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Cold comfort

The common cold is a miserable annoyance – but harmless, right? Not always. Sometimes it can kill, as Debora MacKenzie reports
IN APRIL last year, Paige Villers was finishing basic training at Lackland Air Force Base in Texas when she came down with a cold. She struggled to shake it off. Then came a prolonged battle with pneumonia, followed by an immune over-reaction that killed her.  

“She had symptoms that just looked like a cold or the flu,” Villers’s mother told reporters. “You hear of people dying of pneumonia, but it’s usually older people. Not a 19-year-old in the prime of her life.”

It turned out that Villers had been infected by an adenovirus, a family of viruses that normally causes no more than a common cold. But this virus was a nasty new strain called Ad14, which killed at least 140 people in the US in 2007. The real toll may well have been uncovering is both surprising and disturbing. “It is increasingly clear that these deaths are rarely diagnosed.

The emergence of Ad14 – and the surprising turn it took this year – is a sharp reminder that a harmless cold is not the only possible outcome of the constant battle between people and respiratory viruses. There can be others.

Even before the discovery of Ad14, interest in cold viruses had revived, partly thanks to new technologies that make it much easier to study them. What biologists have been uncovering is both surprising and disturbing. “It is increasingly clear that these viruses can kill,” says Sebastian Johnston of Imperial College London.

The common cold is just that: common. We breathe in 15,000 litres of germ-laden air every day, says Ron Eccles, head of the Common Cold Centre at Cardiff University in the UK. “The respiratory system is constantly under attack.”

While the respiratory system does have formidable immune defences, a slew of viruses are staying one step ahead in the arms race. They cause acute upper respiratory tract infections, aka the common cold. Adults typically have two to four colds a year, while young children have six to ten.

Astonishingly, we have no idea how many viruses lie behind such infections. More than 200 members of nearly a dozen families of viruses are known to cause colds (see “The culprits”, page 47), but it is becoming clear that many more are out there.

The reason for our ignorance is that the traditional method for identifying cold viruses is to grow them in culture. Doctors take a sample of mucus – snot – and add it to a thin layer of human cells in a dish to see what virus replicates. This is how rhinoviruses, thought to cause up to half of all colds, were discovered in the 1960s. However, live viruses often do not survive sampling and culturing, and the method can fail to identify which virus is behind a cold in a third of cases.

Will there ever be a cure?

The realisation that colds can kill (main story) has renewed interest in finding vaccines and treatments. The trouble is that the common cold is caused not by one virus but by hundreds of different ones.

This means a vaccine or drug that works against one of these viruses, or one family of viruses, is usually ineffective against all the others. What’s more, because colds are usually so mild, if treatments cause even minor side effects they can be worse than the disease. Such treatments will never get approval for general use, which is why most companies instead focus on drugs that relieve symptoms.

Nevertheless, some drugs and vaccines are being developed against the cold viruses most likely to turn nasty. A vaccine against RSV, which can cause serious illness in young children and the elderly, is going through clinical trials. It consists of a weakened strain of the virus given as a nasal spray. A treatment for RSV infections, based on RNA interference, is also in development, as are several conventional drugs that target rhinoviruses. The most advanced is pleconaril, which keeps the surface proteins of rhinoviruses from binding to cells. It reduces both the symptoms and duration of a cold.

However, treatments for specific viruses are useless unless your cold is caused by the virus in question – and doctors have no quick way to work out which virus is to blame for a cold. Systems to do this are under development, mostly based on looking for specific DNA or RNA sequences, but none are near to reaching the market.

An alternative approach would be to keep taking drugs that prevent infection throughout the cold season, such as a derivative of the anti-smallpox drug cidofovir which has been shown to prevent infection with adenoviruses. But again, as adenoviruses are only responsible for a few per cent of colds, the benefits hardly justify the expense and risk of side effects from remaining on a drug permanently. An exception is preventing RSV in premature babies, who may die if infected: two kinds of monoclonal antibodies to RSV are available for them.

Short of everyone on the planet isolating themselves for two or three weeks, so existing cold viruses run out of hosts and die out, it is hard to see how we can ever defeat the common cold. Even then, new cold viruses would evolve in time from animal viruses.

Some even question whether it is desirable to try to eliminate colds. “It’s blind speculation,” says Joel Weinstock of Tufts University in Boston in the US, “but the common cold may protect us from more serious viruses.” An occasional sniffle might be a price worth paying if it keeps our immune defences primed.
It’s not the snot

How can 200 or more viruses all cause the same disease, the common cold? The answer is that they don’t – cold symptoms are in fact caused by our immune system’s response to the virus. Viruses that break through our defences usually start replicating in the cells lining the throat, which is why you feel irritation and pain there first. Sore throats often feel as if the virus is being destroyed, but this seldom happens with a cold. Rather, the symptoms are caused by the chemical alarm signals released by immune cells when they detect viruses. The alarm molecules trigger local inflammation and also stimulate sensory nerves, producing the feeling of pain and sneezing.

The most important of the immune signals, or cytokines, is called interferon. It triggers headaches, fatigue, loss of appetite, malaise, nausea, depression and even muscle pain, caused by wastage, which happens a little even with a mild cold.

A day or two later, these early symptoms are followed by a runny nose as the inflammation response spreads. It starts as watery discharge due to tiny blood vessels exuding the watery part of blood. Then glands in your nose starting producing mucus to wash out virus particles. If the mucus turns green, it’s a sign not of bacterial infection – as some doctors think – but that there are lots of white blood cells in it, which carry green iron-containing catalysts for destroying germs.

During this process, the veins in the nose lining dilate. This, not snot, is the main reason for the congestion that makes breathing difficult. Autonomic nerves ensure that the veins in each nostril dilate alternately, about every three minutes, to prevent complete blockage. The tear ducts and sinus passages also become inflamed, making your sinuses hurt and your eyes water.

If the inflammation reaches deep parts of your throat, it triggers coughing. It’s the same response as if something were stuck in your throat. In this case, though, coughing serves no useful purpose, unless the inflammation spreads even deeper to the bronchi, and you cough up the mucus.

It is still not clear whether treatments for cold symptoms slow your recovery or not. Some cold researchers think the typical symptoms help clear infections, but others think they are merely a useless side effect of cytokines. It seems the body’s own cure for a cold is not so much worse than the disease, it is the disease.

“This was a true emergence, the first appearance of this virus. It spread like wildfire”

Now, however, researchers don’t need to grow viruses to identify them. With the help of PCR, which amplifies the amount of DNA in a sample, they can look directly for viral DNA or RNA sequences. To everyone’s surprise, this is turning up cold viruses that are completely new to science, but whose genetic diversity and worldwide distribution suggest they have been circulating in humans for a long time.

In 2001, for instance, Ab Osterhau of Erasmus University in Rotterdam, Netherlands, discovered human metapneumovirus. In adults, hMPV causes no more than a cold, but in babies it can be lethal – like the respiratory virus that goes on a killing spree in 2007 is still causing deaths. Last year, a team at the University of California used especially sensitive PCR to investigate colds in 37 people and found “remarkable and unanticipated diversity”: 30 varieties of rhinovirus, including some previously unknown ones, and two unexpected coronaviruses.

“There are probably more cold viruses out there we haven’t discovered,” says Osterhau, whose group is launching a wide search for viruses in general in humans and animals.

Finding the viruses is fast becoming the easy part – establishing what they do is harder. In years gone by, researchers used to stick samples of new viruses up people’s noses to see what happened. “No one puts novel viruses deliberately into human volunteers any more,” says Kenneth McIntosh of Harvard Medical School – thanks both to liability laws and a healthier respect for the unexpected properties of viruses.

In 2005, for instance, random PCR on children in Swedish hospitals turned up a complete novelty, bocavirus, which has now been found worldwide. Last year two new polyomaviruses turned up in Australia, the US and Sweden. These viruses may well have caused the respiratory tract infections from which they were taken, but no one has yet been able to prove it.

Part of the reason we are so amazingly ignorant about the causes of the world’s most common disease, says Eccles, is that research funding has focused, understandably, on nastier germs. That said, the impact of colds is not trivial: they cost the US economy alone some $40 billion a year.

The reason why colds are usually little more than a nuisance is that it’s not in their interest to make us any sicker than they do. “For a cold virus to spread, the host must be able to walk around shedding mucus on people,” says Eccles. “Any virus that stops you doing that has to become milder, or die out.”

Most cold symptoms are actually caused by the immune system’s response to infections. A virus well adapted to its host provokes the immune system just enough to cause symptoms that help it pass from person to person. For a cold, that means lots of mucus, coughing and sneezing without making you too ill to move.

Turning nasty

For instance, when the bat coronavirus that caused the SARS outbreak jumped to humans in 2002, it was frequently lethal. By 2004, the few SARS cases detected were mild.

Surprisingly, being too contagious can also be a disadvantage for a virus. In populations made up of separate groups that have only occasional contact – villages, say – a virus that very rapidly infects everyone in one village could die out before getting a chance to spread to other villages.

If there is little chance of running out of susceptible hosts, though, nasty viruses can spread. Last year, a team at the University of Sheffield in the UK demonstrated this in live animals for the first time by showing that in moth larvae that had more contact with other larvae, a virus became more communicable – and more virulent.

The analogy with our modern, globalised society is worrying. There are more people than ever before, and more contact between far-flung communities. Does this mean that respiratory viruses could evolve to become more contagious, and thus more likely to cause serious illness?

“In principle, yes,” says epidemiologist Angus Buckling of the University of Oxford. “But it is complex.” There will also be increased mixing of viruses, he says, and competition between viruses within hosts can also affect virulence.

So does increased global travel explain Ad14? “This was a true emergence, the first appearance of this virus in our nation,” says David Metzgar of the US Naval Health Research Center in San Diego, who tracks adenoviruses in their favourite victims, military recruits.

This year, New Scientist can reveal, Metzgar has found that exactly the same Ad14 virus that went on a killing spree in 2007 is still circulating – except that now it is only causing ordinary colds. How is this possible? Because we humans have changed. Frozen blood...
samples show almost no immunity to Ad14 in 2006, so it spread like wildfire. As it spread, a few people who were unusually sensitive to it died. Now most of us have encountered it and have at least partial immunity.

So the state of our defences is just as important to the outcome as the nature of the virus. If a virus is unlike anything we’ve encountered before, or if our defences have been weakened, cold viruses can kill. This is

winter, researchers in the US discovered that ordinary rhinovirus put toddlers in hospital as often as RSV, especially those with asthma.

Such studies show that cold viruses can be very nasty indeed in people with asthma. That’s significant because asthma is rampant in rich countries, especially in children, for reasons we still don’t understand. Asthma involves inflammation of the airways, and cold viruses make this worse by triggering additional inflammatory responses.

The same is true of chronic obstructive pulmonary disease, which constricts the lungs in a similar manner to asthma but on a constant basis, whereas people with asthma have intermittent attacks. The incidence of COPD is rising in developing countries as smoking spreads and average ages rise: it is the world’s fifth most common cause of death now, but the World Health Organization predicts it will be third by 2030.

So people with asthma and COPD are most at risk from cold viruses – unless you count the impact of colds on another kind of pathogen altogether. When people go to their doctor with a cold, up to a third are prescribed antibiotics even though the drugs have no effect on any of the viruses that cause colds. In the absence of any reliable tests, doctors often assume – wrongly – that if cold symptoms last more than a week the cause must be bacterial.

Doctors also give antibiotics to prevent bacterial complications of a viral cold, but a review in 2005 found that unless you have a history of complications, the practice is usually useless. Some doctors also prescribe antibiotics just to placate patients, knowing full well they will make no difference. All these misuses of antibiotics are contributing to the rise of antibiotic-resistant superbugs, which are a massive threat. Put it all together, and the message is clear: we ignore the common cold at our peril.

How to avoid colds

Does cold cause colds? In the 1950s and 1960s scientists put cold viruses in people’s noses and chilled them, or not, afterwards. It seemed to make little difference, so the belief has been dismissed as folklore.

But in 2005 Ron Eccles of Cardiff University in the UK found that more students develop colds naturally after their feet are chilled. Chilling anywhere on the body prompts a reflex cut in blood flow to the nasal lining, a major site of heat loss, which may lower our defences against viruses.

Kids are the other big cause of colds. Cold viruses spread in snot, either sneezed out into airborne droplets or, more often, smeared onto hands which then touch surfaces or other hands, from where they get into people’s noses and eyes.

Children pass on viruses better than adults because they get more snot on hands, wash them less often, and have more physical contact with peers and caregivers. That said, in classic experiments in the 1950s, researchers stained the snot of adults with a fluorescent dye before they engaged in normal activity – and watched in awe as the dye turned up all over the room and its other occupants.

So if you want to avoid catching a cold, keep your nose warm, wash your hands a lot and stay away from children.