mechanisms of their generation are unknown, probable influenza pandemics have, over several centuries, shown marked variation in severity, ranging from mild (e.g., the 1761–
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Genetic Relationships among Human and Relevant Swine Influenza Viruses, 1918–2009.

Yellow arrows reflect exportation of one or more genes from the avian influenza A virus gene pool. The dashed red arrow indicates a period without circulation. Solid red arrows indicate the evolutionary paths of human influenza virus lineages; solid blue arrows, of swine influenza virus lineages; and the blue-to-red arrow, of a swine-origin human influenza virus. All influenza A viruses contain eight genes that encode the following proteins (shown from top to bottom within each virus): polymerase PB2, polymerase PB1, polymerase PA, hemagglutinin (HA), nuclear protein (NP), neuraminidase (NA), matrix proteins (M), and nonstructural proteins (NS). The genes of the 1918 human and swine H1N1 and the 1979 H1N1 influenza A viruses were all recently descended from avian influenza A genes, and some have been “donated” to the pandemic human H1N1 strain.
1762 pandemic) to severe (e.g., the 1833–1837 pandemic, which had a 2% case fatality rate).

It is remarkable not only that direct "all-eight-gene" descendants of the 1918 virus still circulate in humans as epidemic H1N1 viruses and in swine as epizootic H1N1 viruses, but also that for the past 50 years the original virus and its progeny have continually donated genes to new viruses to cause new pandemics, epidemics, and epizootics. The novel H1N1 virus associated with the ongoing 2009 pandemic is a fourth-generation descendant of the 1918 virus. The complex evolutionary history of this virus features genetic mixing both within human viruses and between avian- and swine-adapted influenza viruses, gene-segment evolution in multiple species, and evolution in response to the selection pressures of herd immunity in various populations at

**Background Reading**


Finding Money for Health Care Reform — Rooting Out Waste, Fraud, and Abuse

John K. Iglehart

In their quest to enact health care reform legislation, Democrats’ major challenge is securing the money to pay for greatly expanded insurance coverage and more government regulation in the face of strong Republican opposition and an unsettled private sector. President Barack Obama has emphasized time and again, recently in a letter to Senators Max Baucus (D-MT) and Edward Kennedy (D-MA), that “health care reform must not add to our deficits over the next 10 years — it must be at least deficit neutral and put America on a path to reducing the deficit over time.” As the administration and its congressional allies pursue revenue sources to pay the estimated costs of near-universal coverage ($1.2 trillion over a decade), one potential source that Obama has emphasized is an acceleration of government efforts to pursue waste, fraud, and abuse that sap the health care system of billions of dollars every year.

The National Health Care Anti-Fraud Association, an organization of about 100 private insurers and public agencies, estimates that some $60 billion (about 3% of total annual health care spending) is lost to fraud every year, but that figure is considered conservative. In 2008, government-wide “improper payments” cost the U.S. Treasury $72 billion, or about 4% of total outlays for the related programs. Of that amount, 50% took the form of reimbursements to providers, medical suppliers, and other Medicare and Medicaid vendors. Medicaid had an estimated improper-payment rate of 10.5%, or $18.6 billion, for the federal share of Medicaid expenditures — the highest rate of any federal program.

Improper payments have been a “long standing, widespread, and significant problem” for the federal government, but Congress has not always been willing to appropriate the monies that the executive branch seeks for antifraud activities. In 4 of the past 5 years, Congress rejected Bush administration requests to provide an additional $579 million to combat health care fraud on the grounds that doing so would reduce budgets for curing cancer...