What is the basic ecology of influenza?

All influenza type A viruses likely originated in wild aquatic birds, and they've moved out to other hosts from there. The next layer is the intermediate hosts. Domestic animal species — mainly poultry and pigs — most often transmit the viruses to humans. Once the viruses have found their way from their natural wild hosts into domestic species, they behave differently. Something about these domestic reservoirs seems to increase the virus's ability to infect people.

What are the biggest unanswered questions when it comes to these interspecies jumps?

What, all of a sudden, makes an animal virus a human virus? What specific virologic factors, what host factors, what environmental factors, align to allow that to happen? We're starting to gain greater understanding of the types of viruses circulating in animal populations, but we don't have a firm grasp on which of them we should be most concerned about.

"If there's anything that keeps many of us up at night, it's the H5 virus."

The wildlife component is probably still one of the biggest missing pieces and it's one of the hardest to study. At least with the domesticated species you don't have to chase them around too long to catch them.

Still, we have learned a lot in the past decade. You pick up an old textbook and it'll say if a virus is to jump from the aquatic bird reservoirs to humans, it probably has to go through an intermediate mammalian host, like a pig. The H5N1 strain of the influenza A virus — the bird flu that emerged in Asia in the late 1990s — taught us that viruses can also use domestic poultry as the intermediate host. I can't think of many viruses that can pass directly between birds and humans besides influenza — certainly none that have the same capacity to cause human disease.

Did bird flu teach us anything else?

H5N1 resulted in a lot more resources being put into understanding the animal reservoirs of influenza. Before bird flu emerged, what information we had typically came from fairly confined geographical regions. But in the last ten years we've increased that knowledge a lot, and now we understand more about the virus in different parts of the world. Of course, there are still many gaps to fill, but we're certainly much better off.

Do wild birds experience flu like people do?

Not really. Flu-infected wild birds don't usually appear to be sick. It's a fairly stable host-micro-organism relationship, most likely evolved over millions of years, and the virus doesn't cause many symptoms in the birds. When influenza viruses first enter a new host species, they might cause a lot of disease but mortality drops over time. The virus is now simply using wild birds as a means to propagate and maintain itself. Highly

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Q&A

The flu catcher

Richard Webby studies the ecology of influenza, trying to better understand how certain strains of influenza can leap across the species divide from animals to people. Nature Outlook sat down with him to learn more about his research.

pathogenic forms of avian flu typically arise through evolution in domestic poultry species, and when they transmit back to wild birds, sometimes they've become more virulent or severe and do cause mortality in that bird species. But that's the exception rather than the rule.

How do wild birds transmit flu amongst themselves?

That's still unclear. One research angle is trying to understand hotspots of virus activity. The Delaware Bay region on the US east coast, which my colleagues and I have been studying, is a prime example. Shorebirds stopping in on their northward migration in May to feed on the eggs of spawning horseshoe crabs seem to have a very high prevalence of influenza. There's something special about that environment — probably that there are huge numbers of birds, many of them naive for influenza, coming together in one location at one time — and the virus spreads very rapidly. A few studies looking at those same bird populations further up or down their migratory path have shown much lower influenza burdens. Flu hotspots also appear in Australia, and we have some ongoing studies in Alberta, Canada. But they probably occur in many other parts of the world as well, where waterfowl gather to feed or breed.

How many types of influenza viruses circulate in wildlife?

The influenza virus has two major proteins on its surface: hemagglutinin (H) and neuraminidase (N). Within the aquatic bird populations there are 16 serologically and genetically distinguishable hemagglutinins and 9 different neuraminidases. This is where the flu subtypes get their names, like H5N1. Most — but not all — of the 144 possible combinations have been found circulating in wild birds. When we start to move away from that natural reservoir into domestic animals and humans, the diversity of viruses diminishes.

Are other animals besides wild birds and domesticated poultry and pigs part of the influenza ecosystem?

In terms of wildlife, it's not just birds. We also have good serologic evidence that wild pigs can be infected by flu, and there are very likely other wild hosts that we know nothing about at all. When it comes to domesticated species, horses tend to harbour a horse-specific lineage of influenza virus, though that virus recently transferred to dogs. And the H5N1 bird flu virus and the 2009 H1N1 pandemic virus, which was widely called swine flu, have both jumped into dogs and cats. Exactly what role those animals play in terms of the ecology of flu is unclear, and I don't think we have a good handle on what the true prevalence of the virus is within their populations. But certainly they can be

hosts, they can get infected from other species, and they can probably transfer the virus within their own species as well.

Why does the influenza virus seem to be so active in jumping between animals and people right now?

That's the question everyone is asking. Certainly the much larger demand on protein from the global population and rearing animals in larger numbers in smaller areas play a role in the evolution of some of these viruses. And these practices are also bringing domestic species into more contact with wild species.

What questions are you trying to answer with your current research?

We're focused on understanding how viruses behave over time within a given animal population, whether that be wild bird populations, poultry markets or swine herds. We are going back to some locations repeatedly to understand how the viruses themselves and their prevalences change over time. Then, if we do detect interspecies transmissions, we study

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these viruses in animal models to understand the virologic basis for the differences in epidemiology that we see on the ground. For instance, we're undertaking a fairly large study with colleagues at the National Research Center in Cairo to study people regularly in contact with poultry to understand the real prevalence of the H5N1 bird flu virus jumping into humans. Typically, we only detect the virus in people with severe disease symptoms, since they're the ones that come into hospitals. But that's very likely just the tip of the iceberg — and we have absolutely no idea how big the iceberg is. We've also been going back to some US swine farms to study circulating viruses — how they come into these populations, how long they stay, and how they leave.

It's very practical research. For example, here at this WHO meeting we're using detection data from over the past year to make sure that we have the right diagnostic capacities to detect the most current strains, and ultimately have the right vaccines to protect the public.

Nearly 3 years on, what's the lesson from the 2009 H1N1 swine flu pandemic?

The most important lingering question is finding out what was special about the H1N1 pandemic virus that allowed it to become established in humans. There's a lot of work studying the differences between it and the viruses that were circulating in pigs before the pandemic that never successfully jumped to humans. Had somebody identified the pandemic virus in pigs before the outbreak, nobody would have been

jumping up and down. It had none of the hallmarks that would have had us scuttling to make vaccines against it — no functional PB1-F2 protein, which contributes to a flu virus's lethality, for instance, and no novel gene segments. That's obviously not good. We hope this research will help us predict which viruses we need to be most concerned about.

The H5N1 bird flu virus so far hasn't shown much ability to pass from person to person. What's the likelihood that the worst-case bird flu pandemic scenario will happen?

That's a tough one. The threat of H5N1 becoming a pandemic is likely lower than for any H1, H2 or H3 influenza virus because H5 isn't as contagious in humans. But if there is a virus we do not want in humans, it is the H5 because it's so deadly. One of the hallmarks of highly pathogenic influenza viruses is that they accumulate additional amino acids in the hemagglutinin protein, which are thought to allow the virus to generate a systemic infection rather than just a respiratory tract infection. Only H5 and H7 viruses are known to do this naturally.

H5N1 has had 10 years to try, which tells us that it's not one, two, or even three or four changes that are required for it to become a human pathogen — it's probably more. On the other hand, there are examples of viruses taking several decades to jump species, despite prolonged contact. So we now have a little bit of confidence that H5N1 can't become transmissible easily, but unfortunately I think it's still a possibility. If there's anything that keeps many of us up at night, it's the H5 virus.

Are there other influenza strains that researchers have their eye on as well?

There are a handful of viruses that likely pose the most threat. H5 being one because we know it infects humans and when it does, it causes severe disease. H7 poses a similar concern. Then there are the H2s, which have the capacity to be a successful human pathogen. There was an H2 pandemic in 1957, and the virus disappeared in 1968, so there's a large percentage of the population that has no immunity to that virus now.

What do you find most interesting about influenza?

It still amazes me how little we know about these viruses. There's not a whole lot to them—they're fairly simple viruses — but we really have no good feel at all for what allows them to jump species. It's an exciting field to be in. ■

Richard Webby, a virologist at St Jude Children's Research Hospital in Memphis, Tennessee, directs the World Health Organization's collaborating center for studies on the ecology of influenza in lower animals and birds.

Interview by Rebecca Kessler, a freelance science journalist in Providence, Rhode Island.