A/H1N1 influenza virus

THE BASICS

Do you know your H1N1s from your H2N2s?

Geoff Watts explains the basic science of the influenza virus

The influenza virus has three genera: A, B, and C. All can infect humans, but only A is responsible for illness on the pandemic scale. So it’s A that attracts attention. The virus comes in many different guises. The version currently besetting us—swine flu—is more properly called H1N1 2009, the letters referring to two all important glycoproteins dotted over the surface of the viral envelope. H stands for haemagglutinin: a molecule that anchors the virus to any cell it seeks to enter. No anchorage, no entry. Given the key role played by haemagglutinin, it’s no surprise that this is the antigen used to prepare antiflu vaccines. And then there’s N, short for neuraminidase. Accounting for up to a quarter of the viral surface protein, this is an enzyme that helps invading viruses to digest their way through mucous secretions as they approach the host cell, and later it assists in the release of newly synthesised virus. Neuraminidase too is tactically important to medicine, because the antiviral drugs oseltamivir (Tamiflu) and zanamivir (Relenza), work by inhibiting it.

**Variants**

And so to variability. The H molecule comes not in just one form but in no fewer than 16. Wasteful? Extravagant? Not at all. All H variants retain the capacity to attach the virus to its prey, but each is sufficiently different from the others to fool the host’s immune defences. Neuraminidase also comes in different structural subtypes—nine in all—which can be found in different combinations with haemagglutinin. Although we’re currently plagued by H1N1, it was H2N2 that caused the 1957 outbreak.

Nor is this the full extent of viral variability. Frequent mutation within the viral genome causes single amino acid substitutions in its proteins, notably in the make-up of haemagglutinin. Most of these alterations are concentrated in regions of the molecule that form a set of outwardly projecting loops. Changes in these loops have little effect on haemagglutinin’s core function; but the loops happen to be the parts of the molecule on which the host’s immune system relies to recognise the identity of its attacker. So although a flood of minor modifications are neither here nor there to the virus, they can confuse the host—which is perpetually running to catch up. The greater the change in the virus, of course, the less the chance that any existing host immunity will be effective.

**“Shift” and “drift”**

These processes of antigenic change are referred to as “shift” and “drift”—a distinction that causes some confusion. “Drift” has been used to describe the incremental selection of minor mutations leading to slow changes of the virus over time. “Shift,” by contrast, was originally reserved for the more substantial subtype changes of the H1 to H2 variety. Such categorisation is no longer meaningful. This year’s virus is an H1N1 variant. So was last year’s; no change of subtype. But over the same period more than a quarter of the amino acids in its haemagglutinin protein have “drifted.” Substantial change, by any measure; a drift with as much or more impact than a shift. Better to avoid the terms. More to the point, the extent of this antigenic change has confounded earlier hopes that because the 2008 and the 2009 viruses are both H1N1 variants, last year’s antiflu vaccine would confer some benefit. No such luck.

**Evolutionary dances**

The evolutionary pressures that serve to keep the antigenic carousel spinning are aided by the unusual structure of the influenza virus’s genome. The RNA of which it’s made comes in eight separate segments which, because they are independent of one another, can undergo what’s called genetic reassortment. If two viruses infect the same cell at the same time, they may exchange genes during replication. The new virus particles will then carry a combination of genetic material from both parents. And even that’s not the end of it. Suppose a cell is simultaneously invaded by strains of virus that normally colonise different host species: birds, say, as well as humans. Precisely this is presumed to have happened in 1957 and 1968. The influenza types responsible for those outbreaks arose through the exchange of genes between avian and human viruses. The fact that flu viruses can move—a combination of genetic material from both parents. And even that’s not the end of it. Suppose a cell is simultaneously invaded by strains of virus that normally colonise different host species: birds, say, as well as humans. Precisely this is presumed to have happened in 1957 and 1968. The influenza types responsible for those outbreaks arose through the exchange of genes between avian and human viruses. The fact that flu viruses can move—albeit not easily—between different vertebrate hosts gives them a vastly enlarged reservoir in which to perform their evolutionary dances. They have the opportunity to conjure up new steps which, even if they fail to cut the mustard in a pig, might play well in a man.
Taking all these mechanisms together, it’s clear that the influenza virus has an impressive clutch of shots in its locker. So are there no boundaries to this versatile organism’s flexibility and adaptability? Fortunately there are. Virologists at the US National Institute of Allergy and Infectious Diseases (NIAID) have recently reminded us that only three combinations of haemagglutinin and neuraminidase—H1N1, H2N2, and H3N2—have been found in humans. This, they suggest, implies some limit to the flu virus’s capacity to adapt to its hosts.

Also limited is its capacity to switch host species. One microbiologist who’s published a thoughtful commentary on recent developments in influenza is microbiologist William Gallaher, emeritus professor at Louisiana State University Health Sciences Center. Accidental crossovers from animals to humans happen all the time, he points out, “But usually they don’t transmit to other human beings. They come to a dead end. Take the H5N1 avian influenza. That’s crossed over to human beings hundreds of times just in the past 10 years, but it’s never caused a subsequent infection.” Only a few crossovers, mostly from swine, have ever led to widespread infection in humans—notably, of course, in 1918. And precisely because successful crossovers are rare they’re hard to study. Little is known about the process or the circumstances under which crossover is most likely to occur. Now, in 2009, it seems to have happened again; but all that can be said is that its success seems not to have depended on the acquisition of one magic gene combination.

The three NIAID virologists point out that it’s possible to infer the recent evolutionary history of H1N1. The current variant, they say, is the descendant of two unrelated swine viruses, one of them a derivative of the 1918 human microbe. “Ever since 1918 this tenacious virus has drawn on a bag of evolutionary tricks to survive in one form or another, in both humans and pigs, and to spawn a host of novel progeny viruses with novel gene constellations.” But what do the make-up of the virus and its evolutionary history say about its future? Regretfully, says Gallaher, not a great deal. “I can’t tell you why this [current outbreak] didn’t happen in Wisconsin in 1998 or in Maryland in 2005 because those viruses look similar enough. Why did it take off in Mexico when it didn’t take off then?” But, he adds, maybe if we look closely enough we will eventually find something of sound predictive value. Indeed, as the microbiologists Taia Wang and Peter Palese of New York’s Mount Sinai School of Medicine have pointed out, a coding sequence for the smallest of the viral proteins, PB1-F2, seems to be one marker of pathogenicity. It was present in the strains responsible for the 1918, 1957, and 1968 pandemics. Encouragingly, the current version of H1N1 does not carry it.

Only three combinations of haemagglutinin and neuraminidase—H1N1, H2N2, and H3N2—have been found in humans

Reasons for optimism

In addition, other reasons allow us to be optimistic. As distinct from 1918, we live in an age of antibiotics and antivirals that can prevent the onset of pneumonia. And the virus too may be learning to behave in a more “civilised” manner. Morens and colleagues point out that successive pandemics seem to be decreasing in severity. This diminution, they suggest, reflects evolutionary “choices” that favour optimal transmissibility with minimal pathogenicity: “a virus that kills its host or sends them to bed is not optimally transmissible.”

In the meantime William Gallaher, who has a “significant cardiopulmonary disability” and who has had three encounters with H1N1, remains personally wary of it. “I don’t take this virus for granted. It can kill you. I’ve been very sick with it several times in my life, and I know what a real enemy it can be. If it spread more widely, even in its current form, which is not highly virulent, it could kill a bunch of people.” As he likes to point out, forecasting viral behaviour remains more uncertain even than trying to predict earthquakes.

Geoff Watts freelance journalist, London geoff@scileg.freeserve.co.uk

Competing interests: None declared.


Cite this as: BMJ 2009;339:b3046