Perspectives on Pandemics: A Research Agenda

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During the 20th century, indisputable pandemics of influenza occurred in 1918, 1957, and 1968. The pandemics of 1957 (A/H2N2) and 1968 (A/H3N2) were associated with major antigenic changes in the virus, probably reflecting introduction by recombination of animal virus genes. The 1918 epidemic is beyond the reach of modern virology but, based on seroarcheology, appears to have been caused by a virus very similar to present swine (A/H1N1) influenza viruses. Changes in both principal antigens of the A/H1N1 subtype in 1947 resulted in total vaccine failure and pandemic spread of virus. On the basis of three periods of prevalence in the 20th century, A/H1N1 may be the "default" human virus, although the 39-year persistence of A/H3N2 to the present challenges this view. Only H1, H2, and H3 and N1 and N2 antigens have been found in human influenza viruses, but virologic history is too brief to preclude the contribution of other antigens to future pandemics.

Preface

When I was asked to be a dinner speaker at this meeting, I accepted that kind invitation, believing that both you and I would be sufficiently under the influence of a post-reception glow that my ruminations on things past would not be too unpleasant for either of us. However, meeting the exigencies of programming, my status has changed to that of luncheon speaker, a position in the hierarchy of show business somewhere between the jugglers and the dog act. That may turn out to be appropriate, because I'd like take this opportunity to juggle a few unrelated questions about pandemics that linger on, unanswered, despite the power of new technology and the present abundance of talented investigators.

The successive appearance of influenza A virus major antigenic variants in 1947, 1957, and 1968 suggested to me, 20 years ago, an emerging decennial pattern of pandemic occurrence, perhaps related to jet-age travel, and therefore the possibility of pandemic prediction [1, 2]. It is obvious now that there is no periodicity of pandemics. We now confront a chaotic pattern with the unwelcome persistence of H3N2, the premature return of H1N1, and their unexpected coexistence since 1977.

What, then, are we planning for? In this interpandemic period we are planning for annual epidemics equivalent to hurricanes in the south Atlantic. We know that they will occur each year at the same season, will have different names, and will be variable in severity. In the case of pandemics, we are planning for the equivalent of a tornado in Massachusetts—rare and completely unpredictable until the last minute, when a "weather watch" appears on the TV screen. Our weather watch is a "pandemic alert" when a major antigenic change is detected.

The report of the Federal Interagency Working Group [3], in progress, takes great pains to define a pandemic, and rightly so, because upon this definition hinges the action plan. Although I am in full accord with the definition given, I wish to point out that defining a pandemic is a little like defining pornography—we all "know it when we see it," but the boundaries are a little blurred. Among other things, these blurred boundaries are the substance of a research agenda of unresolved problems from the past, which I believe we must address promptly. Looking back, I find many unanswered questions, the answers to which bear importantly on what to expect in the future.

Historically Remote and Previrology Pandemics

Although serologic archeology reaches back into the mid-19th century and gives important hints of a prior presence of H2- and H3-like viruses, the evidence is certainly not definitive, given our growing appreciation of shared epitopes even among strains of different subtypes [4, 5]. This is an important question because it bears not only on predictions of immune status in populations yet to be challenged but on the puzzling question of virus recycling. Should we look for N8 in the future as a neuraminidase, which, attached to H3, once "made it" in the human population about a century ago [6]?

Looking way back to the 17th and 18th centuries, Hirsch [7] describes 9 instances between 1693 and 1873 in which human and equine epidemics were concurrent. Does this reflect the greater density of the horse population at that time, and, if it does, who was giving what to whom?

When did H1N1 first appear in this century? If in 1908, before 1918 as some serologic assays suggest, then what kind of "shift" occurred in the virus of 1918 when both antigenic and virulence changes are suggested by clinical and epidemiologic evidence?
A/H1N1

Similarly, what happened in 1946–1947 when influenza “A prime” appeared—so antigenically different that vaccines effective earlier were essentially nonprotective. Was this another antigenic (but not phylogenetic) shift such as may have occurred in 1918 based on the slider evidence available?

Recall that extensive studies in the early 1940s had shown significant vaccine-induced protection in the United States Army as well as in Great Britain, [8] yet a vaccine containing 2 (1934 and 1943) H1N1 variants failed on two continents [8]. I personally attended soldiers with this supposedly mild disease that filled the hospital corridors when I was a medical officer at Ft. Monmouth, New Jersey, in 1947. Dr. Philip Loge and I kept detailed records of symptomatology and found the severity of the disease to have been no less than in epidemics described earlier [10]. This epidemic was followed by and overlapped with another, as the wards filled again, this time with patients with streptococcal pharyngitis [10]. (A little later I will comment further on the copathogenic role of influenza viruses and bacteria.)

The Long Life of A/H3N2 (1968–?)

The pandemic virus of 1968 had unusual communicability (reviewed in [15]). Laboratory infections were more common than previously seen, and an unusual number of animal species was infected. Unlike H2N2, but like the putative agent of 1918, it infected and persisted in swine. Was the legacy of residual N2 antibody in the human population protective? There is evidence that it was. Regions visited by H2N2 virus the preceding year suffered far less than other areas that had escaped 1967–1968 epidemics [16, 17]. A well-controlled trial of 1967 H2N2 vaccine in the military by Eickhoff and Meiklejohn [18] demonstrated a protection rate of 50% against Hong Kong (H3N2) challenge. In the absence of N2 antibody, the epidemic by this unusually invasive virus might have been even worse.

The Question of Virulence

Influenza viruses, by themselves, can kill (reviewed in [19]). This was true in 1918, it was true in 1957 and 1968, and it has been true even during the interpandemic periods. It is also true that the vast majority of influenza deaths reflect secondary bacterial infection of the lung [19, 20]. Recent evidence points to the possible participation of bacteria not only as opportunistic invaders of virus-damaged bronchioles, but as enhancers of virus virulence by facilitating hemagglutinin cleavage [21]. On our research agenda should be further investigation of this copathogenicity at a time when we appear to be slipping back toward a preantibiotic era reminiscent of 1918.

Do We Have Any Basis for Predicting the Identity of HxNx, HxN1, or HxN2?

In the last century, we have recognized only H1, H2, and H3 and N1 and N2 as pandemic or interpandemic strain “human” antigens (table 1). It H3N2 disappears, the survivor (H1N1) might become dominant, undergo major antigenic or transmissibility change (as in 1947 and 1918), and reduce the chance for incursion by a novel strain. If both H1N1 and H3N2 continue to cocirculate, the candidate animal virus donor will then have two human virus gene pools from which to derive HxNx.
Infection by either virus of the increasing numbers of immunosuppressed in our population will increase the opportunity for nonimmunoselected virulence mutants to arise in these protracted infections in which the patients act as potential mutant "incubators."

If we do not accept 1947 as a pandemic, then the 11-year prevalence of H2N2 could be viewed as an aberration. But aberration from what? I think that at the present state of knowledge, pursuit of patterns will be unrewarding.

Similarly, the apparent dominance by H1N1 strains in the 20th century may be yielding to the resolute persistence of H3N2. The answer may come in the early 2000’s. The neuraminidase antigen, N2, also seems comfortable in human respiratory tracts and may be destined for, at least, short-term survival.

**Table 1.** Influenza pandemic intervals and subtype prevalence (in the 20th century).

<table>
<thead>
<tr>
<th>Pandemic intervals</th>
<th>Subtype or antigen prevalence</th>
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<tbody>
<tr>
<td>1918–1957 (39 years)</td>
<td>H1N1 (1908)–1957 (49 years)</td>
</tr>
<tr>
<td>1957–1968 (11 years)</td>
<td>H2N2 (11 years)</td>
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<tr>
<td>1968–(1997) (29 ± years)</td>
<td>H3N2 (≥29 years)</td>
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<td>N2 (≥40 years)</td>
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**Perspectives**

The pandemic experience has been a varied one that permits no easy generalizations about the future. Based on our limited store of unequivocal evidence, we can forecast neither the source, the life span, nor the severity of future pandemics. We must be prepared, not only for variations on these past themes, but for ones the virus has not yet exhibited. But we must be prepared for the worst case, which is a double antigen change combined with increased virulence.

The proposition that pandemic strains originate from the reassortment of human and animal viruses is now well accepted and is one that I have not only accepted, but promoted [22]. However, I believe it would be a serious mistake to ignore the possibility of combined antigenic and virulence changes based on nucleotide changes at critical sites in resident human-adapted viruses, that is, within a presently defined subtype. This may have happened in 1918 and to a limited extent in 1947.

In reconstructing the postvirology past and examining vaccine failures with either pandemic or interpandemic strains, more attention should be paid to changes in both principal antigens of the virus, because hemagglutinin and neuraminidase antigenic changes have been shown to be discordant, and this is true of evolutionary studies, as well [23].

In undertaking these studies, I make a plea for monitoring comparative antigenic changes with the same precision and care that we use in sequence analysis and for conducting these studies concordantly.

**References**