We are underestimating, again, the true burden of H5N1 in humans


The recent global spread of clade 2.3.4.4b H5N1 viruses has devastated poultry production impacting national and global food security. Though clade 2.3.4.4 viruses emerged prior to 2014, it was not until late 2020 that major outbreaks in domestic poultry were observed mostly by clade 2.3.4.4b H5N1 viruses. From mid-2021, a dramatic increase in activity and geographical distribution of these viruses occurred. The clade 2.3.4.4b viruses have been able to cross the species barrier to infect terrestrial and marine mammals contributing to an unprecedented infected species list and an unprecedented number of infected animals. Additionally, at least 12 confirmed human cases with three deaths have been reported to the WHO since 2020. Cases were reported from countries in Europe, North America, South America, and Asia.

In Egypt, clade 2.2 H5N1 viruses were first detected in 2005 and became endemic in poultry soon after. Those viruses continued to circulate until 2017 when they were replaced by the sporadically detected clade 2.3.4.4 H5N8 viruses. Clade 2.3.4.4b H5N1 viruses were detected in wild migratory birds in Egypt in 2021, however, no major domestic poultry outbreaks were reported although the virus was detected in domestic ducks and chicken surveyed through research projects. The endemic clade 2.2 viruses caused 359 confirmed human cases of whom 120 died. A cohort study estimated a 2% seroprevalence of anti-H5N1 antibodies among backyard poultry growers suggesting that the true burden of human infections by clade 2.2 viruses was considerably higher than official counts. Further research estimated that the incidence of H5N1 disease in Egyptian poultry growers to be 17 in every 10000 exposed people but with the majority of infected individuals showing very mild symptoms.

Globally, 861 H5 human cases were reported between 2003 and 2019 of whom 455 died. Similar to the situation in Egypt, a meta-analysis concluded that 2% of humans exposed to sick or dead poultry were expected to be infected. Similarly, a meta-analysis conducted on Chinese H5 seroprevalence studies concluded that the seroprevalence may reach 3.2% in poultry-exposed populations. The true burden of H5 infection in humans has been underestimated as global surveillance systems tend to detect only severe cases that require hospitalisation and miss asymptomatic, mild or moderate cases. The extent of clade 2.3.4.4b human infections is unknown, but almost certainly more than the reported number, especially as this virus has shown an ability to infect several non-human mammals on a large scale.

We have been conducting field and surveillance studies for avian influenza in Egypt since 2008. Our most recent efforts were...
focused on studying potential transmission and spill-over routes of avian influenza in live bird markets. We established a study in five of those markets obtaining samples from live domestic and wild birds sold at the markets, the environment (water, air and surfaces), as well as from market workers. Between February 2022 and March 2023, we obtained written consent from and enrolled 394 adult market workers. Of those, 230 were sampled only once while 164 were available for multiple sampling. A total of 830 serum samples were collected. Sera obtained from those workers were tested for antibodies against A/ Duck/Egypt/BA20361C/2022 (H5N1) a clade 2.3.4.4b virus. Thirty-eight (4.6%) of the samples had neutralising antibodies with titres ranging from 1:40 to 1:320 (figure 1). Seropositivity was associated with gender as 5.5% of the male sera had antibodies compared with 0.6% of the females ($\chi^2$ p=0.007). Human seropositivity appeared to follow virus detection in wild and domestic birds sold live in the markets suggesting this as source of virus exposure (figure 2). Thirteen of the individuals who provided more than one sample seroconverted from negative to positive over the course of the study. Of note, our estimate of 4.6% clade 2.3.4.4b H5N1 seroprevalence is more than double that of our earlier clade 2.2 seroprevalence estimate in 2010–2011, more than 10-fold of our estimate in 2015–2017, and more than 20-fold of our calculated rate in 2017–2018 suggesting that the currently circulating viruses are more infectious to mammalian hosts.

The well-recognised limitations of our global zoonotic disease surveillance systems highlight the importance of supplementing data generated from such surveillance systems by data from field research studies at the human-animal-environment interfaces including seroprevalence studies. The scale, geographical scope and increasing list of infected species with clade 2.3.4.4b viruses urge the conduct of additional seroprevalence studies. Such data are essential to counter the substantial virological and provide evidence for proper preparedness and response. If our seroprevalence estimates from Egypt are representatives of true exposure rates across other global regions, this represents a worrying number of opportunities for this avian virus to accumulate mutations adapting it to the human host.

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Data availability statement The data that support the findings of this manuscript are available on request from the corresponding author GK.

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