The rules of contagion-New Scientist

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FRANCE, 1918: a new, lethal strain of influenza sweeps through the trenches, killing even young, fit soldiers. Within weeks the outbreak has spread to ports of call in Africa, North America and onward. Over the next two years, at least 20 million people worldwide will die in the worst epidemic since the black death.

DEMOCRATIC REPUBLIC OF CONGO, 2002: Ebola virus resurfaces, killing nearly 90 per cent of those who catch it. The epidemic does not spread much beyond the country's borders, however, and within months it fades away, leaving a total death toll of just 128.

YOUR TOWN, last winter: cold viruses rage through schools and offices. Almost everyone catches at least one, yet the epidemic rarely causes sufferers more than a few days' stuffiness and discomfort.

Three diseases, three widely different outcomes. Why do some pathogens cause deadly pandemics while others result in just a local crisis or widespread but minor inconvenience? It's no trifling question: if we could answer it, we could predict whether newly emerging diseases are likely to explode into an epic plague or fizzle out like a damp squib, and could also spot potentially fatal diseases lurking in the wings. Better yet, knowing how and why some pathogens take the evolutionary road to Armageddon, we might be able to devise ways to alter their destiny, stacking the evolutionary deck in our favour to produce milder diseases.

You'd be forgiven for calling this wishful thinking. It certainly isn't easy to explain why some pathogens turn really nasty. Yet, as specialists gain insight into the way diseases emerge and spread, they are beginning to understand the complex evolutionary pressures that determine just how contagious a particular disease will become, and how much of a wallop it will pack. So what can these insights tell us about the threat posed by the likes of bird flu and SARS? Can they help us identify other possible pandemics, or even avert the next "big one"?

The key feature to worry about in any disease is its level of virulence - that is, how sick it will make you. For many years, the standard view among experts was that pathogens inevitably evolve to be less virulent over time. After all, the reasoning went, any germ that kills its host is out of a home, so a pathogen should prefer its host to be up and about, spreading the infection to others. The nasty diseases, in this view, are either relative newcomers to humans or else accidental colonists from other species that have not yet reached a gentler evolutionary equilibrium.

Take the H5N1 strain of bird flu. It is certainly nasty now, killing around 50 per cent of the people it has infected so far, but that's because it is not yet readily transmissible between humans. If that happens, it will surely become less virulent so that it no longer poses such a serious threat. Right? "I hear this all the time," says Irene Eckstrand, who directs an infectious-disease research programme at the US National Institute of General Medical Sciences in Bethesda, Maryland. "In fact, there's no data to back it up."

What is emerging instead is a more nuanced view of how virulence evolves. In this new understanding, pathogens can evolve widely different levels of virulence depending on their circumstances. The crucial factor seems to be transmission - and in particular the manner and ease of a pathogen's spread. Diseases such as respiratory viruses, which are passed on by sneezing, coughing and other forms of direct contact, depend on an infected person being able to move around and mingle. For these pathogens, you would indeed expect

evolution to favour low virulence. Sure enough, diseases spread by direct contact, such as the hundreds of viral infections collectively referred to as the common cold, do tend to be innocuous.

At the other extreme, diseases spread by mosquitoes or other vectors have much less to lose by disabling their host. "If a human is feeling a little delirious from malaria, that person will still transmit the malaria as well - even better, since a delirious human is less likely to swat the mosquito," says Paul Ewald, an evolutionary biologist at the University of Louisville in Kentucky, who has been one of the most outspoken proponents of the new view of disease evolution. Again this tallies with reality: vector-borne diseases such as malaria, yellow fever and sleeping sickness are among the world's most virulent infectious diseases. Similarly, water-borne diseases and those spread via faeces are likely to severely sicken their host.

Influenza, which we tend to think of as a respiratory disease, may owe some of its virulence to this principle, since it is transmitted via faecal-oral contact in its native waterfowl hosts. Nevertheless, Ewald is optimistic that the H5N1 strain will become less deadly if it evolves the ability to spread from human to human. In its present form, it targets the delicate cells lining the alveoli, deep within the lungs. To become more contagious, it would have to shift its infection site to somewhere higher up in the lungs to improve its chances of being coughed up in significant numbers. "When it infects the alveoli, you get a lot of damage, you get immune over-response," says Ewald. "When you infect the upper respiratory tract, you don't have that damage. So you should see virulence plummet."

There is another important consideration, though. A pathogen's evolutionary path is also likely to depend on its durability. Those that can survive a long time outside their host - on doorknobs or in bedding, for example - can simply sit and wait for a new host to come to them, rather than depending on their current one to pass them on. In that case, even direct-contact pathogens may pay little price for becoming more virulent.

That's exactly what Ewald and Bruno Walther of the University of Copenhagen in Denmark found when they compared the mortality rate and survival time outside the host for 16 pathogens of the human respiratory tract. The six most deadly, causing smallpox, diphtheria, tuberculosis, influenza, pertussis (whooping cough) and pneumonia, were also able to hang on the longest outside people - up to several weeks or months (Biological Reviews, vol 79, p 849).

With this in mind, Ewald says the first thing public health officials should test when they encounter a potential new disease is the pathogen's durability, which should take little more than a week. "If it's not durable, it is not as much of a concern," he says.

By this measure we should not worry too much about Ebola, which does not last long outside its host and so is unlikely to spark a major epidemic, despite its high virulence. High on Ewald's worry list, however, is the highly durable monkeypox virus, a pathogen that presently occurs mostly in central and western Africa in a variety of host animals, including monkeys, rats, mice and rabbits. Monkeypox was first recorded in humans in 1970, and there have been several outbreaks since, including one in the US in 2003 when people come into contact with infected pet prairie dogs. "To me, these are of more concern than outbreaks of Ebola," says Ewald.

Diseases such as SARS and bird flu, which are much more virulent than their durability would predict, do not follow this pattern because they have evolved in other host species and only accidentally infect humans, says Ewald. If and when they make the jump to humans, natural selection should rapidly lower their virulence, he predicts.

Understanding the forces that influence disease evolution does not only highlight potential trouble spots. Ewald also believes it might let us turn evolution to our own end to discourage serious diseases from emerging. The idea is that any public health measures that reduce a pathogen's ability to move from host to

host should favour pathogens with lower virulence, since they can improve their odds of spreading to a new host by letting their current one live longer.

Ewald cites an example of this in practice. In the early 1990s, the cholera bacterium Vibrio cholerae arrived in Peru from Asia and quickly spread throughout Latin America. Within three years, cholera strains in Chile had evolved to produce less toxin, while in contrast, strains in Ecuador produced more. Ewald puts this down to the fact that Chile's drinking water is generally clean, making it more difficult for cholera to spread from very sick people, whereas the more contaminated water supplies in Ecuador provide an easy transmission route.

In a similar vein, simply mosquito-proofing houses and hospitals in malarial regions should favour the mildest strains of the disease. "If somebody is really sick, they're going to be in bed," says Ewald. "And if they are in a mosquito-proofed dwelling, the mosquitoes aren't going to get to them. They are only going to get to the people that are up and moving around - and those tend to be people with a milder strain."

Further complications

While Ewald's proposals sound like simple good sense, not everyone is convinced by his arguments about the link between virulence and transmissibility. "They're related, of course, but they're related in very complicated ways that often defy the more simplistic efforts at theorising," says Carl Bergstrom, an evolutionary biologist at the University of Washington in Seattle.

For one thing, virulence is sometimes just a by-product of chance events or competition among pathogens within a host, rather than being a long-term evolved response. Jim Bull, an evolutionary geneticist at the University of Texas in Austin, points to polio and meningitis. The pathogens causing both these diseases are common (or at least used to be in the case of polio) and mostly harmless human colonists. They only cause disease on the rare occasions when they invade the central nervous system, which is an evolutionary dead end because pathogens that deep within the body are unlikely to find their way out to a new host.

In addition, the apparent virulence of a disease sometimes has more to do with the host than with the pathogen. Sepsis and meningitis, for example, are dangerous because of our own immune system's excessive reaction to the invaders. "It is the host over-response that leads to virulence. If we didn't over-respond, we would be perfectly okay," says Bruce Levin, a population and evolutionary biologist at Emory University in Atlanta, Georgia. What's more, two new studies indicate that the H5N1 strain of flu does much of its damage in this way, as did the 1918 flu (Nature Medicine, DOI: 10.1038/nm1493, and Nature, DOI: 10.1038/nature05181).

Even something as simple as variation between individual immune responses to a pathogen can be enough to mess up predictions of how virulence evolves. When Bergstrom and his team used a mathematical model of infection to study this, they found that small differences in immune response made a big difference to a pathogen's final virulence (Evolution, vol 56, p 213).

"This was one of many things we came across that left me feeling that virulence evolution may not have these big, beautiful, simplistic, powerful laws when applied at the level of organisms with complex immune systems," Bergstrom says. "I'm a theorist, so I hate to admit this, but for this particular problem, it seems like the details matter tremendously."

Such details have convinced some experts that there is little point in trying to influence the evolution of virulence through measures that affect a disease's transmission. Ewald, however, points out that a pathogen's virulence can sometimes change remarkably quickly. Cholera in Chile is just one example; others include the myxomatosis virus that decimated rabbits in Australia and then evolved into a less lethal form. He does

admit, however, that it is unclear whether these are rare exceptions or the norm. "We really need some experiments here," Ewald says.

For instance, he suggests that development agencies that know they can only afford to install clean drinking water in a certain proportion of villages in an area could do so in a way that would allow epidemiologists to glean some useful information. They could, for example, compare the clean-water villages with the unimproved ones to see whether water-borne diseases have evolved lower virulence in the former. "That, I think, is an ethically acceptable experiment."

Meanwhile, the sorts of measures that public health officials might take to encourage the evolution of reduced virulence can only be to the good. After all, clean water, mosquito netting, even simple measures such as hand-washing and staying at home when ill, are excellent measures to help prevent epidemics in the short term. Any evolutionary benefit would be an added bonus.

Point of no return

Many of the diseases that concern us most did not start out as human diseases at all. Instead, the pathogens that cause influenza, Ebola, SARS and the like began life in other animals and jumped to people by accident. Such cross-infections happen all the time, but most of them sputter out quietly because the pathogen, adapted to its usual host, reproduces poorly in humans or lacks an easy way to get from one person to the next - in short, it is not very contagious. The successful human diseases are the ones that do something about that.

In theory, at least, as long as every person who catches a disease gets it from the original host species, the pathogen's success in that original host will be what drives its evolution, and natural selection will keep it fine-tuned for that species. As soon as a pathogen begins to spread directly from person to person, however, the evolutionary landscape suddenly changes, and the heavy artillery of microbial evolution can be brought to bear on adapting to the new host: us.

This happens when each infected person, on average, passes the disease along to one other person. Pathogens approaching this threshold, although not yet adapted to a human host, have the greatest chance of stringing together a series of person-to-person infections by pure happenstance. That lucky run could give a virus enough time to evolve specific human adaptations, according to mathematical models by Carl Bergstrom from the University of Washington in Seattle and his colleagues (Nature, vol 426, p 658).

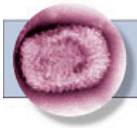
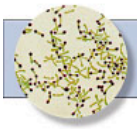
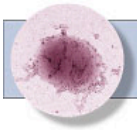
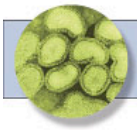
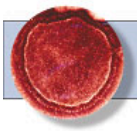
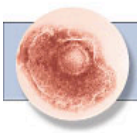
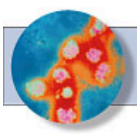
This threshold is a key battlefront in the fight to keep new diseases from jumping to humans. "Even modest gains in reducing the probability of human-to-human transmission can greatly reduce the probability of the virus evolving enough to become an effective pathogen," says Bergstrom. Fortunately, common-sense precautions such as good sanitation and minimising contact with infected people go a long way toward this end already. "When we try to protect healthcare workers from catching bird flu, we are not only looking after them. We're taking a crucial step in reducing the chance that bird flu will emerge as an important human pathogen," says Bergstrom.

There is one other step we can take to reduce the risk of new diseases emerging - one that has been largely ignored of late. Knowing your enemy means careful surveillance of viruses in the wild to compile a rogue's gallery of likely offenders. "There's hardly anyone looking for viruses any more," says Scott Weaver from the University of Texas Medical Branch in Galveston. "We're not even prepared to know what has the potential to emerge out there."

DURABLE AND DEADLY

The most dangerous pathogens tend to be those that can survive longest outside their host

- Deaths per 100,000 people infected
- Survival time outside human host (days)

	Deaths per 100,000 people infected	Survival time outside human host (days)
 Smallpox	10,000	885
 Tuberculosis	5000	244
 Diphtheria	200	370
 Whooping cough	100	12
 Pneumonia	36	29
 Influenza	10	14
 Measles	7	4
 Mumps	5	1
 Parainfluenza	4	5
 Chickenpox	3	1
 Rubella	3	1