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Will the Scourge of the New Avian H5N1 Disappear?

At present, avian H5N1 virus is responsible for the death of billions of poultry birds, of tens of millions of wild birds, and of thousands of mammals, who otherwise would be alive.

Before the year 2015, avian H5N1 killed nearly 60% of poultry workers and others who became infected through close contact with infected poultry. Fortunately, the virus was rarely transmissible among humans. From 2015 to 2020 avian H5N1 fatalities in humans had almost disappeared, since the strains from nature that appeared in poultry markets were no longer deadly to humans. They were, so to speak, "defanged." We thought we were finished with avian H5N1 flu virus. We thought we were in a good place. (Note that all three of the above links open the same information-rich document.) The virus continued to kill poultry and to occasionally infect and sometimes kill people. But as the years passed, the number of human H5N1 cases dwindled.

Another type of virus that has become much less deadly to humans over time is COVID-19. These viruses are of interest here because there are many examples of how new variants of the virus became both predominant in nature and less deadly replacing previously predominant strains. To become predominant, the variant must outgrow previous strains. (The C, O, V, I, and D initials stand for **Co**rona**v**irus **i**nfectious **d**isease and 20**1**9 is the year of the pandemic's beginning.) The variant JN.1 was becoming predominant as described in a Dec 8 2023 article in the U.S. Centers for Disease Control and Prevention, and is now the predominant strain.

New COVID-19 variants have new mutations in the so-called spike protein. Spike proteins help the virus latch onto human cells and play a crucial role in infecting people. Also, the virus likely picks up mutations in other viral proteins, which could destabilize the virus making it much less deadly. The many COVID-19 variants serve as examples that are familiar to us of new strains becoming predominant and less deadly.

Regarding avian H5N1 infections, there are at least two reasons that humans have avoided infection and death. So far, there have been very few human fatalities:

(1) An accident of genome evolution that occurred millions of years ago, an extraordinary bit of luck, protects us from the new avian flu virus, at least for now. A June 28 2023 study published in Nature by several mainly Scottish authors identifies a single protein called BTN3A3 that protects humans and some other primates from the deadly and highly transmissible avian H5N1 flu virus.

(2) In the wild, workers handling dead animals wear personal protective equipment; and in the laboratory; workers are separated from the pathogens they are studying in high biocontainment laboratories.

In dairy farms, there is a notable exception because farm workers work closely with avian H5N1 infected dairy cows. The deadly, highly contagious avian H5N1 in birds and animals seems to have been replaced by a variant that causes only mild illness. In a May 22, 2024 report, there were documented only two mild eye infections in humans, likely conjunctivitis, acquired from the dairy cow virus. Avian H5N1

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infections in cows tend to be mild as well. Both the two cows and humans recovered from the mild infections. Recently, there was a third infection that included mild respiratory illness. This dairy worker reported a cough, congestion, sore throat and watery eyes. The other two patients had only eye symptoms. The worker was recovering. from the respiratory symptoms. These three observations suggest a new variant of avian H5N1 that causes only mild illness. This new variant is a mutated form of the clade 2.3.4.4b variant of avian H5N1. See here and here.

Of course, the sample size is very small, but evidence is presented later that suggests mild illness is widespread in dairy-farm workers.

The Opinion columnist for the New York Times, Zeynep Tufekci is concerned about a pandemic outcome in an opinion titled "This May Be Our Last Chance to Halt Bird Flu in Humans, and We Are Blowing It." She too focuses on dairy cow farmers and their herds and spillovers from animals spiraling out of control perhaps sparking a human pandemic.

There appears to be two responses happening at the same time; that is, they are not mutually exclusive.

(1) Should the new H5N1 variant appearing in dairy cattle and dairy farm workers be encouraged to flourish and perhaps replace the deadly and highly contagious strain that is spreading aggressively internationally? If the new variant became predominant in nature, it could put an end to the future death of poultry birds, wild birds, and thousands of mammals.

(2) Alternatively, should we aggressively vaccinate dairy cows and dairy farm workers to try to eliminate the new H5N1 variant to prevent a possible pandemic?

Both courses of action have complications as those familiar with the dairy cows and farm workers H5N1 infections are aware. Unfortunately, published analyses seem to focus only on preventing a possible pandemic, not on the potential value of a variant that causes only mild illness.

Dairy-farm workers, who acquire mild illness from cow avian H5N1 infections, should be protected against future infections as they have been so-to-speak "vaccinated" against further infection. Whether this variant would spread widely to animals outside dairy farms is an open question.

Is the outcome of protecting animals widely possible? It might be. Consider the following arguments. Infected birds flying should allow avian H5N1 flu to spread to distant locations. Many dairy farms in several states in the U.S. already have infected cows. In a Nature article titled "Bird flu in US cows: where will it end?" there is considerable data and speculation about possible rapid spread of H5N1 avian bird flu among dairy cows and dairy workers infected from cows. Of particular interest from the Nature article, the virus can hop back and forth between cows and birds, a trait that could allow it to spread across wide geographical areas. It is suspected that infection in dairy farm workers is widespread. US officials have not reported severe infections and deaths suggesting that the virus causes only mild illness; otherwise, we would have heard about it. This explanation increases the sample size dramatically.

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In another Nature article titled “Bird flu virus has been spreading in US cows for months, RNA reveals” it is speculated that the many infected dairy cow herds present today likely come from a single source.

Erik Karlsson, a virologist at the Pasteur Institute in Cambodia said that Infected birds are “dead birds flying,” a phrase likely borrowed from “dead men walking,” which was used by prisoners to describe someone on their way to execution. The complete phrase “dead birds flying spreading the disease before succumbing to it” explains how birds can spread avian H5N1 infections to distant locations; and likely explains why birds and seashore mammals in places such as the Galapagos Islands and Antarctica, now have been infected with avian H5N1. Also, it can explain why mammals far inland become infected.

While this supports the argument for a predominant avian H5N1 variant in cows that might lead to only mild infections of humans and animals, there is some data that appears to oppose this argument. Recently, avian H5N1 has been discovered in eleven house mice in dairy cattle farms. Would mice consuming avian H5N1 infected raw milk become mildly or seriously ill? In an NIH-funded study, researchers from the University of Wisconsin-Madison, Wisconsin Veterinary Diagnostic Laboratory, and Texas A&M Veterinary Medical Diagnostic Laboratory used mice to test whether avian H5N1 infected raw milk causes infections versus pasteurized milk. It turns out that mice become infected throughout their bodies, which is not unexpected. Although dairy farm workers are exposed to infected cows, they are not forced to consume the virus as in the NIH study. Even the BTN3A3 protein will not protect humans consuming the virus.

Only the future will tell how all this plays out.