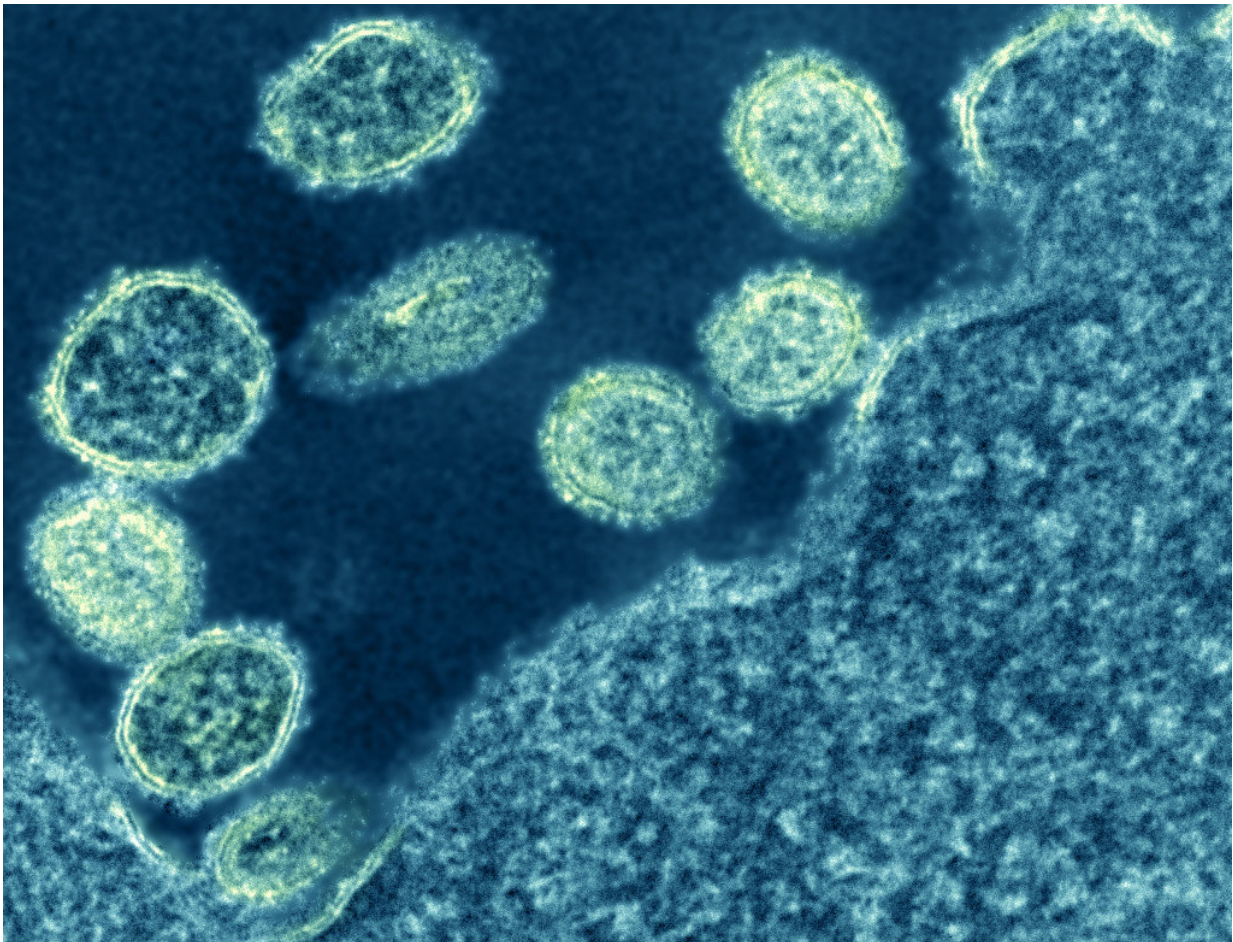


Why pandemic influenza is so deadly – revealed

September 18 2018, by Aartjan Te Velhuis



Electron microscopy image of 1918 influenza virus particles near a cell. Credit: NIAID, [CC BY](#)

The Spanish flu virus infected a third of the world's population 100 years ago and claimed the lives of up to [100m](#) people. The virus continued to evolve and its descendants went on to cause all subsequent flu pandemics, leading to the 1918 pandemic flu to be called the "[mother of all flu pandemics](#)". The US army [predicts](#) that if a similar flu virus emerged today, it would kill 2.8m people in the US alone or six times more than the 1918 flu. How can a virus be so deadly?

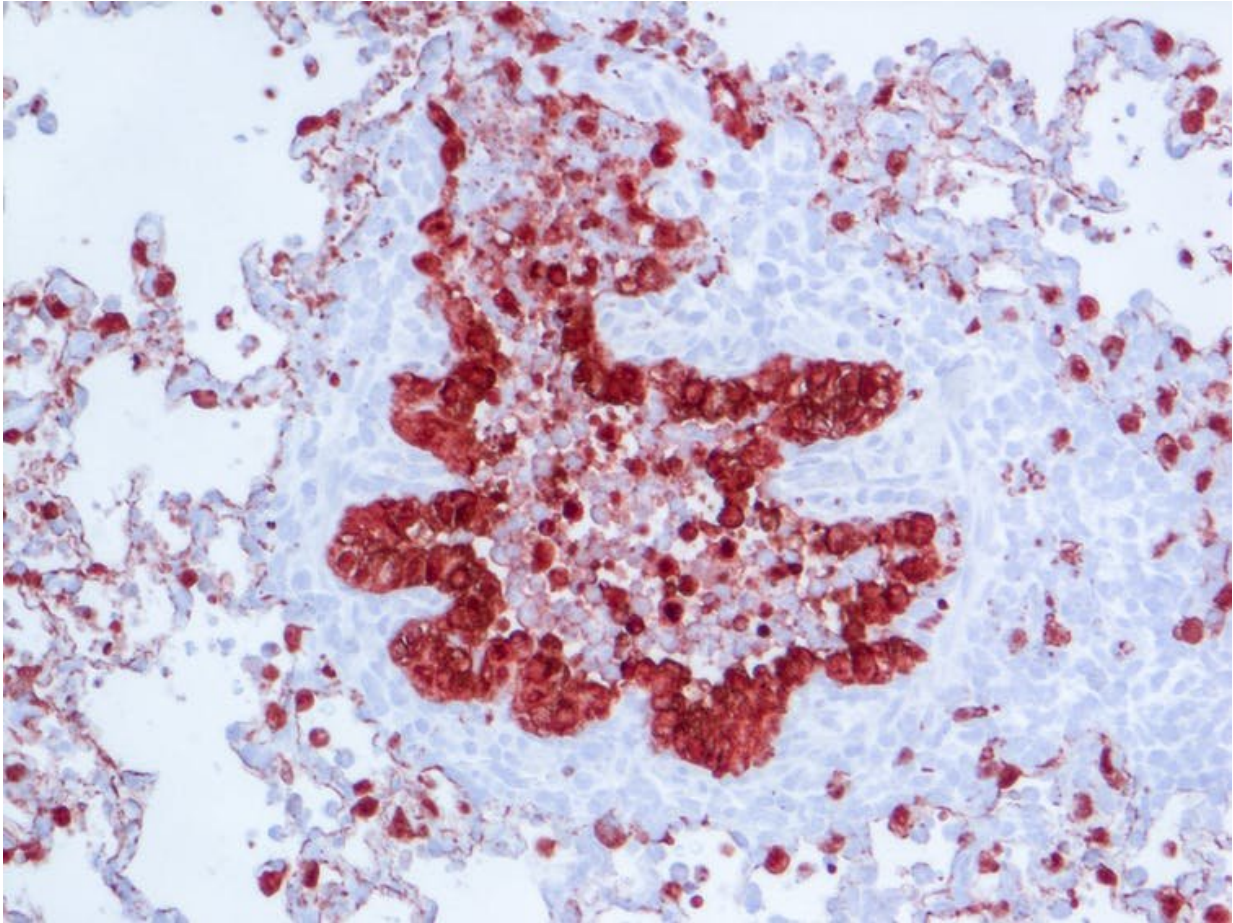
Flu viruses are tiny particles that can enter the cells of a bird or mammal, such as a human. Viruses do this because they have no resources of their own and need to steal components and energy from our cells to copy themselves. They also constantly [mutate and mix](#) their genetic information to adapt to our cells.

To protect us from infection and disease, our immune system can detect flu and fight back in several ways. For instance, [specialised proteins](#) look for genetic material of the [virus](#) inside our cells and trigger signals to warn neighbouring cells that a virus is present.

If necessary, the immune system will even force infected cells to self-destruct to prevent the virus from spreading. Antibodies can also neutralise viral proteins in our airways or "flag" viruses for destruction by specialised immune cells. This is why we use vaccines: to show our immune system the viral proteins of potential future infections so that our bodies are prepared for them.

Our immune system also plays an important role in the severity of infections with [pandemic](#) flu and [bird flu](#). Most of the seasonal [flu viruses](#) that we encounter have become well adapted to us as hosts over time and copy themselves relatively undetected by our immune system. But flu viruses can also "jump" between animals, such as from [birds](#) to humans. This means that we can suddenly be faced with a [type of flu](#), such as an H5N1 bird flu, that we have never seen before and that is not

adapted to our cells.



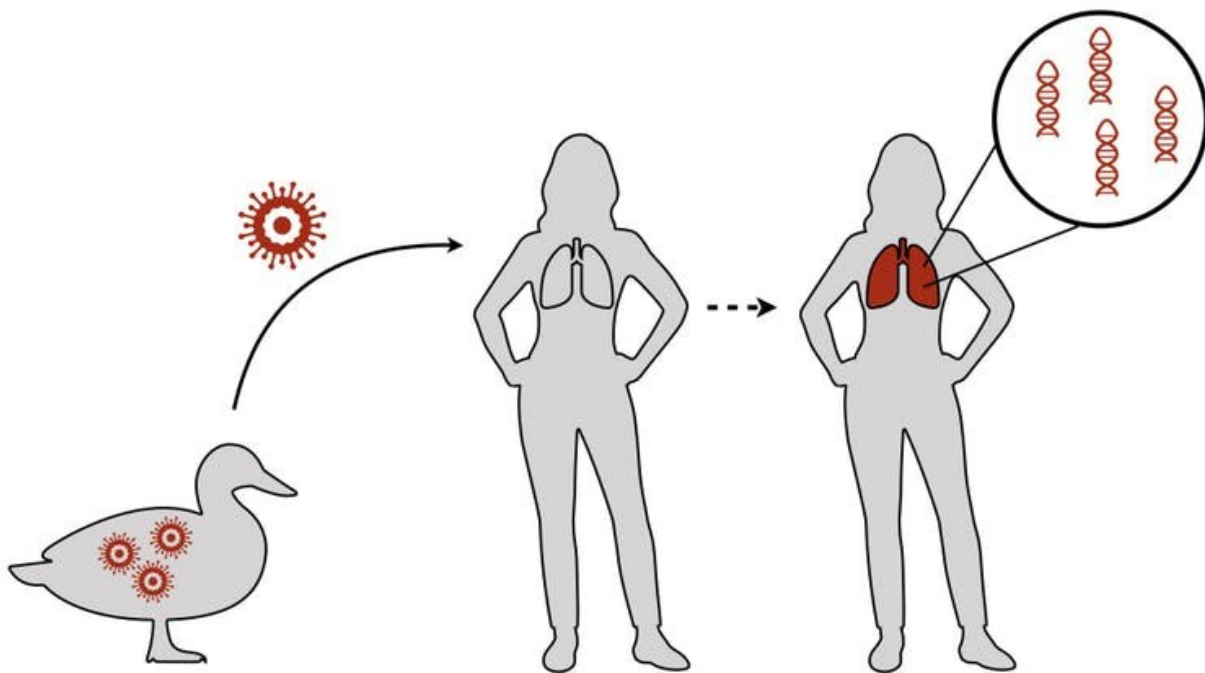
Bronchiole of a lung infected with the 1918 flu virus. Infected cells are stained red. Note the lack of airspace inside the bronchiole due to white blood cell infiltration. Credit: Jurre Siegers and Debby van Riel, Erasmus Medical Centre

Our immune system detects these viruses and launches a violent counterattack, or "[cytokine storm](#)", which is so strong that our lungs fill up with white blood cells, fluid and blood, and we effectively drown.

Spotting viral garbage

We roughly know which viral and cellular proteins contribute to the destructive response. But why it is initiated by pandemic and avian flu viruses is far from clear. In our [recent study](#), we looked at what the immune system "senses" when the genetic information of flu viruses is copied. We found that it focuses strongly on tiny "faulty" molecules of genetic viral information. So our immune system sees viral "garbage", while the normal genome of the virus remains undetected.

The Spanish flu virus and the H5N1 bird flu make more faulty genomes in human lung cells than a virus that is adapted to these cells. Also, when you take the enzyme that copies the genome of a harmless flu virus and change it to make it similar to the enzyme of the Spanish flu virus, this engineered enzyme immediately starts making more faulty molecules and overstimulating the immune response. The original enzyme does not.



Flu viruses that ‘jump’ from another animal, such as a bird, cause severe disease in the lungs. During these infections, the virus produces molecules called mini viral RNAs that trigger strong immune responses.

Dangerous flu viruses make a molecule that causes disease when these viruses get inside our cells. We think this is because they have not had enough time to adapt and are copying themselves incorrectly. This idea is supported by other [recent observations](#) and may be important for diseases caused by other emerging viruses, such as Ebola.

A century after the Spanish flu pandemic, we are finally in a position to better understand what makes pandemic and bird flu viruses deadly. This will help us look for ways to neutralise the harmful molecule and be ready if a new pandemic strikes.

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