EPIDEMIOLOGY

Racing against the flu

Influenza mutates fast and spreads easily, earning a place among humanity's biggest killers.

BY DUNCAN GRAHAM-ROWE

Influenza kills more than 250,000 people each year, worldwide. And with new strains ever emerging, there is always the threat of a repeat of the Spanish flu pandemic of 1918, which claimed more than 50 million lives. Indeed, despite vaccines and antiviral drugs that offer some protection to the vulnerable, nearly a century after that catastrophe we still seem no closer to being able to predict and ultimately stave off such a virulent outbreak.

One reason this has proved so difficult is the speed at which this acute viral infection can spread, transmitted by coughs and sneezes. "It's a very stable respiratory virus that survives well on surfaces and people's hands," says flu specialist Anthony Mounts with the Global Influenza Programme at the World Health Organization in Geneva, Switzerland.

Moreover, the flu virus changes all the time, mutating at the genetic level, which alters the surface level — in the hemagglutinin and neuraminidase antigens that coat it (and provide the familiar H-N designations). These proteins are what our antibodies attach to; by continually changing, these antigens enable the virus to infect people who have developed immunity to other strains. It is because of its ability to rapidly mutate that the virus is able to develop resistance to previously effective drugs, such as oseltamivir (marketed as Tamiflu by Switzerland-based Roche) and amantadine.

On average between 5–15% of the global population are infected each year. Most at risk are children younger than 2 years and adults 65 years or older, as well as people of any age with asthma, diabetes or chronic heart disease. But no one is entirely free from risk. "This was particularly notable in this last pandemic," says Mounts, referring to the 2009 outbreak, in which as many as half of those contracting the disease had fully functioning immune systems and were perfectly healthy beforehand.

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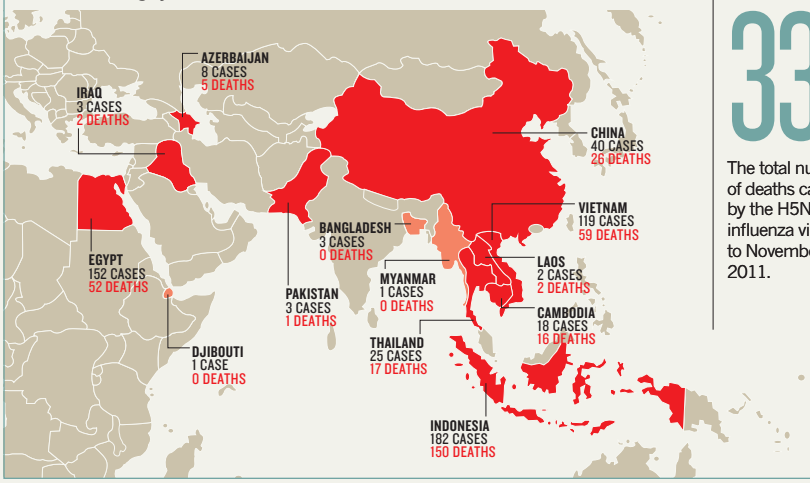
THE FAST OR THE FURIOUS

To exact the greatest toll, influenza needs to be both fast-spreading and highly lethal. Unlike the 1918 'Spanish flu', the two recent outbreaks — H5N1 'bird flu' and H1N1 'swine flu' — only had one attribute each.

THE SLOW BUT DEADLY SPREAD OF H5N1

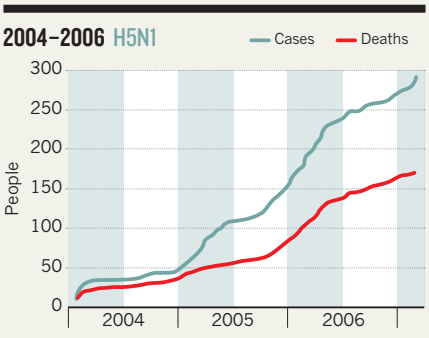
Between 2003 and 2011, H5N1, commonly known as bird flu, spreads across Asia but remains largely an avian virus.



335
The total number of deaths caused by the H5N1 influenza virus up to November 2011.

CASES ON THE RISE

The mortality rate has risen with the number of cases worldwide



60% approximate proportion of fatalities for immunocompetent people infected with H5N1.

H5N1 2003

1890 — RUSSIA
First recorded influenza pandemic. 1 million die worldwide.

1918 — H1N1
PANDEMIC
The origin of H1N1 has been the subject of many studies — some suggest it may have gone directly from birds to humans, while others suggest it may have involved incubation in an intermediate host, such as the pig.

50M
The 'Spanish Flu' caused by the H1N1 influenza virus, kills approximately 50 million people.

1957 — H2N2
1959 — H7N7
ASIA
The second influenza pandemic strikes in Asia, killing 100,000 people worldwide.

Several new strains of influenza emerge throughout the twentieth century, circulating without turning pandemic.

1968 — H3N2
HONG KONG
Flu pandemic kills 700,000 people worldwide. Virus still circulates today.

1977
H1N1 outbreak of Russian flu in China, similar to strain in circulation prior to 1957, spreads around the world disproportionately infecting people under the age of 23.

The virulence of an outbreak is a combination of the viral lethality and infectiousness. These, in turn, depend on which of the three varieties of human flu virus is the pathogen: type A, type B or type C. Type A is by far the most virulent; with 16 known subtypes, it mutates into countless different genetic and antigenic strains at a rate far faster than type B or type C. This ability to mutate quickly allows type A flu to spread faster. All the flu strains discussed in this *Nature Outlook* are influenza type A.

Some of the most virulent strains encountered are those that have managed to pass from other species to humans. The avian H5N1 flu virus had a very high lethality, killing 56% of those who were infected. However it was also not terribly infectious: between 2003 and 2006 there were only 263 cases of H5N1, mitigating its overall impact. In contrast, the H1N1 swine flu virus of 2009–2010 had a case fatality rate of only around 0.03% but, as it can be passed easily from human to human, it was responsible for more than 13,000 cases in a single month.

INFLUENZA MENAGERIE

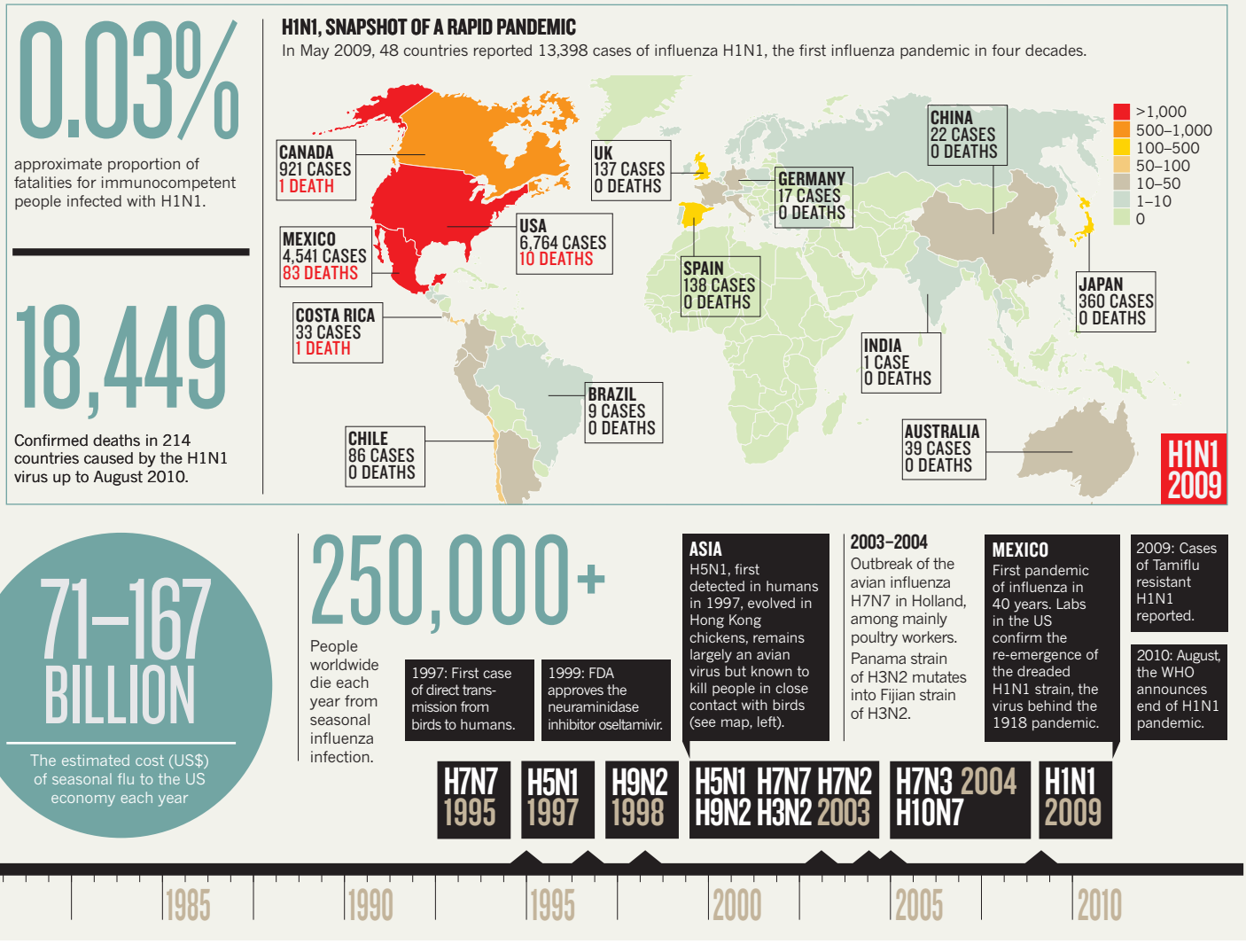
Flu has been found in a variety of mammals, from horses, cats, dogs, and pigs, to seals, ferrets, camels and even whales. But it is mainly through wild aquatic birds that the virus is able to jump species — most likely because the virus originated in these avian species. Although it is next to impossible to predict where and when an inter-species jump is likely to take place, or which of these will result in a particularly virulent human strain, clues are beginning to emerge.

By analysing the genetic and antigenic variations of 13,000 strains of the H3N2 virus, a group led by infectious-disease experts Colin Russell and Derek Smith at the University of Cambridge in the UK were able to track the evolution of the virus as it moved around the world between 2002 and 2007. They found that, at least for the common H3N2 virus, strains tend to originate in East and Southeast Asia, and mutate their way around the world until they end up in what Smith calls an "evolutionary graveyard" in South America — a continent that, in terms of flu at least, he says, is therefore "the safest place to be because you get the biggest warning."

The conditions in Asia are ripe for new influenza strains to emerge, says Russell. For one thing, the virus is able to exist in circulation almost perpetually, giving it more of a chance to mutate. Because tropical countries have no winter, seasonal influenza epidemics typically occur during the rainy season, which can happen at different times of the year in neighbouring places like Bangkok and Kuala Lumpar, says Russell. This means that within East and Southeast Asia there will be an influenza epidemic happening somewhere at any point in a year. "Given the travel and trade between cities and countries in the regions, influenza seems to be able to spread readily from place to place," says Russell. "We often talk about it as being similar to runners passing a baton in a relay race, as viruses move from epidemic to epidemic."

It's a race that researchers, public health authorities, and the public continue — with mixed success — to try to disrupt. ■

Duncan Graham-Rowe *is a science writer in Brighton, UK.*



SOURCES: WHO/GIP AND FAUCI, A. S. MILBANK MEMORIAL LECTURE 1–22 (2006).