Q&A: Josef Järhult

Resistance in the wild

Like all microorganisms, viruses can develop resistance to the drugs meant to treat them, and not only in clinical situations. The rise of environmental resistance to antiviral drugs is a potential disaster we can avert, argues Josef Järhult at Uppsala University in Sweden, especially when it comes to influenza A, the virus that can lead to a human flu pandemic.

MIKAEL WALLERSTEDT

How could influenza A develop resistance to antiviral medicines?

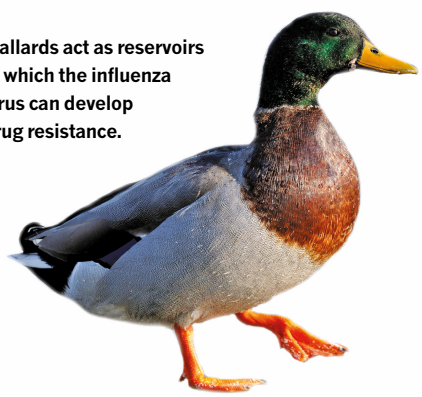
The influenza A virus has high genetic variability and mutates rapidly. It needs only one point mutation to develop resistance to certain antiviral drugs, and such mutations happen all the time.

For H1N1, the virus subtype that caused the most recent influenza A pandemic in humans, the point mutation H274Y affected the shape of the pocket where the antiviral drug oseltamivir (Tamiflu) binds to the protein neuraminidase. Neuraminidase inhibitors such as oseltamivir stop this protein cutting the virus loose from a cell and so stop the virus spreading to other cells. But the drug cannot do that if a mutation stops it binding. Such mutations rob us of a cornerstone of our defence against pandemics.

Where in the environment is it most likely that influenza A will pick up resistance to antiviral drugs?

You have to consider where the virus is going to meet the antiviral in the environment. One place that happens is in rivers. Mallard ducks are natural reservoirs for influenza, and drug residues can enter the rivers in which they live. We have seen in our experiments that low levels of the drug in water can lead to oseltamivir-resistant influenza A viruses (J. D. Järhult *et al. PLoS ONE* **6**, e24742; 2011), which can then be passed on through several generations of mallards, even if the drug is removed from the water (A. Gillman *et al. Appl. Environ. Microbiol.* **81**, 2378–2383; 2015).

For some antivirals, rivers downstream of sewage treatment plants are likely breeding grounds of resistance. Humans pass the active ingredient of these drugs out of their bodies in their urine. Sewage treatment plants do not have the technology to remove antivirals, or pharmaceuticals in general, so these drugs end up in rivers and other natural waters.



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Mallards act as reservoirs in which the influenza virus can develop drug resistance.

Are antivirals reaching rivers in sufficient quantities to bring about resistance?

The highest recorded levels of oseltamivir in river water, 865 ng l^{-1}, were found in Japan during the 2004–05 influenza season (R. Takanami *et al. J. Water Environ. Technol.* **8**, 363–372; 2010). In our work with ducks, we found that the lowest levels at which viruses developed resistance was 950 ng l^{-1}. That's a little higher than the levels measured in the environment but it's the same order of magnitude.

Japan is one of the top consumers of oseltamivir, which is why it has such high levels of the drug in its river water. But several other countries, including the United States, have a liberal policy for oseltamivir. Environmental levels in those nations could be just as high, but no one seems to be checking.

Have viruses that are resistant to antiviral medicines been found in the wild?

There have been a few reports of viruses in wild birds that have an antiviral-resistance mutation. It's uncommon but it's there. Whether this is due to drug pressure or just natural variation, I can't say. Examples from humans have demonstrated that in some circumstances the oseltamivir-resistant flu virus can outcompete all other flu strains, even in the absence of drug pressure. It's rare, but it happens. And if a resistant virus is circulating in wild birds, there is a risk that it will form the basis of a new pandemic or highly pathogenic flu.

Are some drugs more likely than others to give rise to resistant viruses?

Our experiments have shown that zanamivir (Relenza) is less likely than oseltamivir to give rise to genetic resistance in influenza A viruses in wild ducks. But it's still possible.

For any new class of drugs, such as the polymerase inhibitors recently approved in the United States and Japan, we need to study the mechanisms of environmental resistance as soon as possible, before they are used at high levels. If they are not chemically stable, or do not pass through sewage treatment plants intact, resistance may not be a problem. The sooner we know the better, so we have the opportunity to use them prudently or propose sewage treatment techniques to destroy the drugs before they get into the environment.

What can we do to prevent antiviral resistance arising?

There is no simple solution. It's good to keep a broad mindset and take a multidisciplinary approach. The network One Health Sweden, which I chair, brings together doctors, veterinarians, epidemiologists, virologists and others — everyone working on some aspect of problems that include humans, animals and the environment.

In the same way we think about cutting antibiotics use to reduce antimicrobial resistance, we also need to use antiviral drugs more prudently. For example, we should not use oseltamivir for uncomplicated seasonal influenza in otherwise healthy people.

We need effective treatment at sewage treatment plants to reduce the levels of antivirals in rivers. Ozonation treatment works but is expensive and has practical problems. And we need drug manufacturers to not release antivirals and their precursors into natural waters. Researchers in Germany have found oseltamivir's parent compound in the Rhine, probably from a pharmaceutical manufacturer (C. Prasse *et al. Environ. Sci. Technol.* **44**, 1728–1735; 2010).

We also need more monitoring of both the levels of drug residues in the environment and the flu viruses themselves, particularly in wild ducks. Our research shows that it is possible for resistance to develop in the environment. Now it is time to go and find it in nature. ■

INTERVIEW BY NAOMI LUBICK

This interview has been edited for length and clarity.