



Oxford Cambridge and RSA

**Friday 15 October 2021 – Morning**

**A Level Biology B (Advancing Biology)**

**H422/02** Scientific literacy in biology

Advance Notice

**Time allowed: 2 hours 15 minutes**



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## Do Pathogens Gain Virulence as Hosts Become More Resistant?

One of the most remarkable events in the history of infectious diseases occurred in 1950. The myxoma virus (MYXV) was being tested as a biological control agent for the invasive rabbit populations in Australia. The virus escaped from test sites and caused an outbreak of unprecedented scale, speed, and carnage. Within just six months, it was affecting rabbit populations across the country, causing a disease known as myxomatosis. This was a surprising gift for farmers, whose crops were being eaten by hordes of rabbits. Over the next decade, rabbit populations across the country were reduced by 90%<sup>[1]</sup>. Populations have since recovered, but the number of rabbits remains much lower than before the release of MYXV.

The release of MYXV presented an opportunity to study the evolutionary arms race between a pathogen and its host animal. Australian microbiologist Frank Fenner took advantage: he set up experiments that ran for more than 35 years<sup>[2]</sup>. His work has revealed the evolution that happens when a virus emerges in a new host population. Fenner's work has also shed light on how pathogens may evolve in the face of vaccination and genetic engineering, which make hosts more resistant to their infections.

### Virul virulence

Virulence is a measure of the severity of the disease caused by a pathogen. The original strain of MYXV was highly virulent: almost every infected rabbit died within two weeks. Fenner wanted to know what happens when such a virulent virus spreads through a very susceptible host species on a continental scale. He focused on two possibilities. First, the highly lethal virus may evolve to become less lethal. Second, the highly susceptible rabbits may evolve resistance to infection. We now know Fenner's answer: they both happen.

Let's start with the virus. Fenner's work showed that the original, highly virulent MYXV strain was replaced within a few years by strains with fatality rates of 70–95%. Fenner showed that the most virulent virus strains killed rabbits remarkably quickly. The less virulent strains were able to infect more new victims and spread throughout the population. However, the most benign strains of MYXV were also less infectious; host immunity was able to control and clear them more rapidly. As a result, there was a limit to the reduction in MYXV virulence.

Wild Australian rabbits also evolved in the 1950s. Resistance to infection is the ability of an organism to defend itself against pathogens. It can include immunity to pathogens, but other factors may also be involved. The genetic disease resistance some rabbits evolved meant that they could clear MYXV infections more rapidly, and this reduced virus transmission. However, the resistance is not perfect: it does not prevent infection or transmission. The virus was therefore able to evolve in resistant rabbit populations. Viral mutants that were better able to overcome enhanced antiviral host defenses are favoured by natural selection. As a consequence, the virulence of MYXV began to increase again.

### Implications for agriculture

Intensive farming is only possible if infectious diseases can be controlled. Enhancing the resistance of farm animals to infectious disease is an aspiration of veterinary medicine and most agricultural industries. Selective breeding, genetic engineering, and immunisation can all be used to make animals more resistant to infections. However, is it possible that such efforts will unintentionally select for the more virulent pathogens?

If hosts are completely resistant, onward transmission of pathogens will stop, and their evolution will cease as well. But artificially enhanced resistance is often imperfect. Many vaccines used on farms do not render hosts impervious to infection, and animal breeders have yet to produce animals that are 100% resistant to various infections. Given what scientists now know about pathogen-host arms races, we should take seriously the possibility that resistance in farm animals may trigger the evolution of greater virulence in pathogens.

In fact, this may have already happened. Marek's disease virus (MDV) is a highly contagious, cancer-causing pathogen that infects poultry. MDV has become more virulent over the last 50 years<sup>[3]</sup>. When the poultry industry began to grow in the 1950s, MDV caused mild disease and had little economic impact. Nowadays, some MDV strains can kill all unvaccinated birds within 10 days. Unless birds are vaccinated, the losses are devastating. Critically, and for reasons not fully understood, MDV vaccines protect against disease, but they do not destroy the virus.

In a series of experiments, scientists found that hypervirulent strains of MDV can exist only in vaccinated flocks. In unvaccinated birds, the hypervirulent strains kill before they have a chance to be transmitted. Vaccines keep infected birds alive, but vaccination creates the conditions for hypervirulent strains to emerge and persist<sup>[4]</sup>.

There is no question that MDV has become substantially more virulent over the last 50 years. Yet industry losses to Marek's disease are much lower than they were when less virulent strains circulated. Today's hypervirulent MDV strains cause less severe disease in vaccinated birds than milder MDV strains caused in unprotected birds. Current viral strains cause problems only when they infect unvaccinated flocks—for example, organic farms, small outdoor flocks, or farming systems with faulty vaccination practices.

Breeding companies often use selective breeding, in addition to vaccination, in an attempt to enhance resistance in poultry. Particular major histocompatibility complex (MHC) alleles in poultry reduce the severity of symptoms caused by MDV. There are concerted efforts to spread these alleles through flocks of poultry. This selective breeding, as well as the development of genetically engineered resistance<sup>[5]</sup>, may further encourage the evolution and spread of virulent strains. For example, some transgenic chickens suppress the replication and transmission of avian influenza, but don't block it entirely. This is analogous to the antiviral effects of MYXV resistance that arose in Australia's rabbits. Were these GM chickens to become widespread, it is easy to imagine that, just like the rabbits in Australia, they would cause the evolution of hypervirulent viruses. For this reason, some scientists suggest that breeders and engineers try to do something that may seem counterintuitive: breed and engineer birds that are highly susceptible to pathogens.

## References

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4. A.F. Read et al., "Imperfect vaccination can enhance the transmission of highly virulent pathogens," *PLOS Biol*, 13: e1002198, 2015.
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