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OCTOBER 2014. The World Health Organization warns that there could soon be more than 10,000 new Ebola cases in west Africa every week. “We either stop Ebola now – or we face an entirely unprecedented situation for which we do not have a plan,” declares the head of the UN response team. As pictures of the dead lying in the streets race round the world, many fear a runaway pandemic of Hollywood proportions.

In the US, these fears reach fever pitch after a man who had just returned from Liberia dies of Ebola. A teacher who stayed in a hotel 10 miles away from the hospital where the man was treated is told to stay away from school just because she’d been in the same town. A busload of passengers is quarantined when a woman vomits after getting off.

Six months on, the picture is very different. Ebola has faded from the headlines. With belated help from around the world, the outbreak has been contained, if not yet eradicated. In total, just over 10,000 people have died – an awful toll but hardly comparable to the Spanish flu of 1918, which killed around 50 million, or the Black Death, which wiped out half the population of Europe in the 14th century.

The fact that Ebola sparked such panic is perhaps more a reflection of our appetite for books and movies featuring catastrophic plagues than reality. But are those scenarios pure fiction? Are we now advanced enough to beat the worst that nature can throw at us? Or have we just been lucky? Are there viruses out there that are just a few mutations away from becoming unstoppable killers that really could wipe out half the human race?

**Killing potential**

Four factors determine the severity of any disease outbreak, says epidemiologist Christophe Fraser of Imperial College London: how deadly it is; how easily it spreads from person to person; if and how long a person is infectious before symptoms appear; and whether it can be prevented by vaccines, treatments or both. Diseases can wreak havoc even if they have only some of these traits, but it is the ones that score highly on most or all of them that we really need to worry about.

Looking at this way, Ebola is less fearsome than it first appears. True, it is deadly, killing more than half the people it infects, and no vaccine is yet available. But it doesn’t score highly on the other factors. It isn’t easily transmitted, as it only spreads via direct contact with body fluids. And people are not infectious until they start showing symptoms, so they can be isolated or quarantined before passing on the disease to others.

Ebola was therefore never likely to rampage out of control in rich countries. It managed to infect so many people this time round only because of poor healthcare, and because people did not know how to stop it spreading, says Derek Smith of the University of Cambridge, who studies emerging infectious diseases. Once well-established protocols were in place, it was quickly contained even in some of the poorest countries in the world.

If the Ebola virus mutates to become airborne, it would become more of a threat – but most virologists think such a change is unlikely. The virus would have to undergo major changes, such as being able to bind to and infect the cells lining the upper airway. And even when viruses can spread via the air, they do not necessarily run riot. In 2002, for instance, people in China began to die of what was called Severe Acute Respiratory Syndrome. SARS was better at spreading than Ebola, and airborne transmission was implicated in at least one cluster of cases. Within months it had reached dozens of countries, infecting around 8000 people and killing about a fifth of them.

Crucially, though, it scored low on factor three: symptoms appeared before people became infectious, so they could be quarantined before they began spreading the virus. This, along with the rapid discovery of the virus and how it spreads, stopped the...
outbreak within a year. “Most virologists think modern science and public health measures stopped a global and very serious SARS pandemic,” says Smith.

There is one deadly virus that scores very highly on factor three: people with HIV are infectious for years before symptoms appear. This has enabled the virus to spread around the world and kill around 36 million people, even though it is very poor at spreading from person to person.

H1N1 swine flu, by contrast, spreads with ease. It is contagious for about a day before symptoms appear, and when it first emerged in 2009 no vaccines were available. Over half the world’s population was probably infected within the first year, says Smith. Thankfully, the strain was not much more lethal than normal flu, although it was more likely to hit younger people hard.

So none of the diseases that have emerged recently ticks all the boxes in Fraser’s four-point profile of the perfect killer (see graphic). Have we just been lucky? Could such a pathogen emerge in the future?

Public health advances have undoubtedly helped prevent emerging diseases like SARS and Ebola killing many millions. Yet in other ways, we are more vulnerable than ever before. There are now 7 billion of us on Earth – an awful lot of potential hosts for a pathogen to exploit. And thanks to air travel, diseases can spread around the world faster than ever.

There is certainly no shortage of viruses waiting in the wings. Diseases like Ebola are caused by viruses that live in animals jumping into humans: bats are thought to be Ebola’s natural host. And it’s estimated that mammals alone play host to hundreds of thousands of unknown viruses.

We already know that a few are capable of killing people given half a chance. The Nipah virus, for instance, was first identified in Malaysia in 1998 after killing 105 people. Should we be concerned about these kinds of viruses? Definitely, says Ron Fouchier of the Erasmus Medical Centre in Rotterdam, the Netherlands, who helped identify SARS. “Perhaps they could acquire the ability to sustain transmission between people. We don’t know.”

It’s a close relative of SARS that is keeping many virologists awake at night at the moment. MERS, or Middle East Respiratory Syndrome, emerged in Saudi Arabia in 2012. It keeps jumping into people from some animal host, possibly camels. It has infected around 1000 people and killed 400. Fortunately, it rarely spreads from person to person, but the more people it infects, the more opportunities it will have to evolve this ability.

Even if MERS never starts spreading from person to person, another animal virus is certain to at some point. If we don’t stamp on these emerging diseases quickly, as we did with SARS, a global pandemic could result.

The good news, though, is that it is unlikely that an animal virus jumping into humans could instantly acquire the four traits of a perfect killer. In particular, they are usually poor at spreading from person to person. The viruses that spread most readily in people, like the cold-causing rhinovirus, have evolved this ability over countless generations of plaguing our ancestors. And as viruses get better at spreading, they tend to become less deadly — although this may not always be true.

But there is one virus that might be able to acquire all four traits almost instantaneously: flu. New strains of human flu already tick almost all the boxes: they spread readily from person to person, are infectious for at least a day before symptoms appear, and it takes six months to a year to make a vaccine. The one trait they lack is deadliness. By contrast, some animal strains of flu, such as the H5N1 bird flu that emerged in 1996, are extremely deadly when they manage to infect people but very rarely pass from one person to another.

Influenza viruses not only have a high mutation rate, they also have a nifty trick up their sleeve: they can “reassort”. The flu genome consists of eight pieces of RNA. When two different flu strains infect the same cell, their progeny can have a mixture of RNAs from both strains — and thus a mixture of their characteristics. “At least three out of four pandemics of the last century emerged upon reassortment of flu viruses in humans or pigs,” says Fouchier.

Colossal threat

So the crucial question is whether mutation, reassortment or both could create a form of flu that combines the deadliness of some bird flu strains with the infectiousness of the strains that circulate in people. Such a virus would be a colossal threat, capable of killing on a catastrophic scale. This is what Fouchier and others have been trying to find out.

In 2012, after tinkering with the H5N1 virus and seeing if they could infect ferrets, he and his colleagues announced that with just a few mutations in two genes, the H5N1 bird flu strain might be able to spread readily in humans. First, the virus would have to become capable of binding to receptors on epithelial cells in our upper respiratory tract. In most viruses, such as Ebola, this requires major changes, but with bird flu only minor tweaks will do it. Second, it would have to be able to replicate effectively at a lower temperature, because the human upper respiratory tract is cooler than the gut of the bird. Altogether just five mutations might do the trick — and there

**Could a flu virus emerge that combines the deadliness of bird flu with the infectiousness of human strains?**

| Plague potential |
|------------------|
| Four main factors determine how severe a disease outbreak will be. We are yet to face a virus that ticks all the boxes |

| Deadliness | Kills a large proportion of infected people |
|------------|------------------------------------------|
| Ebola      | {red}✓{/red}                             |
| SARS       | {green}✓{/green}                         |
| HIV        | {green}✓{/green}                         |
| H1N1 swine flu (2009) | {green}✓{/green} |
| H5N1 bird flu | {red}✓{/red} |
| MERS       |                                          |

| Spreads readily | Infected people rapidly infect others |
|-----------------|--------------------------------------|
| Ebola           | {red}✓{/red}                         |
| SARS            | {green}✓{/green}                     |
| HIV             | {green}✓{/green}                     |
| H1N1 swine flu (2009) | {green}✓{/green} |
| H5N1 bird flu   | {red}✓{/red}                         |
| MERS            | {red}✓{/red}                         |

| Hard to contain | People become infectious before showing any symptoms |
|-----------------|-----------------------------------------------------|
| Ebola           | {red}✓{/red}                         |
| SARS            | {green}✓{/green}                     |
| HIV             | {green}✓{/green}                     |
| H1N1 swine flu (2009) | {green}✓{/green} |
| H5N1 bird flu   | {red}✓{/red}                         |
| MERS            | {red}✓{/red}                         |

| No vaccine at first | It takes months at least to mass produce a new vaccine |
|---------------------|------------------------------------------------------|
| Ebola               | {red}✓{/red}                         |
| SARS                | {green}✓{/green}                     |
| HIV                 | {green}✓{/green}                     |
| H1N1 swine flu (2009) | {green}✓{/green} |
| H5N1 bird flu       | {red}✓{/red}                         |
| MERS                | {red}✓{/red}                         |
are other strains of H5N1 out there that already have two of these mutations, which the nasty strain could acquire by reassortment.

Could this really happen? “We found that it’s certainly within the realms of possibility,” says Smith, whose team has investigated how easy it might be for the virus to mutate in this way.

This sounds extremely alarming, but there are two big “buts”. Firstly, while 60 per cent of people hospitalised with H5N1 bird flu have died, Fouchier thinks that many mild infections have gone undetected, meaning it is not as deadly as it appears.

Secondly, while it might not take many mutations for H5N1 to become more infectious, the same mutations could well travel as deeply into the bodies of other people before reaching cells they can infect.

So when bird flu viruses mutate to target the upper respiratory tract, they may become less deadly. But even if this process reduced the lethality of an airborne virus by 10 or even 100 times, it would still be thoroughly nasty, Smith says, killing perhaps 1 in 200 people – on the scale of the 1918 Spanish flu pandemic.

And this is as much as we know for now. While it seldom makes headlines any more, the threat from bird flu certainly hasn’t gone away. In fact, it has grown worse. Not only is H5N1 still circulating in wild and domestic birds, but a nasty new H7N9 bird flu emerged in 2013. “Based on what we know, it would require only a little bit of tweaking to acquire airborne transmissibility,” says Fouchier.

If it did, could we stop a 1918-style virus rampaging around the world? The vaccine for 2009 H1N1 swine flu arrived only after the first wave of infections around the globe, but Fouchier thinks we might do better next time. “If we recognise the threat very, very early, there’s a good chance we’d be able to protect some of the at-risk groups in time,” he says. “We certainly should be able to protect everybody for the second wave.”

So Fouchier and Smith think the death toll from pandemic flu will never be as high as 1918. Fraser thinks otherwise: we can’t assume that a virus with similar properties won’t emerge in future, he says. “And there is little evidence that we could effectively control the global spread of such a virus.”

The number of deaths is also only part of the story. The Ebola outbreak may only have killed 10,000, but the impact on the most-affected countries has been devastating. Whole countries have been shut down for days at a time, with borders closed, regions quarantined, schools shut for months and flights cancelled. Nearly half of workers were unable to earn a living even as food prices rose. Developed countries may be even more vulnerable to this kind of disruption, as their societies are so much more complex and interdependent.

For those who fear a sci-fi-style apocalyptic plague, though, the idea that the biggest threat is a rerun of the 1918 flu pandemic may be reassuring. But no one can be sure what’s coming next. “Viruses are unpredictable,” says Fouchier. “There will always be new ones that come when they’re least expected.”

And while it doesn’t seem likely, the possibility that we’ll find ourselves facing a particularly nasty one cannot be ruled out. “It is feasible to imagine worse epidemics than we have experienced in the last century,” says Fraser. “I would advocate preparing for such eventualities.”

It is not just wild viruses we need to worry about. Fouchier’s tinkering with H5N1 triggered a storm of controversy: might the engineered viruses start a pandemic if there was a slip-up in the lab? Was the published work tantamount to a recipe for creating a terrible bioweapon? There are good grounds for concern. The 1977 flu pandemic was probably caused by the escape of an old human flu strain from a lab, for instance.

The furore over Fouchier’s work has led to an effective ban on this kind of flu research for now, but flu is not the only threat. In 2001, New Scientist revealed that biologists had accidentally created an extremely deadly version of a rabbit virus. In 2003, “biodefence” researchers in the US deliberately altered a mouse virus in this way. Could a deadly virus capable of spreading in people be created accidentally or deliberately, and somehow escape the lab? Let’s hope we never find out.

Emma Young is a freelance writer based in Sheffield, UK