GOING VIRAL

VIRUSES MAY BE SO TINY THAT SCIENTISTS NEED ELECTRON MICROSCOPES JUST TO SEE THEM, BUT THEY ARE THE CAUSE OF SEVERAL DISEASES THAT CAUSE IMMENSE HUMAN SUFFERING. STILL, NOT ALL VIRUSES ARE BAD, AND SOME RESEARCHERS THINK THEY MAY EVEN HAVE PLAYED A PART IN THE ORIGINS OF CELLULAR LIFE. **RACHEL SULLIVAN** PUTS ON HER LAB COAT AND GOES SEARCHING FOR BUGS

PHOTOS: CORBIS

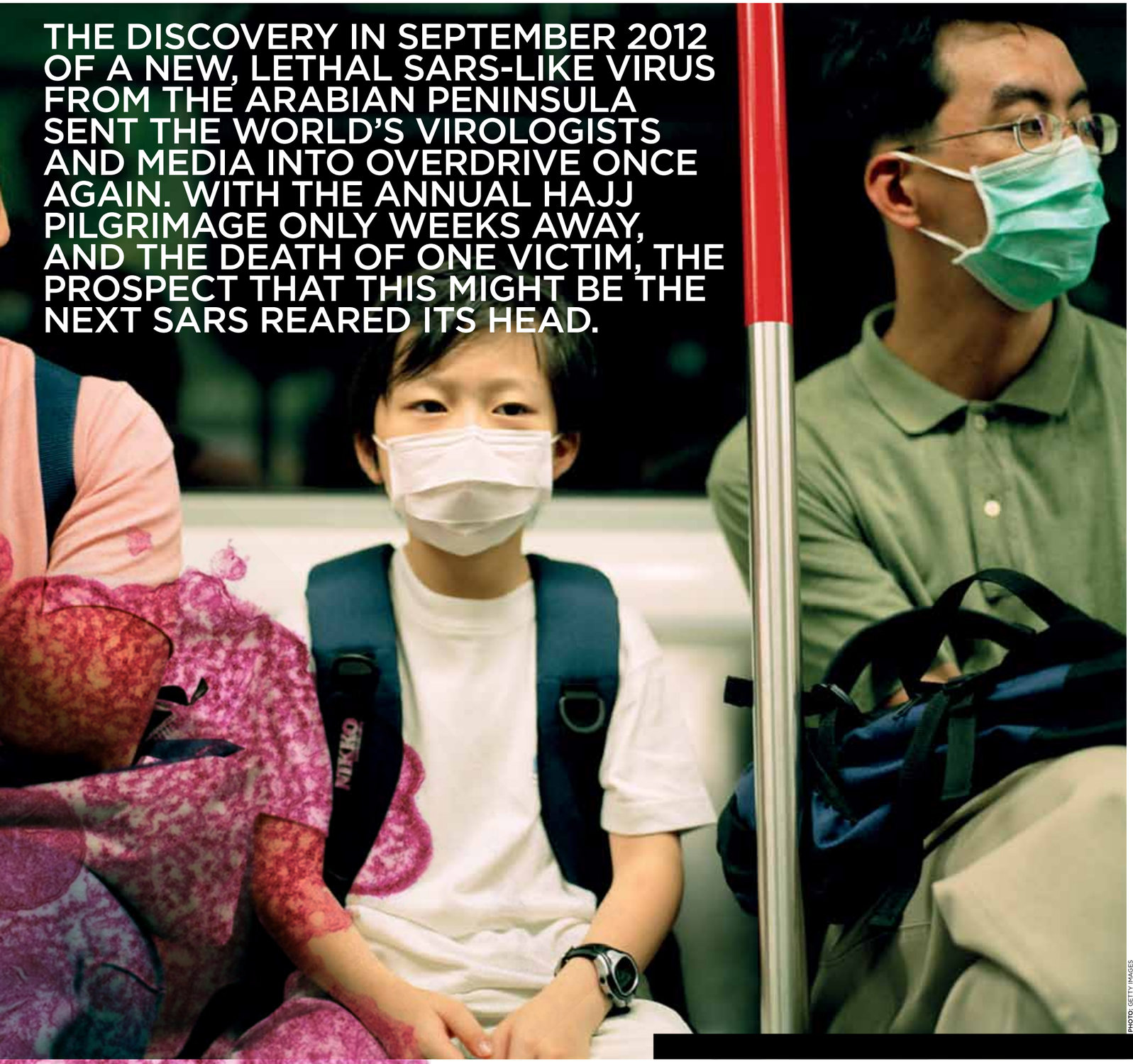


PHOTO: GETTY IMAGES

THE DISCOVERY IN SEPTEMBER 2012 OF A NEW, LETHAL SARS-LIKE VIRUS FROM THE ARABIAN PENINSULA SENT THE WORLD'S VIROLOGISTS AND MEDIA INTO OVERDRIVE ONCE AGAIN. WITH THE ANNUAL HAJJ PILGRIMAGE ONLY WEEKS AWAY, AND THE DEATH OF ONE VICTIM, THE PROSPECT THAT THIS MIGHT BE THE NEXT SARS REARED ITS HEAD.

Scientists from as far afield as Saudi Arabia, the Netherlands, the United States and the United Kingdom swung into action to identify the new virus, determine its origins, and crucially, pinpoint its ability to pass between humans.

Fortunately the disease seems to have stopped with the two men. Fears of a pandemic subsided, and health officials relaxed — ready to gear up again at the next hint of trouble.

We live in a time of headline-making viruses. The past 15 years have seen four significant viral health emergencies — Nipah virus in 1998, West Nile virus in 1999, SARS in 2003 and the pandemic H1N1, or swine flu, in 2009. Along with dozens of others, viral diseases such as dengue fever, Japanese encephalitis, rabies and bird flu (H5N1) are ever-present issues in Asia — while globally, viruses are responsible for an estimated 15 to 20 percent of all cancers.

These days, authorities are more aware of new threats, and are better able to detect and respond to them than at any time in the past. But with more sophisticated detection technologies, are we still more at risk of viral attack now than at other times in our history? And are viruses really the enemies that we think they are?

VIRUSES BY NUMBERS

"Viruses have a huge impact on how life systems operate," says viral ecologist Dr Mark Young from the Montana State University, in the United States. His research revolves around trying to understand the ecological and evolutionary role of viruses, as well as how they might be used as nanotechnology biomaterials, such as smart-drug delivery systems. "We have not even scratched the surface of understanding viruses on this planet. But what we do know is that we would not be the humans we are today without the presence of viruses," he says.

"We know of approximately 5,000 viruses so far, and estimate that science has seen less than .0002 percent of viruses on the planet," Young explains. "Conservative estimates suggest that there are 10^{31} [10 billion trillion, trillion] virus particles in circulation on the planet at any one time. If we assume that the average particle is 100 nanometres, and we lined them up, it would take 200 million light years to travel from one end to the other."

"There are also an estimated 10^{24} infections per second. But to put this in perspective, at around four billion years, Earth is only 10^{17} seconds old," he adds. In other words humans, and all other forms of life on this planet, are constantly under assault from a force that we can barely comprehend.

Unsurprisingly then, the course of human history has been shaped by our interactions with viruses. Since smallpox, caused by the variola virus, emerged over 3,000 years ago in either India or Egypt, epidemics have decimated populations. Until it was officially deemed eradicated in 1979, smallpox killed around 30 percent of those infected and left up to 80 percent of survivors with deep scars on their faces. It killed indiscriminately, felling rich and poor alike, and according to the World Health Organisation (WHO), included Queen Mary II of England, Emperor Joseph I of Austria, King Luis I of Spain, Tsar Peter II of Russia, Queen Ulrika Eleonora of Sweden, and King Louis XV of France among its horrendous death toll.

The Spanish Flu pandemic of 1918 infected a fifth (some sources even say a third) of the world's population and had a death toll of between 20 million and 50 million people — killing more people than World War I. And in 2010, there were an estimated 34 million people living with HIV/AIDS, which has already claimed 25 million lives.

SMALL YET MIGHTY

Yet despite being surrounded by viruses, very few of them make us sick, and even fewer are universally lethal if untreated. Viruses infect all types of life, from animals and plants to bacteria and archaea — the simple, single-celled microoganisms thought to predate all other life forms — raising interesting questions about the evolution of viruses themselves (*see page 32*).

At around 20 to 300 nanometres long, viruses are about one-thousandth the size of an average bacterium, and consist of genetic information (either DNA or RNA depending on the type of virus) surrounded by a protein coat. This acts as a kind of time capsule, protecting its dormant

contents until conditions are right to "go viral".

Viruses require a host cell to function. Highly specific and varying widely in shape, a particular virus usually matches the receptors on the type of cell it wants to infect, sort of like a lock and key mechanism.

They may be transmitted by animal vectors such as mosquitoes, through droplets when we cough or sneeze, via food and water, or by sexual contact. Once inside us, they attach to their preferred cell type — cells of the respiratory system in the case of cold and flu viruses, or the immune system in the case of the human immunodeficiency virus, commonly known as HIV.

Once locked on, they release their genetic material, either by injecting it or by dissolving into the cell, then force it to manufacture new viruses. The viruses then break free of the host cell and spread quickly throughout the body.

Not all viruses "launch" immediately. Some retroviruses (so called because they create DNA from RNA, instead of the more usual other way round) such as herpes and HIV mix their genetic instructions with those of the host cell, so that when it reproduces, the viral code is copied into the host cell's offspring — allowing the virus to be transmitted to others without affecting the host. This period may last for quite some time, even years, before an environmental or predetermined genetic signal triggers the "sleeping" code. Then the infected cells go into overdrive.

Of course, it's no good staking all of your hopes on a single host, and some viruses have evolved cunning ways of making sure they reach as many potential new hosts as possible.

One of the more dramatic examples of this occurs among European gypsy moth (*Lymantria dispar*) caterpillars. An infected — and terminally confused — caterpillar uses the last of its strength to climb high into a tree, ensuring that when it dies and its corpse decomposes, its disease-carrying cells will spread far and wide.

Virus-driven behavioural change is not limited to insects. "Rabies may cause aggressive behaviour and difficulty in swallowing, leading to enhanced transmission through biting and contact with infected saliva," explains Dr W. Ian Lipkin, director of the Center for Infection and Immunity, and professor at Columbia University's Mailman School of Public Health, in the United States. "Rhinoviruses irritate nasal cells, leading to sneezing and transmission. Enteric viruses cause diarrhoea, with similar effects."

He adds, "I have also speculated that the herpes simplex type 2 virus, that causes genital herpes, may stimulate the sacral ganglia (pelvic nerve cells), leading to increased sexual activity — which promotes virus transmission."

While most viruses pass through our bodies unnoticed, when under attack the body's immune system defends itself against the viral assault by producing infection-fighting white blood cells (known as T-cells) and by releasing antibodies and pyrogens, chemicals that cause the body temperature to rise. Because virus particles usually replicate and spread most effectively at normal body temperature, this fever slows and eventually stops the viral spread.

VIRUSES REQUIRE A HOST CELL TO FUNCTION. A PARTICULAR VIRUS USUALLY MATCHES THE RECEPTORS ON THE TYPE OF CELL IT WANTS TO INFECT

The damage may already have been done though. If you have sneezed, coughed or otherwise exposed someone before you are clear of the virus, thousands of new particles may have been released.

CANCER LINK

Although they may leave you feeling ill for a few days, the body is often able to shrug off the more common viral diseases. For more serious infections, treatment options are restricted: antiviral drugs, while successful in treating some conditions, are limited in their effectiveness because many viruses have the ability to mutate rapidly. In the wake of increasing numbers of (bacterial) superbugs that have arisen, partially due to the indiscriminate use of antibiotics to combat infections, questions are now also being asked about the wisdom of creating broad-spectrum antivirals — assuming such a thing is even possible.

Apart from stopping outbreaks at their source, one of the most effective weapons against viral infection is of course, vaccination. The smallpox vaccine was first developed by Edward Jenner in 1796, after he had observed that milkmaids infected by cowpox did not catch the related smallpox. Indeed, the French chemist and microbiologist Louis Pasteur is regarded as one of the founding fathers of microbiology, remembered not only for having invented pasteurisation — but also for developing the first vaccine against rabies in 1885.

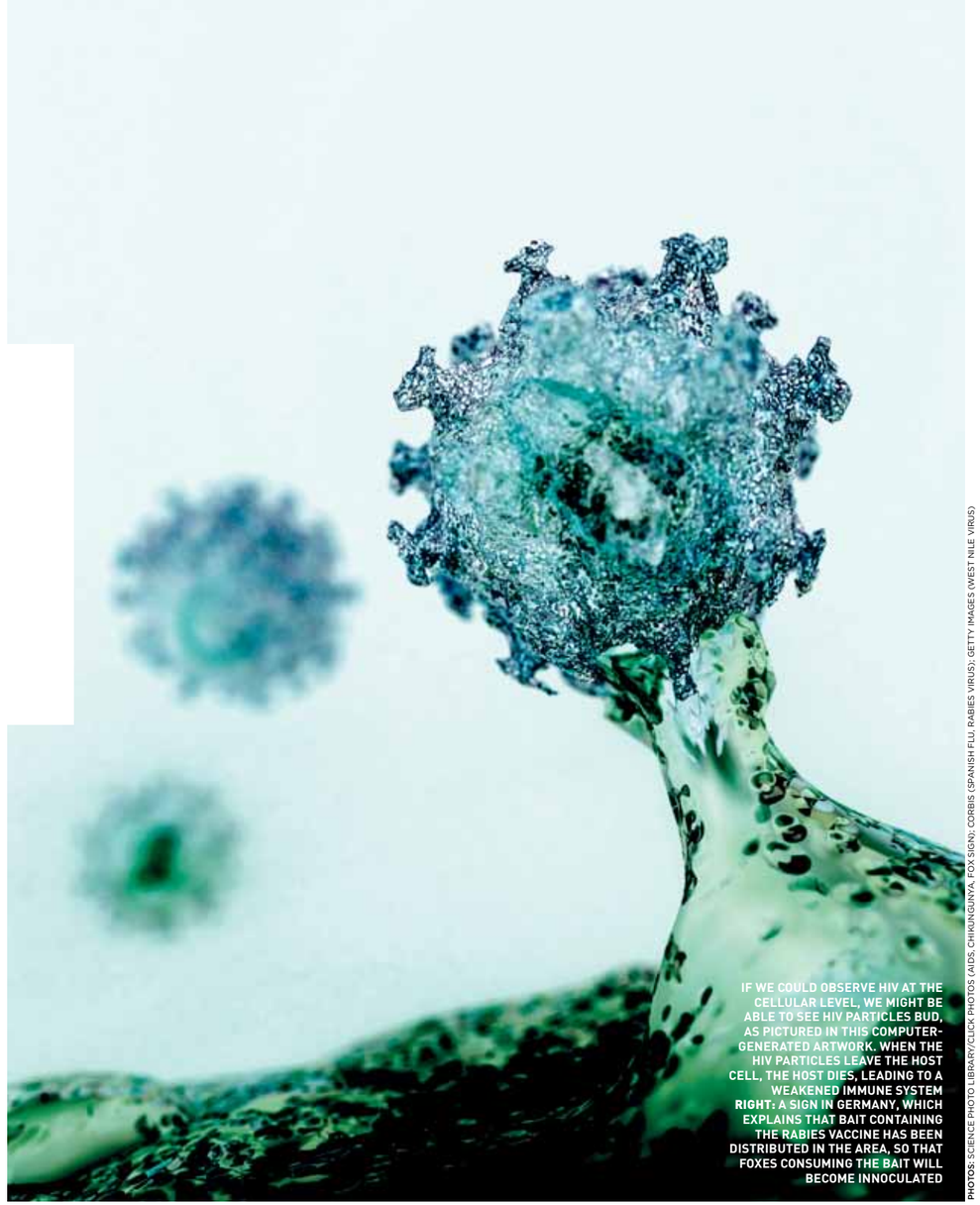
Today, scientists are developing vaccines that will not only target viruses, they may also help us cut cancer rates. In Australia, the University of Queensland's Dr Ian Frazer says that 20 percent of the global cancer burden is caused by viruses: "The glandular fever virus is responsible for lymphoma. Hepatitis B and C cause liver cancer, which is around five percent of the global cancer burden," he notes. "And the recently discovered Merkel cell polyomavirus causes a rare but lethal form of skin cancer."

Frazer, who is also chief executive officer and director of research at the Translational Research Institute, discovered a vaccine for the human papillomavirus (HPV), which causes both cervical and anal cancer, among several other unpleasant things.

"Most people catch the virus at some time in their lives and get rid of it on their own, but there are a few with persistent infection who are at risk of developing cancer, though this requires other factors," Frazer explains. "HPV is a fairly stable virus. In fact there is little evidence that it has changed over the past 20,000 years, which makes it relatively easy to vaccinate against. Unlike the flu, which mutates regularly."

Frazer and his team came up with a then-groundbreaking technique — which he says is now commonly used for manufacturing a vaccine — by causing cells to create a protein capsule (the "shell" of the virus) that self-assembles outside the human host, without the infectiousness of the live virus.

The vaccine, known as Gardasil, has now been used to immunise almost 50 million girls and women worldwide according to Frazer, with programmes in Australia, Europe and the United



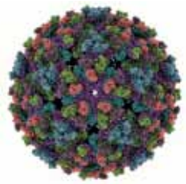
IF WE COULD OBSERVE HIV AT THE CELLULAR LEVEL, WE MIGHT BE ABLE TO SEE HIV PARTICLES BUD, AS PICTURED IN THIS COMPUTER-GENERATED ARTWORK. WHEN THE HIV PARTICLES LEAVE THE HOST CELL, THE HOST DIES, LEADING TO A WEAKENED IMMUNE SYSTEM **RIGHT:** A SIGN IN GERMANY, WHICH EXPLAINS THAT BAIT CONTAINING THE RABIES VACCINE HAS BEEN DISTRIBUTED IN THE AREA, SO THAT FOXES CONSUMING THE BAIT WILL BECOME INNOCULATED

PHOTOS: SCIENCE PHOTO LIBRARY/CLICK PHOTOS (AIDS, CHIKUNGUNYA, FOX SIGN); CORBIS (SPANISH FLU); GETTY IMAGES (WEST NILE VIRUS)

VIRUSES UP CLOSE

CHIKUNGUNYA

TRANSMITTED BY **INFECTED MOSQUITOES,** CHIKUNGUNYA DISEASE IS **RARELY FATAL,** BUT THE SYMPTOMS CAN BE DEBILITATING. ASIDE FROM **SEVERE JOINT PAIN,** NAUSEA, FEVER, HEADACHE AND VOMITING ARE ALSO COMMON. AT THE MOMENT, THERE IS **NO VACCINE OR ANTIVIRAL TREATMENT**

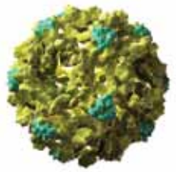


SPANISH FLU

THE 1918 SPANISH FLU PANDEMIC HAD AN UNLIKELY TARGET — MANY OF THOSE WHO DIED WERE **BETWEEN 20 AND 40 YEARS OLD.** THEIR IMMUNE SYSTEMS WENT INTO OVERDRIVE TRYING TO ERADICATE THE VIRUS, AND IN THE PROCESS **DESTROYED THEIR LUNGS.** PATIENTS WOULD STRUGGLE TO BREATHE AND EVENTUALLY **DROWN IN THEIR OWN FLUIDS**

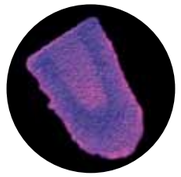
WEST NILE

THE MAJORITY OF WEST NILE VIRUS INFECTIONS ARE ASYMPTOMATIC, BUT IN **20 PERCENT** OF CASES, WEST NILE FEVER MAY OCCUR. IF THE INFECTION INTENSIFIES, THERE IS RISK OF **PARALYSIS, CONVULSIONS OR COMA.** ROUGHLY **ONE IN 150 PEOPLE** WITH WEST NILE VIRUS WILL DEVELOP THIS MORE SERIOUS FORM



RABIES

FEAR OF RABIES STEMS NOT ONLY FROM ITS **HIGH FATALITY RATE,** BUT ALSO ITS **BIZARRE SYMPTOMS,** AMONG THEM EXCITABILITY, HALLUCINATIONS, AN ABNORMAL FEAR OF DRAFTS OF AIR, AN INABILITY TO SWALLOW, AND CONVULSIONS. EVENTUALLY, THE VICTIM WILL **DIE FROM CARDIAC OR RESPIRATORY FAILURE,** USUALLY WITHIN A FEW DAYS



VIRAL ORIGINS

The origins of viruses remain mysterious, and the discovery by **Dr Mark Young,** from the Montana State University, in the United States, of viruses living in pools of boiling acid in Yellowstone National Park revealed their ability to survive in hostile conditions that may reflect Earth's early days.

How old are viruses? These acid pools are dominated by archaea, a stream of life we know little about, and the viruses that infect them. They allow us to make connections across of domains of life. Archaea predate eukaryotic life — such as plants, animals and fungi — but whether viruses precede cellular life, on which they depend to reproduce, is a point of contention. Modern viruses date back to three billion years, the origins of cellular life, but without fossil records we can only speculate. In the past we thought there was no chance of finding viruses in fossil records. Now, with advances in technology it is quite possible that we will — on Earth and elsewhere.

Where did viruses come from, if they predated, or did not evolve with, cellular life? All cellular life today has viruses associated with it. There were life-like processes before the evolution of cells, and virus-like entities were clearly important for driving cellular evolution. It is reasonable to think that virus-like agents were present prior to the formation of cells. These virus-like entities, which include introns and vivoids (small pieces of RNA with virus-like characteristics), carry out catalytic processes and do not code, but still cause disease. We look at present-day viruses, and from there make our best guesses about where they came from.

Is it possible to backtrack through viral evolution by decoding their genomes? We have two major challenges: the rapid rate of mutation, and the extensive horizontal gene transfer between viruses and the cells they occupy. When we look at the genomes of all animals, there is evidence of direct interaction of viruses with cellular genomes. In general, life is amazingly adaptable. It is not a unique property of viruses to mutate — they are just quicker than cellular life. They have an incredible ability to create variation, and respond to changing orders of magnitude faster than cellular life.

Kingdom. Since the vaccine's introduction in Australia in 2007, one study found a 93 percent decline in genital warts in women under 21 years of age, and a 73 percent decline

"WE THOUGHT THERE WAS NO CHANCE OF FINDING VIRUSES IN FOSSIL RECORDS. NOW IT'S QUITE POSSIBLE WE WILL — ON EARTH AND ELSEWHERE"

in women aged between 21 and 30, leading scientists to predict that genital warts could be eradicated among young people in the country, and decrease HPV-related cancers.

"The disease works by infecting skin cells and causing them to multiply, until a great mountain of cells builds up into a wart. But proliferating cells is not cancer," Frazer explains. "There is something else at work. If you can keep cells dividing, the chances of a mistake are greater, and this could lead to cancer."

He adds, "Despite looking at different environmental and genetic factors, it is not clear why some people develop cancer. Cancers caused by viral infections are distinctive; the infection leaves a footprint." Frazer is currently working on a genital herpes vaccine, with

PHOTOS: CORBIS (MOUSE, H1N1 AND RABIES VACCINE)

"NUDE" MICE

This mouse (*pictured*), has a deficient immune system, and is used for AIDS research. So-called "nude" mice have been very useful in the study of xenografts, transplanted tissues and tumours from foreign species such as humans — and are a vital part of research into immunodeficiency. The mice are hairless due to a gene mutation resulting in a non-functional or rudimentary thymus, an organ that is part of the immune system. Nude mice produce a reduced number of mature T-cells, a type of white blood cell essential to the immune response.

NOTED VACCINES

H1N1 SWINE FLU VACCINE

THE RESPONSE TO THE 2009 PANDEMIC IN THE UNITED STATES WAS COLOSSAL. IN THE **FIRST THREE MONTHS** OF A VACCINATION PROGRAMME, AROUND A **QUARTER OF THE POPULATION** WAS VACCINATED. THE VACCINE CAME IN TWO FORMS: A "LIVE" NASAL SPRAY, WHERE A WEAKENED VERSION OF THE VIRUS WAS INSERTED IN THE NOSE, AND AN "INACTIVE" INJECTION OF THE DEAD VIRUS

RABIES VACCINE

VACCINATION AGAINST RABIES CAN EITHER BE **PREVENTATIVE** — GIVEN TO SOMEONE WHO HAS NOT BEEN EXPOSED — OR CAN BE ADMINISTERED **AFTER A BITE.** IN THE FORMER, THE PATIENT IS INJECTED WITH THREE DOSES SEVERAL DAYS APART. IN THE LATTER, THE PERSON IS GIVEN FOUR DOSES. UNTIL **1980** IN THE UNITED STATES, PATIENTS UNDERGOING VACCINATION REQUIRED **23 TO 30 PAINFUL SHOTS IN THE ABDOMEN**

HPV VACCINE

THERE ARE TWO HPV VACCINES ON THE MARKET, **CERVARIX AND GARDASIL,** WITH THE LATTER ALSO AVAILABLE TO MEN. STUDIES HAVE FOUND THAT HPV VACCINATION **MAY BENEFIT PEOPLE INFECTED WITH HIV,** AS THEY SUFFER FROM WEAKENED IMMUNE SYSTEMS AND ARE MORE VULNERABLE TO HPV'S SYMPTOMS. IT IS RECOMMENDED THAT **FEMALES AGED 11 TO 26 YEARS OLD** BE VACCINATED

H5N1 BIRD FLU VACCINE

AS BIRD FLU SPREAD, GOVERNMENTS BEGAN TO **STOCKPILE VACCINES.** NOT SURPRISING, CONSIDERING ITS HIGH FATALITY RATE. IN 2004, THE US GOVERNMENT **STORED 20 MILLION DOSES OF A VACCINE** AGAINST THE "VIETNAM" STRAIN OF BIRD FLU. HOWEVER, THE H5N1 VIRUS MUTATES VERY QUICKLY, AND THE **"INDONESIA" STRAIN HAS SINCE BECOME PREDOMINANT**

DANGER FROM DOGS

In their new book, *Rabid: A Cultural History of the World's Most Diabolical Virus*, writers Bill Wasik and Monica Murphy note rabies has been known since roughly 3,500 BC. Yet despite Louis Pasteur's vaccine being available for almost 130 years, rabies continues to kill around 55,000 people every year, mostly in impoverished regions of Africa and Asia.

Rabid covers Pasteur's groundbreaking work, including contemporary observations of his team's efforts at collecting infectious saliva from dogs with the disease, which works its way slowly through the nervous system until it reaches the brain. In case they were bitten during this procedure, researchers kept a loaded revolver within their reach, so that if one of them was accidentally bitten, "the more courageous of the two others would put a bullet in his head".

The book also documents the recent rabies outbreak in the Indonesian island of Bali, home to around 300,000 strays. Following lobbying by animal welfare groups and health organisations, attempts to cull the dog population were replaced by a mass dog vaccination programme. The first phase involved 400 trained dog catchers vaccinating 270,000 dogs over a six-month period, and reportedly led to an 85 percent reduction in human deaths, and 80 percent fewer cases in dogs.

The programme was carried out by the Bali Animal Welfare Association, with support from the World Society for the Protection of Animals (WSPA) and the Balinese and Australian governments. It is ongoing, to ensure that so-called "herd" immunity levels are maintained at 70 percent in the island's canine population. The programme was so successful in Bali that it is also being rolled out under the banner of "Collars not Cruelty" by WSPA in other countries with rabies outbreaks.

BIOLOGICAL WEAPON

Following the official declaration of smallpox's eradication, small supplies of the live virus were kept by several research institutions, sparking fears that it could be released either accidentally or on purpose. It is a valid fear, considering that there is currently no proven cure for the disease, and it can be lethal — the most common version has a fatality rate of 30 percent. Prevention is in the form of vaccination, and for most people it is safe and effective. Side effects, such as groupings of lesions (*pictured right*) may occur, but they are very rare and will often go away on their own.

PHOTOS: AFP (MAIN); CORBIS (SMALLPOX)

trials set to begin next year, and is also undertaking research into the virus underlying a common type of skin cancer. "New technologies are allowing us to look at large amounts of genetic information very quickly, and at a minimal cost. We are looking for the signature that genetic information is being used in pre-cancers in skin," he says.

MASS INFECTIONS

While viruses infect all forms of life, pandemics, or mass infections, are a relatively recent phenomenon, and are a function of our highly connected world — typified by increasingly dense urban populations, and close relationships with animals. While infection with zoonoses (animal diseases that can cross over to humans) is fairly common, it is only when they mutate and begin to spread from one human to another that alarm bells go off.

"Three-quarters of emerging infectious diseases originate in animals," says Columbia University's Lipkin, who has over 30 years of experience in diagnostics, microbial discovery and outbreak response. He and his team have discovered or characterised more than 500 infectious agents, including Borna disease virus, West Nile virus, Lujo virus and human rhinovirus C, and worked with the WHO and the People's Republic of China during the 2003 SARS outbreak. Lipkin was also one of the scientific consultants on the film *Contagion*, which described the emergence of a pandemic zoonosis modelled on the Nipah virus.

"Influenza is endemic in fowl," he says. "Nipah and Hendra originated in bats. Bats also harbour rabies and the SARS coronavirus. Rodents carry arenaviruses such as Lassa fever virus, Lujo virus, and hantaviruses." Viruses like Ebola, Marburg and HIV originated in primates and receive a lot of press, he notes. However, despite our close evolutionary relationship, "it is not true that all or even most of the lethal human infections originate in primates," he asserts.

> "IN THE PAST, VIRUSES THAT ENTERED RURAL COMMUNITIES WOULD LIKELY HAVE GONE EXTINCT. BUT NOW LOGGING ROADS PROVIDE ACCESS TO URBAN AREAS"

Much of the focus on tracking new viruses tends to focus on tropical Africa and Asia, where people live in close proximity to animals, though swine flu emerged from Mexico, surprising many virus-watchers. "In the past, viruses that entered rural communities would likely have gone extinct. But now logging roads provide access to urban areas. And critically, what happens in central Africa, doesn't stay in central Africa," observed the well-known virus-hunter Dr Nathan Wolfe at a TED talk he gave in 2009.

Wolfe is founder and chief executive officer of Global Viral Forecasting Initiative. In his recently released book, *The Viral Storm: The Dawn of a New Pandemic Age*, he chronicles the changes in human behaviour that have shaped our experience with pandemics, and argues that rather than just treatment, prevention should define future interactions between humans and deadly viruses. This, he notes, can be achieved by working with the poorer communities that are often ground zero for new outbreaks.

Wolfe's knowledge comes from over a decade of hunting viruses, and was inspired by his early work in Cameroon, in west-central Africa, where local villagers relied on wild game, or bushmeat, for protein. It quickly became clear that when hunters came into contact with animal fluids during butchering, they became especially vulnerable to hosting new bugs.

In his speech, Wolfe argued that medical science spends a lot of its energy trying to tackle things that "are already completely adapted to humans", making them particularly difficult to address. This was the case with HIV. "AIDS and the virus that causes it, HIV, was discovered in the 1980s. But in fact this virus crossed over into humans decades before, from chimpanzees where the virus originated, into the humans who hunt these apes," he noted. "If we'd been there, seen the disease make the jump between species, how might that have transformed the nature of the way this pandemic emerged?"

Wolfe and other researchers are working to study the earlier interface, or what has been labelled "viral chatter", the study of the movement of agents into the human population.

"We want to capture that moment, and move to a situation where we can capture them early," he says. "To study viral chatter we need to get to populations with intensive contact with wild animals — and collect blood from those people and other specimens."

The researchers have already established a network of thousands of individuals, who monitor and regularly collect samples from hunters and the animals that they have caught. "It allows us to identify as yet unknown viruses from animals, including retroviruses like HIV, while also teaching hunters to decrease the risk of disease transmission from animals to themselves and their families," says Wolfe.

PREDICTION IS KEY

Wolfe's global monitoring effort is being supported by Google

LIFE-THREATENING REACTIONS OCCUR IN 14 TO 52 PER MILLION PEOPLE VACCINATED AGAINST SMALLPOX

WHEN THE BIRD FLU PANDEMIC STRUCK IN 2003, CHICKENS SUCH AS THESE IN CENTRAL BALI, DIED IN THE HUNDREDS AND THOUSANDS ON A DAILY BASIS. ALTHOUGH MANY PEOPLE FEARFULLY AVOIDED EATING CHICKEN, EXPERTS ADVISED THAT COOKED POULTRY WAS UNLIKELY TO BE INFECTIOUS

PHOTO: VW/CLICK PHOTOS

PHOTOS: CORBIS (MAIN); REUTERS

LEFT: DURING THE SARS SCARE, SOME PEOPLE, LIKE THESE ENTERPRISING CHAPS IN VANCOUVER, CANADA, SOLD SURGICAL MASKS FOR HIKED UP PRICES **BELOW:** SARS STRUCK HARD AND FAST IN CHINA, AND THE COUNTRY HAD THE HIGHEST KNOWN DEATH TOLL WORLDWIDE

MIX AND MATCH

The H1N1 swine flu brought the word "pandemic" into the public consciousness, but only resulted in 18,500 confirmed deaths worldwide, according to World Health Organisation statistics. Researchers were concerned because pigs are what is known as a virus-mixing vessel. They are susceptible to infection by highly interchangeable swine, human, and avian influenza viruses. As such, scientists feared that if a pig infected with the highly contagious H1N1 picked up a more lethal avian influenza strain, and the two viruses mixed their genetic material, a perfect storm of infection might result.

and the Bill & Melinda Gates Foundation. "We neglect the problem at our own peril," he says. "So we are not just working with hunters in central Africa, but are also working in live animal markets and wet markets in China and Southeast Asia, which is where SARS emerged."

Severe Acute Respiratory Syndrome, or SARS, caused 812 known global fatalities, including 348 in mainland China, 298 in Hong Kong and 32 in Singapore. Its spread was halted due to widespread initiatives including improved hygiene practices such as enforcing bans on public spitting and discouraging shared meals, quarantine for those who had been exposed, and the closure of schools in China. In Singapore, constant temperature checks were implemented, and every time someone entered most public buildings, their temperature was taken. Thousands of travellers at airports had to pass through heat-sensitive scanners, which monitored abnormally high body temperatures that might have been an indication of early stages of infection.

"Historically, the way we've focused on disease control when it comes to pandemics is very much a reactive, responsive approach," Wolfe said at his book launch, noting that science has now "crossed the threshold" into having organisations and governments recognise the importance of prediction, and stopping deadly bugs before they spread. He said the effectiveness of this also depends on our "risk literacy", or the ability of individuals to compare and interpret relative risks.

"While we may not perceive them in the way that we perceive more visually traumatic risks like hurricanes and earthquakes, they represent, in many ways, more profound threats," he commented.

Columbia University's Lipkin points out that the future is certainly not all doom and gloom, with several factors improving global surveillance and response. These include technical advances such as high-throughput gene sequencing, which enables researchers to quickly diagnose a viral disease, as well as improvements in public health infrastructure in both the developed and developing world, and the pooling of knowledge gained in both veterinary and human research — a concept known as One Medicine. A document known as the *Revised International Health Regulations*, adopted in 2005 in the wake of the SARS epidemic, has also helped formalise protocols for information exchange and technology transfer between affected countries.

"The result," says Lipkin, "is a greater likelihood of early detection of pandemic threats."

The effectiveness of global surveillance and response initiatives can be seen in the case of Chikungunya fever, a viral disease that was first isolated in 1953 in East Africa, and has now emerged as a major threat in Southeast Asia, the Pacific region and Europe.

"After years of being in hiding, Chikugunya is suddenly on the rise, with periodic outbreaks since 2005," says Dr Lisa F. P. Ng, Principal Investigator at the Singapore Immunology Network, which was launched a few years ago by the country's Agency for Science, Technology and Research, or A*STAR.

RESEARCH IS ALSO MAKING IT CLEAR THAT OUR RELATIONSHIP WITH VIRUSES IS NOT ALWAYS ADVERSARIAL. IN SOME CASES, IT MAY EVEN BE MUTUALLY BENEFICIAL

"Vector-borne infectious diseases (arboviruses) are emerging or resurging due to climate change, socio-demographic changes, and genetic mutations in the pathogens," she explains. "There could be a number of explanations for this. The landscape has changed, with development moving closer to the disease's natural habitat, and bringing people into closer contact."

Ng says Chikugunya initially appeared in the early 1950s in East Africa, producing a wave of fever that first spread, then died down. The condition causes severe joint pain and debilitating chronic illness for up to two years after infection. The disease has some similarities to dengue fever, caused by another insect-borne virus.

"There were outbreaks in India in the 1960s, then everything went quiet," she notes. "Then there was a huge outbreak in 2005 in the Indian Ocean islands, notably in Reunion Island and others such as Mayotte and Mauritius. The virus had mutated, allowing Asian tiger (*Aedes*) mosquitoes to become vectors. And very few people had protection."

Of Reunion Island's population, more than 30 percent were infected, she says, with many people returning to France from the French colony taking the disease with them.

"There have been sporadic outbreaks throughout Southeast Asia, including in Singapore," she adds. In the latter case, it was brought into the country by a returning foreign worker, and spread via mosquitoes to other workers living in the suburb of Little India. "Thanks to reporting protocols, the outbreak was contained," Ng says. "But it gave researchers the opportunity to closely study the immune response of patients."

BREAKTHROUGHS

Finding out what makes mosquitoes and other similar vectors immune to the viruses they carry may hold the key to managing arboviruses, which could in turn lead to improved vaccines and other control measures for mosquito-borne viruses such as dengue, Chikugunya and West Nile.

"Until now, very little was known about the defensive anti-viral response of insects," says Dr Peter Walker of CSIRO's Australian Animal Health Laboratory. "Unlike humans and other mammals, insects lack key components of the immune response, including antibodies, T-cells and many important cytokines (substances secreted by immune cells to signal other cells), such as interferon."

In his research, he found that instead, mosquito cells sense the presence of a virus by detecting its small, foreign genome. This stimulates the secretion of a protein called Vago, which signals a defensive response to limit the infection.

"This is the first demonstration that such a mechanism exists in mosquitoes or any other invertebrate," Walker notes.

"We are now looking at how viruses such as West Nile and dengue overcome the defensive response of the mosquito — and how we can use this knowledge to increase [human] resistance to infection and decrease the efficiency of disease transmission," he adds.

VIRAL FRIENDS

While death and disease often grab the headlines, new findings are also making it clear that humans' relationship with viruses is not always adversarial. In some cases, it may even be mutually beneficial.

For instance, researchers have recently discovered a non-disease-causing virus that kills breast cancer cells in the lab, in addition to a harmless skin virus that kills acne-causing bacteria. Then there is the vesicular stomatitis virus, which belongs to the same family as the rabies virus — it not only appears to kills cancer cells, but also blocks attempts by the cancer to damage the immune system.

Montana State University's Dr Mark Young believes people should start to view viruses in a broader context — rather than just seeing them as wholly disease-causing agents.

Viruses are not necessarily our enemy, he notes. "We think that, because they cause diseases in us. But when we look across the spectrum of the ecosystem, they are incredibly beneficial — they are essential for ecosystem function and for the diversity of life on this planet," he explains. "They have numerous beneficial effects for the operation of host cells. Many viruses completely replicate cycles, without killing the cell."

In fact, Young suggests that viruses may actually play a large part in determining who we are as a species. "A significant proportion of the human genome is made up of viral sequences — humans would not be human without their presence. We are a mosaic of viral and cellular sequences," Young says. "All life forms we have looked at are the same. There is no question that viruses and cellular life are inextricably linked."

VIRAL VORTEX

In some cases, they can be almost 100-percent fatal. In others, they can kill more people than a World War. Humankind has good reason to fear viruses, despite the fact that most of us happily go day-to-day with trillions of them nestled in our system

"An inefficient virus kills its host. A clever virus stays with it," said **Dr James Lovelock,** chemist and earth scientist

1999

It is difficult to pinpoint when the phrase "going viral"...well, went viral, but many people narrow it down to **1999** or **2000**

YEARS

The cells of a black **American** woman, **Henrietta Lacks**, were taken from her without her knowledge in **1951**. Since then, they have been used in laboratories to study the polio vaccine, the effects of the atomic bomb, cloning and gene mapping. Known as **HeLa cells**, they are the first technically immortal human cells ever grown. The cells can grow indefinitely. **Sixty years** after her death, Lacks is still technically "alive"

100

So much genetic material has been grown from Lacks' cells that their total weight is estimated to be about **50 million tonnes** — heavier than **100 Empire State buildings**

1986

The **first computer virus epidemic** occurred. Named **"Brain"**, this relatively harmless virus, stored on floppy disks, was created by a **19-year-old** and his brother. Before that, programs that could self-replicate and infect other machines existed, but were not called viruses

1,000

VIRUSES

In the late **1990s**, an estimate put the number of computer viruses in circulation at roughly **10,000**, with **300** to **400** new viruses created each month

100+

COLDS

Scientists have identified **100** versions of the **common cold** virus, but theorise that there could be as many as **200**

TEN

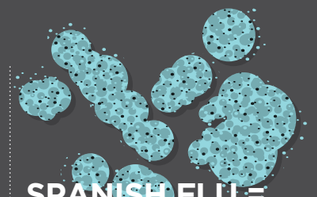
MILLION

1914 to **1918**: There were an estimated **10** million combat fatalities from the **World War I** conflict

ONE

THIRD

1918 to **1919**: The Spanish Flu pandemic infected **one-third of the world population,** and killed roughly 50 million (some estimates say up to 100 million)



SPANISH FLU = 5 TO 10 WWIs

Some sources say that the **Spanish Flu** killed more people in **one** year than the **Black Death** did in one century, and a higher loss of life in **24** weeks than **AIDS** caused in **24** years

1,000

TIMES MORE

Damp hands spread germs **1,000** times more effectively than dry hands. Hope that scary fact doesn't make your palms sweaty

90%

WIPEOUT

When Europeans began to trade with and forcefully colonise the New World of the Americas, they brought the **smallpox virus** (known as the variola virus) with them. The Europeans had achieved some immunity through generations of exposure, but not the tribes of the **New World**. **Smallpox** spread fiercely, killing around **90 percent of indigenous populations**

10 BILLION TRILLION, TRILLION

According to **Carl Zimmer**, author of *A Planet of Viruses,* there are **10 billion trillion, trillion viruses on Earth.** That number, more easily read as **10 to the power of 31**, is more than the number of stars in the universe

ONE

BILLION US$

Koalas (*Phascolarctos cinereus*) bring in roughly US$1 billion in tourism revenues for **Australia**

100,000

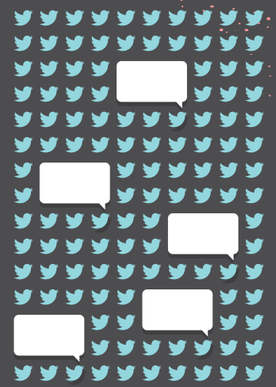
TO 43,000

A report stated that from **2003** to **2009**, koala numbers dropped from **100,000** to fewer than **43,000**, due to deforestation and infection from two surprising diseases: **chlamydia** and a koala version of AIDS known as **KIDS** (Koala Immune Deficiency Syndrome), caused by the KoRV retrovirus

120

YEARS

Recent sampling of century-old koala skins show that koalas have been **dying** from this retrovirus for at least **120** years



120

MILLION

After analysing **120 million retweets** (reposting of users' messages) by 12.5 million Twitter users, researchers said they still had **no idea** how to predict what causes certain **tweets to spread "virally"** after becoming massively popular

TEN

TRILLION TIMES

A virus invades a microbe host **10** trillion times a **second** around the **world**

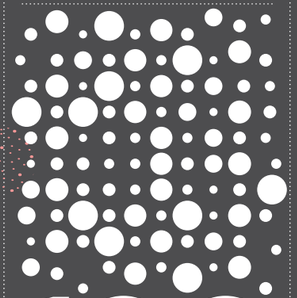
55,000

DEATHS

The World Health Organisation says that more than **55,000** people **die of rabies each year**

100%

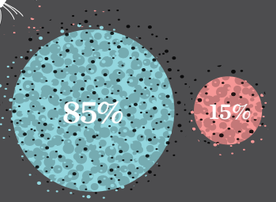
Close to absolute mortality rate: The rabies virus ***(Lyssavirus rabies)***, usually passed on to humans through animal bites, has a **near-100-percent mortality rate** once symptoms appear. Symptoms include pain at the site of the bite, an inability to swallow, convulsions, sudden violence and fever



100

TRILLION

The human body is made up of roughly 100 trillion cells, but only about **10 trillion are actually human cells.** The rest is made up of bacterial and viral cells. So our human cells are **outnumbered** — by about 10 to 1



15%

An estimated **15 percent of all human cancers** may be caused by viruses

SARS

MONEY-KILLER

2003: **SARS** (severe acute respiratory syndrome) outbreak hit the world, especially in **Asia**

8,098

PEOPLE

were infected **worldwide,** and **774** died

US$20 billion—US$60 billion: Due to reduced tourism, public spending and business confidence, all of which arose from fear of SARS, the **economic loss in Asia alone** was calculated to be between US$20 billion and US$60 billion, depending on the economic model used

Considering the relatively small scale of the disease, the economic loss clocked in at a monumental **US$2 to US$6 million per person infected**

ILLUSTRATION: MARK McCORMICK