Influenza Vaccine — Outmaneuvering Antigenic Shift and Drift
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The winter of 2003–2004 will be remembered as a year in which stories about influenza dominated the news and patients young and old clamored for influenza vaccination. This intense interest is the result of the confluence of multiple circumstances. The onset of the annual influenza epidemic came earlier than expected and was accompanied by reports of severe disease in previously healthy children, associated with the isolation of antigenically variant influenza viruses represented by the prototypic strain A/Fujian/411/2002 (H3N2). There was concern that the available influenza vaccine would not be optimally effective against this strain of virus, but at the same time, the unexpectedly high demand for vaccination led to shortages in many areas. Perhaps it should not come as a surprise that this infinitely adaptable pathogen has again found a way to thrust itself into our consciousness. How are these events linked, and how do they fit into our overall understanding of influenza?

Influenza is a serious illness that causes excess morbidity and mortality in most years. It is estimated that influenza is responsible for an average of 51,000 excess deaths annually in the United States, with a range from about 7000 to about 72,000 deaths in any given year. Influenza vaccine is protective against influenza-related death and hospitalization in all age groups. What is perhaps more noteworthy than this year’s epidemic is the extent to which we routinely accept these vaccine-preventable deaths without much comment. The effects of influenza are felt most keenly at both ends of the age spectrum. Most people know that older adults have disproportionate morbidity due to influenza. But young children also have increased risks of hospitalization and complications. Because of these increased risks, the Advisory Committee on Immunization Practices recently began to encourage influenza vaccination for all children 6 to 23 months of age.

What is it about influenza viruses that allows them to hold over our health every year? These enveloped viruses contain two important glycoproteins on the viral surface. The hemagglutinin is the viral attachment protein that also mediates the entry of the virus into the cell by fusion. The neuraminidase is an enzyme whose main function is to facilitate the cell-to-cell spread of virus. The immunology of influenza is, in a sense, very straightforward. Antibody against the hemagglutinin is neutralizing and is very protective against infection and illness. Antibody against the neuraminidase can reduce the severity of illness.

Because solid immunity is induced by infection, influenza would quickly cease to exist except in children unless it evolved ways of defeating the immune response. The hallmark of influenza viruses is antigenic variation, which comes in two forms: antigenic shift and antigenic drift. Antigenic shift, which is seen only with influenza A viruses, results from the replacement of the hemagglutinin and sometimes the neuraminidase with novel subtypes that have not been present in human viruses for a long time. The source of these new genes is the large reservoir of influenza viruses in waterfowl, in which 15 antigenically distinct subtypes of hemagglutinin and 9 subtypes of neuraminidase have been identified. The consequences of the introduction of a new hemagglutinin into human viruses is usually a pandemic, or a worldwide epidemic, resulting in hundreds of thousands or millions of influenza-related deaths.

Of more relevance to this year’s experience is the phenomenon of antigenic drift. Drift is a subtler process than shift and involves the accumulation of mutations within the antibody-binding sites in the hemagglutinin (see Figure), the neuraminidase, or both that abrogate the binding of some antibodies. Because of these mutations, the resulting viruses cannot be inhibited well by antibodies against previous strains, and it is easier for them to spread throughout a partially immune population. Antigenic drift occurs in both influenza A and influenza B viruses, but the pattern observed is somewhat different for the different viruses. Whereas drift variants of A (H1) viruses and B viruses often cocirculate with multiple coexisting lineages, influenza A viruses of the H3 subtype evolve more rapidly. Antigenic-drift variants of the H3 viruses occur more often, and new variants tend to replace older variants quickly, so that the evolution of the H3 hemagglutinin is more linear than that of other subtypes.
The extent of antigenic drift is usually assessed by determining the nucleotide sequence of the hemagglutinin of new variants and evaluating the ability of antiserum against the old virus to inhibit the new virus. Variants of epidemiologic significance typically have multiple amino acid changes in the hemagglutinin, occurring at more than one antigenic site. As compared with the previously circulating H3 viruses represented by A/Panama/2007/99, the A/Fujian/411/2002 virus has 13 amino acid changes involving multiple antigenic sites. Two changes, at positions 155 and 156 in the top-most antigenic site (see Figure), are characteristic of all the A/Fujian-like viruses that have been isolated so far (Klimov A: personal communication). Antibodies raised against the A/Panama virus have titers one quarter as high when tested against the Fujian virus — a finding that is consistent with a moderate degree of antigenic drift.

Epidemiologically significant antigenic drift, particularly in H3 viruses, is often accompanied by the relatively early onset of a more severe influenza epidemic. A similar phenomenon was observed when the A/Sydney/97 viruses replaced A/Wuhan/95-like viruses in 1997. Other factors may also be influencing the shape of this year’s influenza epidemic. In particular, there has been relatively little H3 virus activity in the United States for the past three years; there is therefore a relatively large cohort of susceptible children, which is probably playing...
an important role in transmission. In fact, the most
dramatic reports of severe disease this year have
been those of influenza in young children.

In addition to influencing the nature of the yearly
influenza epidemic, antigenic drift must be taken
into account when strains are being considered for
inclusion in influenza vaccines. Strain selection is
an ongoing and complex process, involving the co-
ordinated efforts of national and international or-
ganizations. Surveillance for new influenza strains
is conducted year-round by the Centers for Disease
Control and Prevention and the World Health Or-
ganization. The HA1 regions of the hemagglutinin
gene of new viruses are sequenced, and their reac-
tion with serum from experimentally infected fer-
rets is tested. The extent of epidemic activity of new
viruses is assessed in an attempt to predict which
viruses will emerge as predominant in the next year’s
influenza season. If a substantially new variant is
identified, it must be prepared as an influenza vac-
cine in time for the next vaccination season.

Influenza vaccines are produced in eggs, but not
all new antigenic variants replicate well in this sys-
tem — a case in point being the A/Fujian virus. Be-
cause no suitable high-growth A/Fujian-like virus
was available when this year’s vaccine had to be pro-
duced, the vaccine was made with the A/Panama/
2007/99 virus as the H3 component. It is important
to realize that even though this strain is not an op-
timal match for the epidemic virus, it is still likely
that it will provide some protection, particularly in
adults. It is not possible to predict accurately at this
time how much protection will be provided.

One way to generate updated influenza vaccines
more rapidly would be to use substrates other than
eggs, such as mammalian cells, for vaccine produc-
tion. One might use recently described genetic tech-
niques to generate viruses that have better growth
characteristics in eggs. Considerable effort in these
areas is under way. In addition, there is continued
research into vaccines that might provide better
protection against drift variants or that might not
require annual updating at all. Recent data suggest
that live influenza vaccines, such as the nasally
administered cold-adapted vaccine, may induce a
broadened antibody response that could provide
protection against drift variants within the same
subtype. Other strategies for inducing mucosal
immunity have also been reported to offer poten-
tial protection against multiple subtypes. Finally,
some investigators are pursuing vaccines based on
conserved antigens, such as the M2 protein, that
may be a route toward a universal influenza vac-
cine.

Ultimately, the experiences of 2003–2004 may
help us deal with influenza epidemics more effec-
tively. The public awareness and media attention
that accompanied reports of severe illness in chil-
dren have resulted in greater recognition of both the
severity of influenza in all age groups and the ben-
efits of influenza vaccine. This recognition may spur
increased use of vaccination and help us achieve
the goals for vaccine coverage encompassed by the
Healthy People 2010 initiative. In turn, increased de-
mand for vaccine will encourage manufacturers to
continue producing it, possibly in greater quantities.
Increased production is a critically important path
toward developing the surge capacity that will be
needed to deal with new pandemic viruses when they
occur. Finally, more manufacturers may become in-
terested in this area, spurring the development of
additional types of influenza vaccines. Influenza will
probably never be completely subjugated, but with
appropriate effort and resolve, there should be op-
imism about the control of this important patho-
gen in the future.

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