

Flu hotspot found in Asia

Influenza strains then radiate worldwide.

Rachel Courtland

The breeding ground for new influenza strains is centered in East and Southeast Asia, new research suggests. The virus bounces around countries in the region before emerging worldwide to cause seasonal epidemics.

Each year, officials struggle to predict which strains of flu will spread globally, killing up to 500,000. Pinpointing a reservoir for the disease could help focus surveillance efforts on countries where new, harmful strains get their start six to nine months before appearing elsewhere.

The conclusions come from two independent studies of the influenza virus. One, released today by *Science*, locates the virus hotspot by mapping global changes in hemagglutinin, the influenza protein that can trigger or bypass the human immune response¹ (#B1). The other paper, appearing today in *Nature*, examines the virus's full genome to show that a reservoir must exist for new flu strains² (#B2). New variants can lurk in this reservoir for years before a rapid series of critical rearrangements allows the virus to emerge.

The flu hotspot theory is not new, but the results seem to provide a more comprehensive picture of how influenza emerges and makes its way around the world. "This is not a new hypothesis, but this is new evidence," says computational biologist Steven Salzberg of the University of Maryland in College Park. "There's a lot more data now, and it makes it a lot more clear that's what's going on."

Sink or swim

To get a detailed picture of how influenza circles the globe, the *Science* group analyzed World Health Organization data on roughly 13,000 human influenza A viruses (of the subtype H3N2) from six continents, collected between 2002 and 2007. H3N2 is largely responsible for today's flu epidemics.

A trail of changes in the viruses' hemagglutinins show that viruses each year seem to bear the most resemblance to strains collected in East and Southeast Asia. Cities that are near each other in the region may play host to epidemics at different times of the year, allowing the viruses to overlap and continually evolve. A 'winning' strain may then emerge from this reservoir to spread around the world some months later.

Having escaped the reservoir, a virus will spread to other continents before fizzling out at the end of a season. "Areas outside Southeast Asia are essentially the evolutionary graveyards of influenza virus," says co-author Colin Russell, a biologist at the University of Cambridge in the UK.

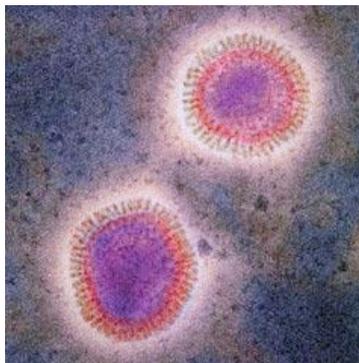
A reservoir is only one idea of how flu virus is thought to spread. Some epidemiologists have speculated that the virus may linger in a region, waiting for the next cold season. Others have suggested that flu may move back and forth between the northern and southern hemisphere, an idea that would explain why flu epidemics seem to pop up in winter months. This new study does not suggest an explanation for seasonal variation in flu incidence.

Still, pinning down the location where these viruses emerge could help vaccine officials predict which strains will emerge in the coming year, say study authors. "This now tells us where to look to find out what the evolutionary pressures are in detail," says co-author Derek Smith, a bioinformaticist with the University of Cambridge.

Shuffling the deck

Understanding how new strains of influenza are selected could be the key to forecasting epidemics farther in advance. Authors of the *Nature* paper say that although some hemagglutinin variants seem perfectly suited to crash the immune system, sometimes the protein is configured unfavourably to work with the rest of the virus.

"It's not just the hemagglutinin that's evolving that's critical. It's how the hemagglutinin interacts with the rest of the genome," says biologist Edward Holmes of Pennsylvania State University in University Park.



The influenza virus evolves in local reservoirs before spreading worldwide.

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Holmes and colleagues used 1,300 publicly available genome samples from New York state and New Zealand to look at viral diversity over 13 seasons of flu. The team found the virus does not linger in either area from year to year. Instead, slightly or dramatically altered versions seem to emerge each year from some reservoir.

Some flu strains seem to undergo rapid genetic rearrangements and, after lingering for a number of years in the background, emerge as a new, epidemic variety. The data show this occurred in the 2003–2004 season, one period when the flu vaccine failed.

Analyzing both H3N2 and H1N1, the subtype that caused the 1918 outbreak, the team also confirmed an alternating relationship between the two flu strains [3 \(#B3\)](#). As a particular variant of H3N2 weakens, sometimes a virulent strain of H1N1 will emerge, as it did last year.

The path to better flu surveillance is unclear. While Russell and Smith call for increased surveillance in East and Southeast Asia, more focused monitoring may not help predict which strains emerge.

Although it may be time to re-examine the balance of surveillance, “I don’t think they’ve made the argument that increased surveillance in the tropics is necessary,” says Salzberg. “What we really care about is not which viruses are going around in the tropics, but which ones are fit enough to escape.”

References

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Flu study sheds light on how it spreads

By Roger Highfield, Science Editor

Last Updated: 6:01pm BST 16/04/2008

The biggest studies of their kind have shown how seasonal flu epidemics are born in the Far East, sweep westwards and then die out in South America, crucial intelligence to improve influenza vaccines.

Annual influenza epidemics are thought to infect 5-15 per cent of the world population each year, cause three to five million cases of severe illness, and between 250,000 and 500,000 deaths.

The studies show how epidemics of the most common type of influenza virus, A (H3N2), are seeded by viruses that originate in East and Southeast Asia and migrate around the world.

The new findings suggest that by focusing surveillance efforts on East and Southeast Asia, researchers may be able to extend their forecast of the flu strains most likely to cause epidemics, which may in turn help experts decide which strains should go in the flu vaccine each year.

One study is reported in the journal *Science* by scientists at the University of Cambridge, in collaboration with scientists from the World Health Organisation Global Influenza Surveillance Network, found that each year since 2002 influenza A (H3N2) viruses have migrated out of what the authors call the "East and Southeast Asian circulation network" (which includes tropical, subtropical, and temperate countries) and spread throughout the world.

Although the current the flu vaccine works well, and protects the 300 million people vaccinated each year, from time to time, a new strain emerges after the vaccine strain selection has already been made.

One of the serious challenges to creating flu vaccines is that the global migration pattern of influenza viruses has been a mystery. Several competing hypotheses have emerged including migration between the Northern and Southern hemispheres following the seasons, migration out of the tropics where influenza viruses were thought to circulate continuously, and migration out of China.

Now the analysis by Colin Russell in Cambridge and his colleagues of 13,000 samples of influenza A (H3N2) virus, which revealed that new strains emerge in East and Southeast Asia and then about six to nine months later reach Europe and North America.

Several months later still, the strains arrive in South America. Once viruses leave East and Southeast Asia they rarely return and thus regions outside of East and Southeast Asia are essentially the evolutionary graveyards of influenza viruses.

For reasons that are not well-understood, flu epidemics typically occur during the winter months in the temperate regions of the northern and southern hemisphere and in tropical countries, flu epidemics often coincide with the rainy season.

Because there is variation in the timing of the rainy season in different parts of East and Southeast Asia, combined with the wintertime epidemics in the temperate parts of the region, the overlap in the timing of epidemics gives the opportunity for influenza viruses to circulate year round in East and Southeast Asia.

The authors find that this year-round circulation allows East and Southeast Asia to serve as the source of influenza A (H3N2) viruses for epidemics in the rest of the world.

"Flu epidemics appear to be driven by seasonal factors such as winter, or rainy seasons. So there can be cities that are only 700 miles away from each other, such as Bangkok and Kuala Lumpur, which have epidemics six months apart.

"There is a lot of variability like this in East and Southeast Asia, so lots of opportunity for an

epidemic in one country to seed an epidemic to another nearby country, like a baton passed by runners in a relay race," said Derek Smith of Cambridge, another author.

The finding is complemented by another study, published in *Nature*, by Prof Edward Holmes of The Pennsylvania State University, and colleagues who examine in detail the evolutionary dynamics of human influenza A virus at both the genetic level - across the entire genetic code of the virus - and in terms of epidemiological data to suggest that the virus follows a 'sink-source' model in which new lineages arise one after the other from the tropical parts of the planet later to die out in other areas. "Briefly, our results agree," he says. "We now know where the influenza A virus comes from every year."

Currently, there are many strains of the influenza virus that appear only in birds, which are natural viral reservoirs. So far three of these viral strains - H1N1, H2N2 and H3N2 - have caused epidemics in humans as influenza A. Of the three, H3N2 is the dominant strain, responsible for most influenza infections each winter, with lower levels of H1N1.

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The Washington Post

Researchers Chart Flu's Global Journey

Strains Arise in Asia, Die in S. America

By David Brown
Washington Post Staff Writer
Thursday, April 17, 2008

New strains of seasonal influenza virus all arise in East or Southeast Asia and take a largely predictable route around the world before dying out for good in South America, the global glue-trap for the pathogen.

That is the conclusion reported yesterday by a large team of researchers who analyzed the genetic ancestry of about 13,000 virus samples collected from six continents over a five-year period to answer long-standing questions about the flu's life cycle.

The findings help explain the biological mechanisms that underlie two long-held observations about flu: New strains tend to appear first somewhere near [China](#), and Australia's flu season is a preview of what will happen in North America six months later. They also help explain why one winter's flu is always at least a little bit different from the previous winter's, even though the virus disappears over the summer.

The researchers hope the insights may help virologists better predict what strains of virus to include in annual flu shots, which must be manufactured anew each year. Although usually accurate, those predictions occasionally miss, as they did this year when the North American vaccine provided little protection against the strain causing most illness.

"If we want to know what will be happening in a year, we really need to pay attention to what is happening in East and Southeast Asia," said Derek J. Smith, a biologist at the University of Cambridge in England.

Previously, scientists were uncertain how and where influenza virus evolves between epidemics, which occur in winter in temperate climates.

One theory was that flu virus survives largely unnoticed each summer, with the first cases each winter caused by leftover -- and slightly changed -- strains. Another theory held that the virus dies out completely in temperate climates each summer but flourishes year-round in tropical zones, which are the nurseries for new variants. A third theory was that all new strains come from China, largely because of its population density.

The researchers analyzed virus samples collected from 2002 to 2007 and compared the molecular fingerprints of the gene for hemagglutinin, the protein that gives flu strains their distinct identities.

They found that each year's dominant strain in Europe, the Americas or other regions was traceable to ancestors first seen in a large region of East and Southeast Asia (an area bigger than China alone). It was never directly descended from a strain seen in temperate zones the previous year. In fact, the evidence strongly suggested that flu virus goes extinct each summer in temperate climates -- there is none left to smolder and evolve.

What the researchers now believe happens is that the world is reseeded each year by new, slightly different variants. "The strains are coming out [of Asia] fully formed," Colin A. Russell, one of the researchers, said in a telephone news conference.

The route the new strains then take seems to reflect both proximity to East Asia and the amount of travel between regions. The first stops are Australia and the Pacific islands known as Oceania, which the virus

reaches about three months after it arises in Asia. Three to six months later it crops up in Western Asia, Europe and then North America. The last stop is South America.

"It is a surprise to everyone that South America is the end of this seeding hierarchy," Russell said.

But why is East-Southeast Asia always the starting point? The researchers believe it's because of the unusual concentration of different climates there. The region has both tropical environments, where flu flourishes during the rainy season, and temperate zones. There are places that are relatively close -- Russell cited Bangkok and Kuala Lumpur, Malaysia, 700 miles apart -- that have totally different flu seasons.

This effectively allows new strains to be passed around the region like a baton in a relay race, even though in each climate zone the virus completely dies out once a year.

The reason new variants don't cause epidemics if they are carried back to East Asia from elsewhere is because people already have immunity to them. They're old news. At least that's the theory.

The Science paper complemented one published this week in the competing journal Nature.

Edward C. Holmes, a biologist at Pennsylvania State University, and his collaborators studied about 1,300 influenza virus samples gathered from New York state in the Northern Hemisphere and New Zealand in the Southern Hemisphere over 12 years. They examined the genetic fingerprints of all eight gene segments of the flu virus, not just hemagglutinin.

They found that one region's year-to-year virus strains were not directly descended from each other but instead appeared to come from a "reservoir" population somewhere, Holmes said. He added that the results were "completely compatible" with the Cambridge group's findings.

The Penn State group also found that new, successful flu variants weren't just ones that had different hemagglutinin proteins to which people were not likely to be immune. Many also showed evidence of having traded genes with other flu viruses, with some of these "reassorted" strains more successful than those that evolved by small steps.

Neither of these papers address the origin of flu viruses that cause severe global pandemics such as the one that killed at least 50 million people in 1918 and 1919. Those arise from the mixing of human flu viruses and ones carried by birds or pigs -- a much rarer event than the predictable evolution of human viruses year to year.

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Flu comes fresh from Asia each year, study finds

Wed Apr 16, 2008 10:06pm BST

By Maggie Fox, Health and Science Editor

WASHINGTON (Reuters) - Flu viruses evolve freshly somewhere in east or southeast Asia every year, spreading around the world over the next nine months before dying out, researchers reported on Wednesday.

Genetic analysis by two teams of international researchers show that there are just a few initial sources of annual, seasonal influenza epidemics. The viruses spread around the world from these before dying.

Then every year, new strains emerge to infect people, according to the studies published in the journals Nature and Science.

One team led by Edward Holmes of Pennsylvania State University could not pinpoint the source but said that both H3N2 and H1N1 strains of influenza appear to arise every year from a "reservoir," perhaps in the tropics.

A second team led by Colin Russell and Derek Smith of the University of Cambridge in Britain analyzed 13,000 samples of H3N2 flu taken since 2002 to demonstrate this source must be in east and southeast Asia, perhaps a different place every year.

"For over 60 years the global migration pattern of influenza viruses has been a mystery," Russell told reporters in a telephone briefing.

Many experts have long believed Asia, and specifically China, to be the source of most influenza viruses.

Others hypothesized that flu viruses migrated back and forth between the northern and southern hemispheres, or that they cooked year-round in the tropics, to pop out every once in a while to the rest of the world, Russell said.

"We find that viruses come out of east and southeast Asia as a region each year and it is not any one particular country that is the continual source of influenza viruses. So it is not as simple as saying out of China, because out of China is not the whole story," Russell said.

RAINY SEASONS

In tropical regions, flu tends to break out in the rainy season. "In east and southeast Asia there is a there a lot of variability in the timing of the rainy season and the timing of the epidemic," Russell said.

"Bangkok and Kuala Lumpur are only 700 miles apart but they have their flu epidemics at completely different times of year." This means flu epidemics can be occurring almost year-round in Asia, he said.

Then the viruses die out every year in the Americas, Europe, Australia and the rest of Oceania, making these areas "evolutionary graveyards," Russell said.

Even if travelers carry the flu viruses back from the Americas to Asia, for example, people living in Asia are already immune to those particular

variants.

The World Health Organization estimates that annual influenza epidemics infect between 5 percent and 15 percent of the world population each year, cause 3 million to 5 million cases of severe illness, and between 250,000 and 500,000 deaths,

About 300 million people get the flu vaccine each year. Without it, said Smith, a person can expect to catch the flu about once every 10 years.

Smith said the findings are important for the experts who formulate the new flu vaccine each year. It typically includes a cocktail of three strains, and the scientists try to predict which strains will cause the most trouble each year.

"If we are trying to predict what will happen a year from now we should be paying attention to what is happening in east and southeast Asia," he said.

The researchers said their study does not have any bearing on what might happen in a pandemic of a new source of flu, such as the H5N1 virus now circulating mostly among birds in Asia, Europe and Africa.

(Editing by Will Dunham and Cynthia Osterman)

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When East Asia sneezes, the rest of the world is infected with a nasty dose of flu

Mark Henderson, Science Editor

The discovery of how strains of the flu virus emerge in Asia, circulate around the continent then migrate to start seasonal epidemics elsewhere may help scientists to improve immunisation programmes.

Research by an international team led by scientists from the University of Cambridge could help experts to select which strains to include in seasonal vaccines each year.

Asian countries such as China, South Korea, the Philippines, Thailand and Malaysia are responsible for "seeding" new outbreaks of influenza that spread around the world, because of the region's unique climatic conditions, which mean that the virus circulates all year around.

Flu normally causes epidemics during the winter in temperate zones, and during the rainy season in the tropics. The reasons for this are poorly understood, though it is thought that it may reflect natural vitamin D levels, which are raised when people are exposed to sunlight, or greater indoor crowding during cold or wet spells.

The timing of the tropical rainy season varies in different parts of East and SouthEast Asia, and these regions also lie in close proximity to temperate parts of the continent where flu thrives during the northern hemisphere winter. This creates an overlap so that the virus is always active in at least part of the continent. This constant circulation means that outbreaks in one country can spread rapidly to its neighbours. New strains of the virus that evolve are likely to be carried around the world by international travellers.

Derek Smith, of the University of Cambridge, who led the study with his colleague Colin Russell, said: "Flu epidemics appear to be driven by seasonal factors such as winter, or rainy seasons. So there can be cities that are only 700 miles from each other, such as Bangkok and Kuala Lumpur, that have epidemics six months apart.

"There is a lot of variability like this in East and SouthEast Asia, so lots of opportunity for an epidemic in one country to seed an epidemic to another nearby country, like a baton passed by runners in a relay race."

In the study, which is published in the journal *Science*, Dr Smith and Dr Russell analysed more than 13,000 samples of the commonest strain of the influenza virus, H3N2, collected worldwide by the World Health Organisation Global Influenza Surveillance Network in 2002-07.

This showed that new strains tend to emerge first in East and SouthEast Asia, before reaching Europe and North America about six to nine months later, and South America several months later still.

The viruses rarely circulate back to Asia: although it is possible for flu strains to return, by the time that they do so there is usually enough immunity among Asian populations to prevent fresh outbreaks.

A second study, by a team at Pennsylvania State University, published in the journal *Nature*, has reached similar conclusions.

The findings are important, as improved surveillance of the spread of flu will assist efforts to select the right strains for seasonal vaccination. Each year scientists must pick three strains for inclusion in the vaccine, about eight months before immunisation programmes are started and almost a year before flu will actually strike.

"The ultimate goal of our collaboration is to increase our ability to predict the evolution of influenza viruses," Dr Smith said.

Annual influenza epidemics are thought to infect between 5 and 15 per cent of the world population each year, according to the WHO. This results in between three million and five million cases of severe illness, and between 250,000 and 500,000 deaths.

Flu strains start in Asia, studies say

By David Kohn

April 17, 2008

New flu strains originate in East and Southeast Asia, then make their way around the world before they go extinct in South America, according to two studies released yesterday.

This conclusion will enable public health agencies to focus their surveillance on Asia and will increase researchers' ability to quickly develop effective influenza vaccines.

"Asia is the place we should be watching. We didn't know that," said Edward Holmes, a biologist at Penn State University and the author of one of the studies. The papers appeared in the latest issues of Nature and Science.

Flu surveillance extends around the world today, but Holmes said the new findings would change that focus to Asia.

Both studies looked at the influenza genome and analyzed mutations from different regions. Scientists then constructed a model that explained how the virus traveled around the world.

"This is very important work," said Steven Salzberg, a computational biologist at the University of Maryland. He has also studied flu mutations and geography.

Until now, the global course of influenza has remained mysterious. The illness strikes year-round in the tropics but only during the winter months in temperate regions. Some scientists thought that in temperate areas, the virus lay dormant, reactivating with cold weather. Others suspected Asia as the starting point but lacked conclusive proof.

"There's never been any concrete evidence to say that the virus came from East and Southeast Asia," said Derek Smith, a professor of infectious disease informatics at Cambridge University in England. Smith was a lead author on the Science study. He and his colleagues analyzed 13,000 flu samples from around the world.

Once a new strain of flu evolves in Asia, it takes six to nine months to reach North America. The earlier researchers can identify a strain, the sooner they can begin working on a vaccine.

No one knows why flu strains die off in temperate regions. Some researchers think the virus may thrive only in climates that are either cold and dry, or hot and wet. Others suspect that increased density in winter months - people stay inside because of the cold - enables the virus to infect more hosts. But no one knows. "If I knew that, I'd be more famous than I am," Holmes said.

Orioles vs. Yankees

Friday	4/18	7:05
Saturday	4/19	7:05
Sunday	4/20	1:35

Flu kills up to half a million people a year worldwide, according to the World Health Organization. Different strains circulate each winter, so scientists must continually develop new vaccines.

The researchers looked at the H3N2 and H1N1 subtypes. These are human strains, different from the H5N1 strain of avian flu, which is deadly to many birds.

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Flu Tracked To Viral Reservoir In Tropics

ScienceDaily (Apr. 16, 2008) — Each winter, strains of influenza A virus infect North Americans, causing an average of 36,000 deaths. Now, researchers say the virus comes from a viral reservoir somewhere in the tropics, settling a key debate on the source of each season's infection.

"We now know where the influenza A virus comes from every year," said Edward Holmes, professor of biology at Penn State. "And because we now know how the virus evolves, we have a much better chance of controlling it."

Currently, there are many strains of the influenza virus that appear only in birds, which are natural viral reservoirs. So far three of these viral strains -- H1N1, H2N2 and H3N2 -- have caused epidemics in humans as influenza A.

Of the three, H3N2 is the dominant strain, responsible for most influenza infections each winter, with lower levels of H1N1. However, little is known about how these two strains spread on a geographical scale, and how whole genome of influenza A virus evolves.

Holmes and his colleagues analyzed complete genomes of 1,032 strains of H1N1 and H3N2 viruses sampled over a 12-year period from New York state in the northern hemisphere and New Zealand in the southern hemisphere.

The researchers noticed that over time, both strains follow a distinctive pattern. In seasons where the H3N2 strain is dominant, H1N1 is not and vice versa.

"We found that the two strains peak at different times, and seem to be directly competing with each other" said Holmes, whose findings appear online in *Nature*. The results also indicate that compared to the H3N2 strain, the H1N1 strain exhibits far less genetic diversity, although it is not clear why.

Holmes says his results also show that the influenza A virus is frequently exchanging genes by reassortment -- when multiple human influenza viruses infect a single person and shuffle their genes -- which sometimes allows the virus to acquire a new haemagglutinin, a protein that facilitates the entry of viral particles into the host cells.

These new haemagglutinins sometimes cause vaccines to fail, explained Holmes, whose work is funded by the National Institutes of Health.

"The critical thing is unless you understand the way the genome evolves, you will not understand why vaccines work during some years and fail during others," he added. "We can now show that vaccines failed in some years because new haemagglutinins appeared."

The Penn State researcher says his analysis not only indicates how the influenza virus is evolving, but also where new strains are being generated.

Each year new strains appear in the northern hemisphere, infect people and then burn out. However, patterns of genetic diversity within the viruses suggest the strains are coming from a global source population. The researchers believe that there must be some reservoir somewhere that every year

generates new strains that are injected each season into the north and the south, and then burn themselves out.

"We know the strains are dying out every year in the northern and southern hemispheres. So they're surviving somewhere else, and we think it is a reservoir in the tropics," Holmes said. "It tells us that to really understand how the influenza virus evolves on a seasonal basis, and to make the best vaccine, we need to focus our surveillance on the source population in the tropics, especially in places such as Southeast Asia."

Other researchers on the paper include Andrew Rambaut, University of Edinburgh; Oliver Pybus, University of Oxford; Martha Nelson, graduate student, Penn State; Jeffery K. Taubenberger, Laboratory of Infectious Diseases, NIH, and Cecile Viboud, Fogarty International Center, NIH.

Adapted from materials provided by [Penn State](#).