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The Battle Against Bugs Gets Serious

Researchers fear that a boom in the number of bird viruses may portend more deadly outbreaks. They're racing to find ways to predict, track and stop them before it's too late

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With Alexandra A. Seno in Hong Kong and Michael Hastings in New York

It's not easy for a workaday bug to turn itself into a deadly human pathogen capable of causing, say, a flu pandemic. In the past few years, plenty of ambitious viruses have knocked themselves out trying. The bird flu of 1997 was particularly deadly--it killed a third of all people infected. But authorities were able to wipe it out (they had to kill more than a million chickens) before it found the right combination of genetic mutations that would have enabled it to spread from humans to humans. The outbreak killed only six people, but it was a close call.

What's got flu hunters spooked this season is the persistence with which these new bird viruses keep trying to make the jump to humans. Earlier this year 30 million chickens had to be exterminated in northern Europe because they were infected by a bird virus. In early December yet another new virus killed 20,000 chickens and infected many others in farms near Seoul, forcing South Korean health officials to impose a 10-kilometer blockade around all poultry farms. When 3,000 ducks at yet another farm stopped laying eggs, officials --exterminated the lot. In mid-December they put more than 100,000 chickens and ducks to death. Sooner or later, one of these new bugs is bound to find the right genetic code to break the species barrier. "The Big Flu is knocking on the door," says Robert Webster, a virologist at St. Jude Children's Research Hospital in Memphis, Tennessee, who's currently doing research at the University of Hong Kong. "The virus is trying on different combinations to come up with the truly deadly one."
Flu isn't the only worry, or even the biggest one. The SARS epidemic last year showed that new diseases can come from left field--in the case of SARS, from a cold like virus of mammalian origin. SARS, though deadly, spreads slowly through a population, giving health officials time to contain it. The persistence of viral transgressions is a clue that something has changed in the delicate balance between

humans and microbes. It may be climate change or the proliferation of airplane travel or a globalized food trade--or all of the above. Whatever the cause, the Big Fear is that some new type of bug will arise that kills like SARS and spreads like the flu, leading to loss of life on a grand scale.

Health authorities are responding to these new threats by increasing vigilance--reporting new outbreaks quickly and taking decisive measures to block their spread. Aside from China's secretive handling of health data, such "shoe-leather epidemiology" worked to good effect in the SARS outbreak. But the battle is also being waged in research labs. Scientists are looking, in particular, to new technologies that will help predict the emergence of new diseases and track the progress of old ones--and, most important, that can improve response times at moments of crisis.

A big part of the challenge is for clinicians to look past the most obvious causes of patients' symptoms--a big departure from the way medicine has been conducted for the past 100 years. "The idea used to be that when you hear footsteps, you look for the most likely cause--a horse, not a zebra," says Dr. Peggy Hamburg, vice president for biological programs at NTI in Washington, D.C. "Nowadays doctors need to look for the zebra."

To make such wide-ranging diagnoses possible, scientists are trying to develop chips that can test for a wide variety of diseases. Joe DeRisi, a biologist at the University of California, San Francisco, has developed a two-by-six-centimeter glass slide that contains more than 11,000 viral DNA sequences. Since viral DNA doesn't tend to change much when a virus mutates, such DNA chips wouldn't need to be updated every time a new strain comes along. "If a virus is from Mars, we'll miss it," says DeRisi. "But most viruses aren't things that are totally new." To use the chip, doctors would take a swab of saliva from the patient and wipe it on the slide. Tiny fluorescent molecules would light up in a specific pattern to reveal the presence of a target virus. The idea is to get these chips, still in the research stage, into the hands of research stations around the globe to identify viruses as quickly as possible.

Improving our ability to track outbreaks would also shorten response times. To that end health researchers are applying data-mining techniques--the same ones that allow planners at Wal-Mart to predict how many party hats they'll sell on New Year's Eve in Des Moines, Iowa--to get a jump on patterns that would indicate that a virus is spreading. Lauren Ancel Meyers, a biologist at the University of Texas at Austin, and mathematician Babak Pourbohloul at the University of British Columbia's Center for Disease Control have studied SARS outbreaks in Toronto and Vancouver with an eye to discerning the underlying principles of their dispersion. When SARS hit in early 2003, "health authorities tried a hodgepodge of different interventions," says Meyers, "but policymakers didn't really have a way to quantify how effective those interventions would be." They might have done better had they known ahead of time that the disease was likely to spread quickly in Toronto but not in Vancouver.

Meyers and Pourbohloul think "percolation theory" is the key to making such predictions. Percolation theory is an obscure branch of applied mathematics that is used to explain how liquids move through an aquifer, but it also happens to be well suited to describe how diseases spread through a population. The two scientists are working to develop this math into a general-purpose model that would take into account how much each hospital worker is likely to come into contact with other workers and patients; demographic data about the distribution of households, school districts, employment and hospitals in a city, and airplane traffic between continents. "The goal is to provide a tool kit to help decision making," says Meyers.

Even better than responding to new outbreaks would be the ability to predict where they might occur. Biologist Roland Regoes at Emory University in Atlanta thinks it might be possible to identify bugs that are likely to evolve into pathogens before they --actually do so. Infectious organisms mutate while they're being transmitted from host to host, and if the bug gets lucky, it turns into a pathogen. Virologists generally measure how dangerous a bug could get by figuring out how likely it will be to get passed around a lot, increasing its chances of hitting on a deadly mutation.

The problem with that approach is that it doesn't take into account the possibility that a bug will evolve in such a way that it increases its own transmissibility, which would vastly increase its potential danger. Scientists may, in fact, already be underestimating the danger of some viruses, just as they underestimated monkeypox when an outbreak occurred in the United States in June. Monkeypox, similar to smallpox, is highly contagious among monkeys, but has a low rate of transmission among humans. In a paper published in December in the journal Nature, Regoes and his colleagues argue that monkeypox could easily mutate into a more transmissible form. He proposes that scientists pay closer attention to such viruses, and he advances a formula that he thinks better takes into account the possible mutations.
Quicker and more reliable methods of coming up with new vaccines are perhaps the greatest need in the battle against bugs, but scientists aren't optimistic. The most common method of making vaccines--using live viruses that have been modified to confer immunity without causing disease--hasn't changed much in decades. "We're reaching the end of that string," says Fred Murphy, a veterinary doctor at UC Davis.
One promising new approach is to use bits of viral DNA, rather than viral proteins, to trigger immunity. This method seems to have worked with the recent Ebola vaccine, now undergoing clinical tests, and it may be possible to use this for other pathogens.
Over the long term, some scientists are hoping that evolutionary biology can provide new strategies for coming up with better vaccines. Paul Ewald, a biologist at the University of Louisville in Kentucky, believes that it may be possible to devise vaccines that encourage a virus to evolve into milder variants. The current diphtheria vaccine, invented in the 1920s, used just this kind of evolutionary effect by accident. The vaccine consisted of a mild form of the diphtheria toxin, which stimulated the immune system to produce defenses against it. It also removed the evolutionary advantage of the diphtheria strain that produced the toxin. As a result, milder forms of the diphtheria bug evolved and pushed out the toxin-producing one, leading to a milder form of the disease. Such an evolutionary approach might also work for other diseases, like HIV, that have until now resisted vaccines.
Since vaccine making is fraught with risks and uncertain payoffs, pharmaceutical companies haven't been especially keen to devote R&D resources to it. In many other areas of public health, especially in the developing world, problems aren't so much technical as financial. "This is an important issue, and we've been complacent about it," says NTI's Hamburg. "We're likely to see more disease in the next few years, not less." Winning this battle will take more money as well as innovative thinking.
Outbreak: This year's rash of flu cases may be a precurser to faster and more deadly diseases
The Bugs Up Close (top to bottom) A rogue's gallery of deadly viruses -- influenza, two human coronaviruses, smallpox and the highly contagious Ebola
Help May be Near: Using viral DNA instead of viral proteins may soon lead to vaccine for Ebola