Avian Influenza: why do we need to share genetic data?

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Highly Pathogenic Avian Influenza, Italy 1999-2000

Technology, Management & Market

Awaiting the Next Big One

The 20th century's flu pandemics

YEAR	COMMON NAME/SUBTYPE	POSSIBLE SOURCE	DEATHS
1918	Spanish flu/H1N1	Pig or bird host of mutated H1N1 virus	40 million
1957	Asian flu/H2N2	Mixed infection of animal virus, human H1N1 and avian H2N2 strain in Asia	2 million
1968	Hong Kong flu/H3N2	Mixed infection of animal virus, human H2N2 and avian strain	2 million

Soldiers suffering from the 1918 flu in an emergency hospital at Fort Riley in Kansas.

One WHO Expert on SARS Finds Flu More Frightening

Doctor Deems World Unprepared for Long-Awaited Pandemic That Could Cause Trouble

By Gautam Naik

AS AN EXPERT on SARS, Klaus Stohr works 16-hour days, sometimes in virtually the same clothes as the day before, and often juggling three phone calls at once. But his chief worry isn't SARS. It's the flu.

Not any old flu, but a long-awaited influenza pandemic that could spark a massive world-wide crisis in public health. This sort of virus could circle the globe in less than six months, long before a vaccine is ready. Though antiviral drugs exist, not a single country has stockpiled them in anticipation of an outbreak. And there are glaring cracks in the flu pandemic surveillance systems of many countries, especially those in the developing world.

"We're not prepared," says Dr. Stohr, the scientist who heads the World Health Organization's influenza program and is also leading the agency's fight against severe acute respiratory syndrome. Compared with the devastation of a flu pandemic, he adds, "SARS will be something to smile about."

Influenza is one of the oldest and most common diseases known to man. But a flu pandemic would be a lot harsher than the flu bug that sickens millions of people around the world and kills tens of thousands of them each year. Annual flu outbreaks occur when the structure of the virus undergoes small changes, permitting it to evade the immunity that people have acquired from previous infections or from vaccinations. But sometimes the surface proteins of a flu virus change substantially, and nobody has immunity against such a bug. If it also acquires the ability to spread from person to person, the stage is set for a lethal pandemic.

The damage can be catastrophic. The Spanish flu pandemic of 1918 killed more than 40 million people, while those of 1957 and 1968 together felled some four million. By comparison, SARS is a lot less infectious, and it has caused fewer than 750 reported deaths so far.

Global jet travel and urban overcrowding increase the risk. The WHO projects that in developed countries alone the next pandemic could cause as many as 2.3 million hospitalizations and 650,000 deaths in less than two years. The toll in developing countries could be worse. Countries that belong to the WHO have recognized the danger only recently, passing a resolution underscoring the need to improve flu surveillance and response.

Influenza pandemics have occurred historically at 25-year intervals. Since the last one occurred 35 years ago, the conclusion is hard to avoid: We're due. "It's not a matter of if, but when, this will happen," says Albert Osterhaus, a Dutch scientist [illegible] pandemic preparedness. "I'm far more frightened of influenza than I am of SARS."

So is Dr. Stohr, who trained as a veterinarian in the former East Germany and later became an expert in diseases that jump from animals to people. He joined the WHO in 1992, and two years ago, he was named head of the WHO influenza program and was asked to revamp it.

The program then was poorly regarded. Focusing on vaccine development and reacting slowly to global outbreaks, it largely responded to flu as if it were only a problem for developed countries. Dr. Stohr discovered that he faced an uphill task when he tried to get appointments with some scientists, flu-vaccine makers and governments, and was turned down.

But thanks to his strong scientific credentials and unflappable manner, Dr. Stohr was able to persuade potential partners to let the WHO take a bigger role in coordinating the fight against the disease. The WHO's flu-watching network today consists of 112 labs in 83 countries. One of its jobs is to determine the composition of each year's flu vaccine, so work can begin early on vaccines. Another is to look for the Big One, Dr. Stohr's phrase for the expected flu pandemic.

Klaus Stohr

Since 1976, there have been some half-dozen outbreaks of flu deemed to be unusual, and possibly marking the start of a pandemic. Authorities feared the worst in 1997, when an avian-flu virus, known as H5N1, apparently spread from chickens to sicken 18 people in Hong Kong, killing six, and causing a health emergency. That year, when Dr. Stohr went to Hong Kong to advise health authorities, he was forced to stay in an out-of-the-way hostel to avoid dozens of news-hungry journalists.

On the WHO's recommendation, authorities in Hong Kong and southern China destroyed more than a million chickens, preventing the further spread of H5N1 to people.

The string of unusual infections in recent years, including avian flu and SARS, suggests that the Big One may not be far off. Says Dr. Stohr: "These are signals from Mother Nature. If we don't prepare for the pandemic now, complacency will be paid for in human lives."

WSJ.com Journal Link: *WSJ.com subscribers can see an interactive graphic tracing the path of the infected people who fueled the SARS outbreak, in the Online Journal at* WSJ.com/SARS

Le Monde

www.lemonde.fr

MARDI 3 FÉVRIER 2004

Grippe aviaire : l'épidémie devient extrêmement dangereuse

Juppé fait face à so… la droite critique le…

Documento riservato della Casa Bianca pubblicato dal «New York Times»

Virus, rapporto segreto Usa: milioni di morti, ospedali in tilt

L'influenza aviaria in Europa: duemila tacchini colpiti in Turchia

Gli esperti europei di influenza riuniti a Malta. Il nostro Paese deve aumentare le scorte di antivirali, pronto il piano di emergenza

«Il virus dei polli colpirà 16 milioni di italiani»

Crovari: epidemia inevitabile. Le previsioni: 150 mila vittime. Un commissario in ogni Asl

Spanish influenza 1918-1919

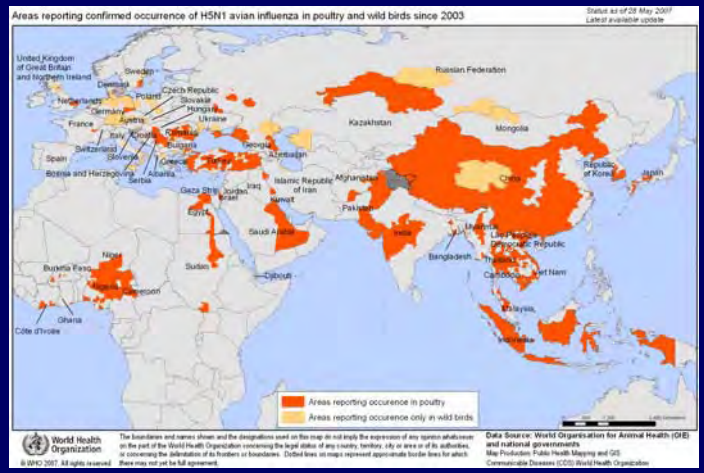
20-40 million dead

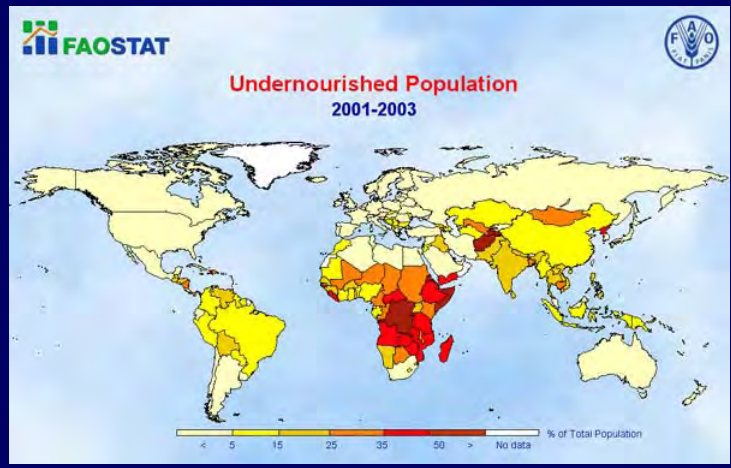
Pandemic potential

- Direct infection of humans with AI
- Generation of a new pandemic virus through genetic reassortment between an avian and mammalian virus

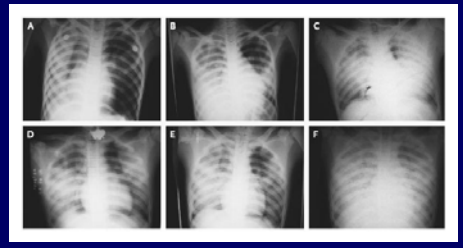
H5N1 epidemic-a disease of global relevance

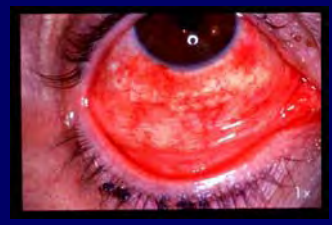
- H5N1 has become endemic in poultry in several parts of the world
- It is capable of infecting a variety of birds (@50 species) and 10 species of mammals
- For every human that is infected, at least 1 million animals are infected
- It represents a threat for food security in developing countries

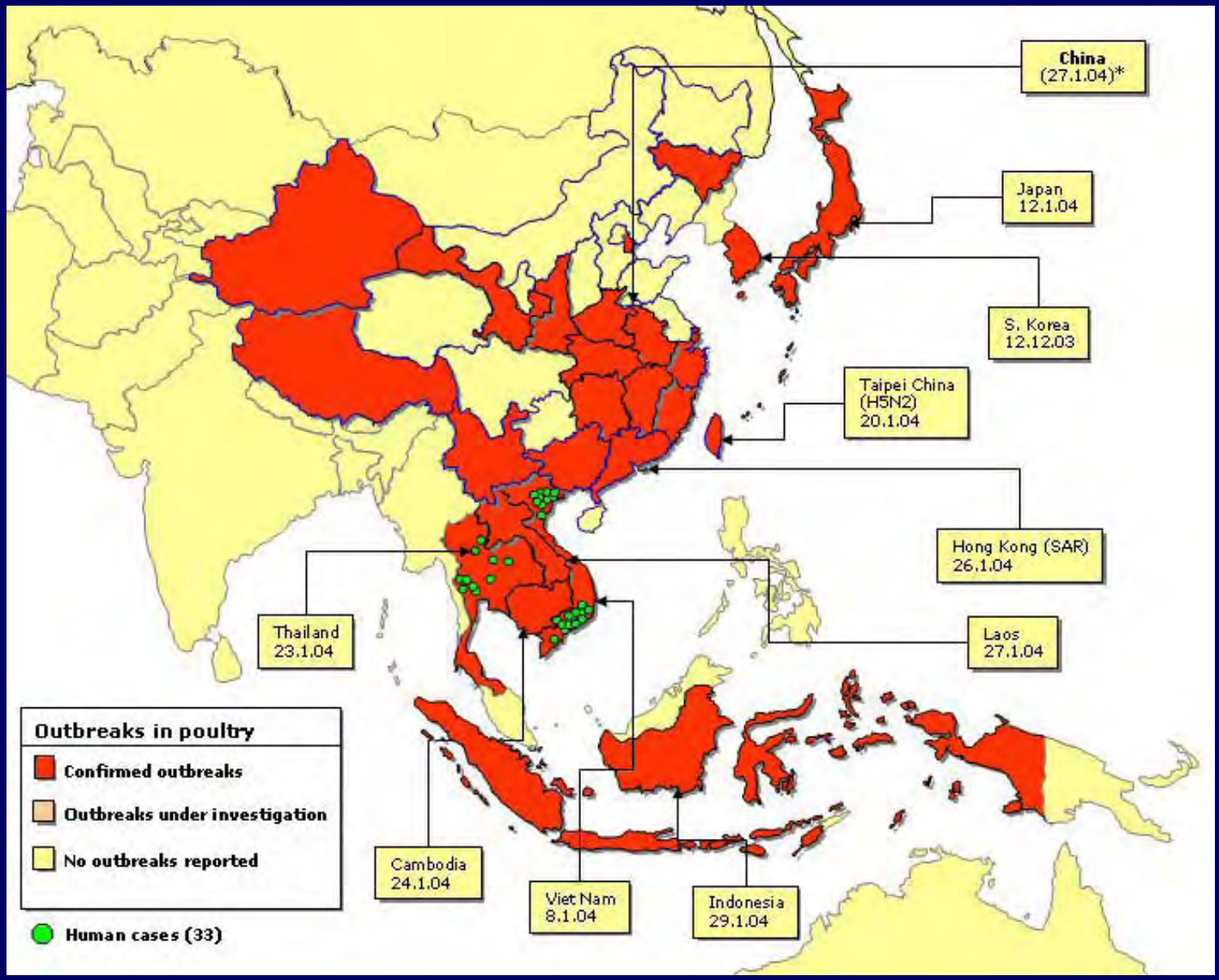




H5N1:evolution of a panzootic






China
(27.1.04)*
Japan
12.1.04
S. Korea
12.12.03
Taipei China
(H5N2)
20.1.04
Hong Kong (SAR)
26.1.04
Laos
27.1.04
Thailand
23.1.04
Cambodia
24.1.04
Viet Nam
8.1.04
Indonesia
29.1.04
Outbreaks in poultry
Confirmed outbreaks
Outbreaks under investigation
No outbreaks reported
Human cases (33)

“Atypical” characteristics of the H5N1 epidemic

- Involvement of waterfowl
- Spill-over to wild birds
- Billions of susceptible birds in certain affected areas
- Peculiarity of husbandry/social practices
- Infection of mammals
- Human health implications

Raw duck blood pudding- Vietnam

Courtesy D.Senne

Live bird market - Vietnam

Chicken carcases placed over pond on catfish farm in Indonesia


Catfish feeding on chicken carcass
©Martin Williams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www.drmartinwilliams.com


Photo credit: Fabio Frisca (FAO Vietnam)

H5N1: unprecedented eco/epidemiological situation

Other species

Wild bird reservoir

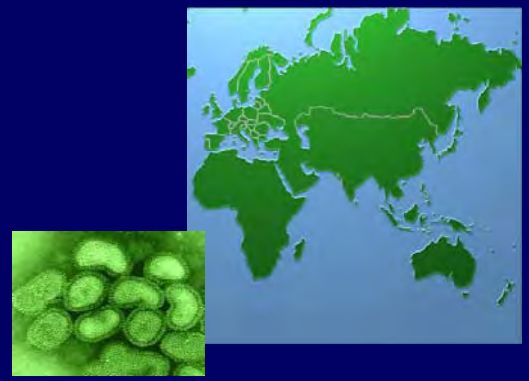
Industrial poultry

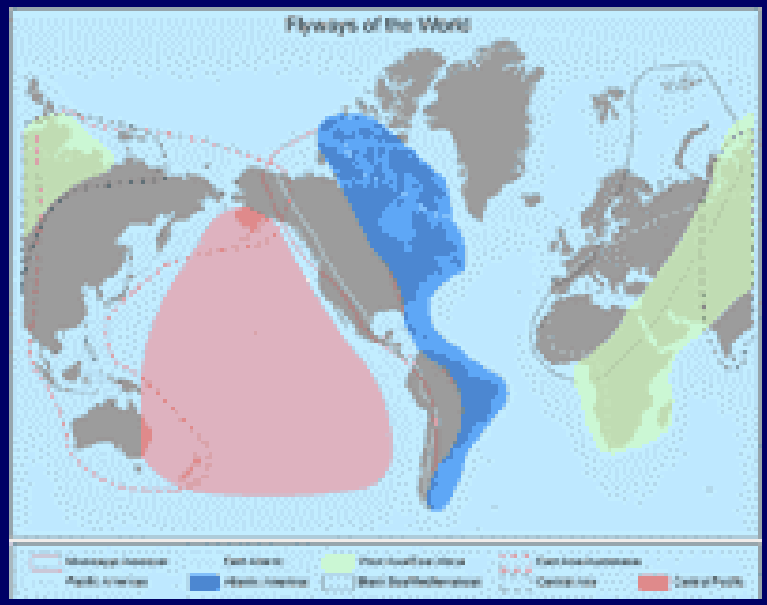
Rural poultry

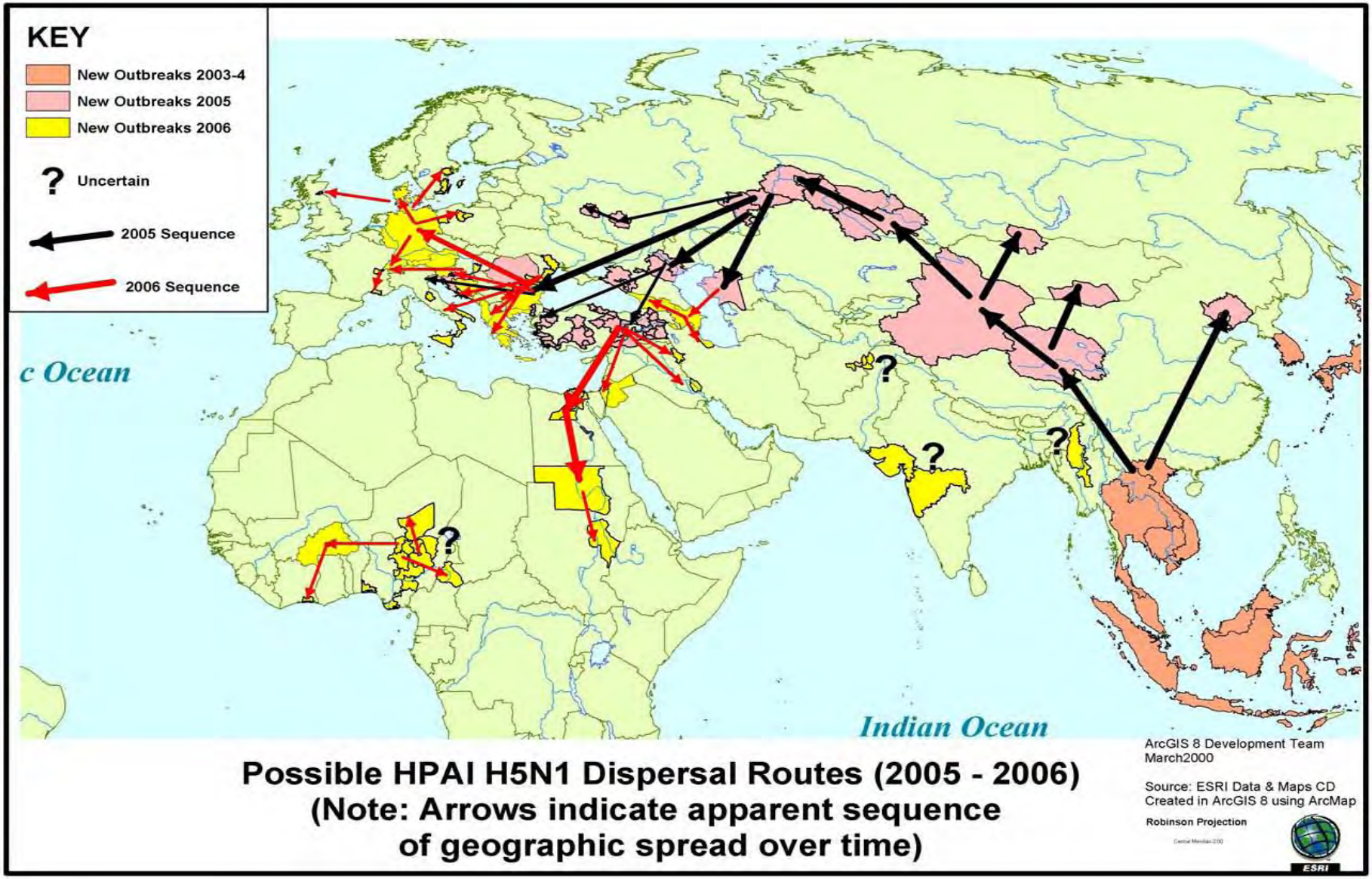
Live bird markets

Poultry reared in the open

Spread from East Asia







Early 2006 – H5N1 reaches Africa

HPAI –in Africa

- Is reducing one of the primary sources of protein to the undernourished population
- Is spreading in an uncontrolled manner (10 countries have notified infection in one year)
- Concern about human health implications in HIV infected, poverty stricken population

First appearance of H5N1 in Africa

- IZSVe was the first laboratory to isolate the H5N1 African strain
- Genetic characteristics of the first African isolates would shed light on H5N1 epidemiology and pathogenicity
- We declined offer to deposit sequence in password protected database (only 15 labs had access) and deposited the full sequence in GenBank


www.sfondi.org

Science
3 March 2006 | $10

Showing her cards. Ilaria Capua says she will submit H5N1 sequences from her lab to public databases immediately.

AVIAN INFLUENZA

As H5N1 Keeps Spreading, A Call to Release More Data

PARIS—An impassioned call by a prominent Italian influenza scientist has renewed the debate about how to balance global health against scientists' needs to publish and countries' demands for secrecy. On 16 February, Ilaria Capua of the Istituto Zooprofilattico

tricky from the start. WHO, FAO, and OIE encourage countries to send virus samples to specialized reference labs that can confirm the outbreak and study the virus further. Some have been reluctant to do so because they worry about intellectual-property rights or pot

dozens of individual governments, Brown says.

Capua counters that just isolating and sequencing a virus that comes in the mail does not give researchers the right to sit on the data—especially not at a government lab. "Most of us are paid to protect human and animal health," she says. "If publishing one more paper becomes more important, we have our priorities messed up." Governments can often be persuaded to release the sequences, adds Capua, who repeated her call at an OIE meeting in Paris on Monday and also plans to submit it to ProMED, an e-mail list about emerging infectious diseases.

WHO agrees that in an ideal world, scientists would share their data widely and voluntarily, says Wenqing Zhang of the agency's Global Influenza Programme. But because that's not happening, the agency created a special secured section at the Influenza Sequence Database at Los Alamos National Laboratory in New Mexico in 2004. Currently, some 15 labs have passwords to access these data, says Zhang, including WHO's eight reference labs. The system is invaluable for WHO, she adds, as it helps the agency track the virus and adjust risk assessments if necessary.

Virologist Yi Guan of the University of

THE WALL STREET JOURNAL

MONDAY, MARCH 13, 2006

Scientist Rebels Against WHO Over Bird Flu

Scientists around the world, racing to discover how avian influenza is spreading and whether it is evolving toward a pandemic strain, face a dilemma: Should they share their interim findings widely, show them only to a select set of peers, or keep them to themselves until they can publish papers, often critical to their careers?

Now, a lone Italian researcher has cast a harsh spotlight on the WHO's system, suggesting that it places academic pride over public health - and snubbing it by posting prized bird-flu data in plain view.

Ilaria Capua

Ilaria Capua, a 39-year-old Italian veterinarian working on avian influenza in a government lab, last month received a sample of the virus in the mail from Nigerian health authorities. The virus had just attacked birds in Nigeria, the first confirmed case of the disease in Africa. The sample was something of a prize, a chance to study a specimen and explore how it spread from its stronghold in Asia.

Within days of isolating the virus, Dr. Capua says, she got an offer from a senior scientist at the WHO in Geneva, whom she declined to name, to enter her finding in the closed system. She could submit the virus's genetic information, or sequence, to the database. In exchange, she would be given the password to the WHO's massive stash of data. A spokesman for the WHO confirmed that the offer was made.

Instead, Dr. Capua posted the gene sequence in a public database accessible on the Internet. She also sent a letter on Feb. 16 to around 50 of her colleagues urging them to do the same with their bird-flu samples.

"If I had agreed" to the WHO's request, she said in an interview, "it would have been another secret sequence."

The New York Times

EDITORIAL

Secret Avian Flu Archive

Published: March 15, 2006

At a time when health authorities are racing to head off a possible avian flu pandemic, it is distressing to learn that the World Health Organization is operating a secret database that holds the virus's genetic information. A lone Italian scientist has challenged the system by refusing to send her own data to the password-protected archive. Instead, she released the information publicly and urged her colleagues to do the same. She is surely right. The limited-access archive should be opened or bypassed immediately to encourage research on this looming health menace.

The campaign by Ilaria Capua, an Italian veterinarian who works on avian influenza, was spotlighted in recent articles in the journal Science and The Wall Street Journal. The hidden data could be of immense value in determining how the virus is evolving and in developing effective vaccines or drugs. The possibility of breakthroughs can increase only if many more scientists can analyze the data.

nature

Vol 440 | Issue no. 7082 | 16 March 2006

Dreams of flu data

The lack of an accessible store of information is undermining the fight against avian flu.

"Confidentiality of sensitive national outbreak surveillance data assured!" This prominent guarantee on the website of the South East Asian Nations Infectious Diseases Outbreak Surveillance Network says it all. Open sharing of data often ends when it could compromise trade or other national interests.

Three cheers, then, to Ilaria Capua of the Tri-Veneto Region Experimental Ani al Health Care Institute in Italy, who last month threw down t let to her colleagues by refusing to put her latest data on N nd Italy in these private networks. Instead she uploaded them Bank and called on her colleagues worldwide to do likewise. this way can researchers establish and track the global patte e evolution of the bird-flu virus.

Imagine scie anywhere being able to log on to a publicly available, sear Internet database, updated in real time, with full clinical and sequence data on each human case, and accurate and complete poultry data. Dream on. The WHO's clunky online *Global Health Atlas*, which gives rough aggregate data for many diseases, doesn't have a

"The world badly needs a database for outbreaks of avian flu."

nature

CORRESPONDENCE

NATURE|Vol 440|30 March 2006

Shared data are key to beating threat from flu

SIR — We fully support Ilaria Capua in her call for avian-influenza researchers to release data to the public, rather than store them in restricted databases, as reported in your Editorial "Dreams of flu data" (*Nature* **440**, 255–256; 2006). Keeping sequences secret, whatever the motivation, slows down scientific progress and hinders efforts to protect public health. The influenza genome sequencing project (www.niaid.nih.gov/dmid/genomes/mscs/influenza.htm) has, in the past year, sequenced more than 1,000 complete genomes of human influenza and

washingtonpost.com

Bird Flu Fears Ignite Debate on Scientists' Sharing of Data

By David Brown
Washington Post Staff Writer
Thursday, May 25, 2006; A20

The issue gained public attention in February when Ilaria Capua, a 40-year-old virologist at the Tri-Veneto Region Experimental Animal Health Care Institute in Italy, sequenced the first H5N1 sample from Africa, isolated from a chicken farm in northern Nigeria. Someone at WHO invited her to contribute it to the Los Alamos data, but she declined and instead filed it in GenBank.

nature

Action stations

The time for sitting on flu data is over.

Concern about the accessibility of data on flu strains remains an acute issue, which research administrators and political leaders should step forward and address.

Indonesia has become the hot spot of avian flu, with the virus spreading quickly in animal populations, and human cases occurring more often there than elsewhere. Yet from 51 reported human cases so far — 39 of them fatal — the genetic sequence of only one flu virus strain has been deposited in GenBank, the publicly accessible database for such information.

And last week in China, researchers belatedly published details of the appearance of human-to-human transmission. In the Sumatra event, the transmission did not spread beyond the family.

Yet scientists outside the WHO networks have no access to these data. The problem last year spurred the US National Institutes of Health (NIH) to create a consortium to sequence and make public thousands of flu strains from humans and birds. Very quickly, this more open approach led to the useful discovery that viruses swap genes with each other more frequently than had been previously thought.

"H5N1 sequences should be promptly deposited in a publicly accessible database."

Some political leaders are drawing the appropriate conclusions. Dennis Kucinich (Democrat, Ohio) and Wayne Gilchrest (Republican, Maryland) are circulating a letter in the House of Representatives

Veterinary virologists lead by example

CORRESPONDENCE

A global initiative on sharing avian flu data

The global spread of the H5N1 avian influenza virus has already extensively damaged economies worldwide and food safety in developing countries. The spread of infection to new ecosystems results in adaptation of the virus to new hosts, including humans, which amplifies the potential for a flu pandemic. Because it is recognized that avian influenza viruses may be the precursors of the next human pandemic virus, their genetic evolution should be tracked in detail and promptly investigated.

The full support of the international scientific community is therefore urgently needed to understand better the spread and evolution of the virus, and the determinants of its transmissibility and pathogenicity in humans. This in turn demands that scientists with different fields of expertise have full access to comprehensive genetic sequence, clinical and epidemiological data from both animal and human virus isolates.

Several countries and international agencies have recently taken steps to improve sharing of 'influenza data' [1], following the initiative of leading veterinary virologists in the field of avian influenza. The current level of collection and sharing of data is inadequate, however, given the magnitude of the threat. We propose to expand and complement existing efforts with the creation of a global consortium — the Global Initiative on Sharing Avian Influenza Data (GISAID; http://gisaid.org) — that would foster international sharing of avian influenza isolates and data.

Scientists participating in the GISAID consortium would agree to share their sequence data, to analyse the findings jointly and to publish the results collaboratively. Data would be deposited in the three publicly available databases participating in the International Sequence Database Collaboration (EMBL, DDBJ and GenBank) as soon as possible after analysis and validation, with a maximum delay of six months. The six-month deadline for data release is expected to become shorter as the consortium gains experience and works out its operating procedures.

GISAID's policies for rapid and complete data release are modelled on those established for community resource projects. These policies have successfully been employed previously, for example by the International HapMap Project (www.hapmap.org) — a project to map, and make freely available, data on DNA sequence variations in the human genome.

The GISAID consortium will be comprised of scientists from around the world working in the fields of animal and human virology, epidemiology and bioinformatics, as well as experts in intellectual property issues. An international panel of distinguished scientists will be formed to govern the charter and to advise the consortium.

As an international collaborative effort, GISAID offers many benefits to the world as a whole, as well as to individual scientists and to groups participating in the consortium. It would encourage valuable collaboration among researchers in industrialized countries and in the developing countries that are hit hardest by avian influenza. It would also attract international attention to the need for increased funding and technical assistance to help affected countries build comprehensive and sustained disease-surveillance programmes.

Peter Bogner*, Boris Caya[illegible], Alexey J. Cox, David J. Lipman§ and others

*Chief executive, the Bogner Organization, 877 Fifteenth Street, Santa Monica, California 90403, USA

†Chair, Scientific Committee of the OFFLU (OIE/FAO Network...

‡Director, Influenza Division, Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, Georgia 30333, USA

§Director, National Center for Biotechnology Information, National Institutes of Health, 8600 Rockville Pike, Bethesda, Maryland 20894, USA

[A full list of signatories to this letter as of 23 August 2006 is available as supplementary information at [url to come]]

1. [illegible]
2. [illegible]
3. [illegible]
4. [illegible]

GISAID- Global Initiative on Sharing Avian Influenza Data

www.gisaid.org

Nature Correspondence 24 Aug, 2006

Signatories:

70 leading scientists,6 Nobel Laureates

Open access, free database which will contain human and animal influenza virus sequences and protects intellectual property

Veterinary initiatives promoting genetic data sharing to support the global H5N1 crisis

- OIE/FAO: support and promote data sharing
- OFFLU network – collects strains and sequences and promotes deposit in open access databases
- EPIZONE: EU Network of Excellence, WP 6.2 aims at understanding AI epidemiology through the generation and analysis of sequence data

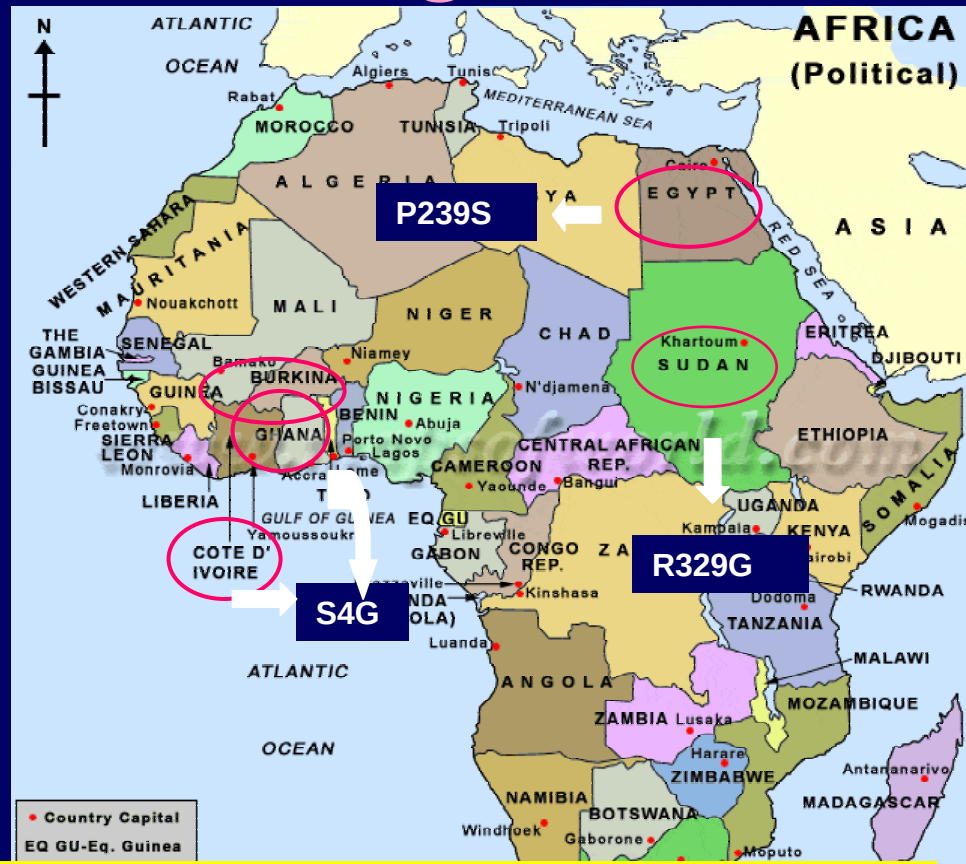
•WHO is now supporting sequence data sharing

H5N1 improving our understanding

- Control in the animal reservoir is a prerequisite to the management of the pandemic potential
- The comparison between strains is essential to increase knowledge on AI epidemiology and human health implications
- Consensus from health officials to release sequences must be sought

Phylogenetic analysis and molecular changes: results for HA gene

- All the sequences of the Egyptian strains cluster together.
- The first isolate from Ghana clusters with recent Ivory Coast strains.
- Unique amino acid changes in the HA molecule were identified in viruses circulating in a given country or geographical area



COUNTRY	AA SUBSTITUTION	HA sequences available in GenBank (No.)	HA sequences with characteristic substitution (No.)
Sudan	**R329G**	**10**	**10**
Egypt	**P239S**	**39**	**39**
Ghana, Ivory Coast, Burkina Faso	**S4G**	**1** Ghana **6** Ivory Coast **8** Burkina Faso	**1** Ghana **6** Ivory Coast **8** Burkina Faso

Global Initiative on Sharing Avian Influenza Data

- all users agree to share their own data, as well as clinical, epidemiological, biosafety and regulatory information
- all users agree to credit the use of others' data and acknowledge the source of genetic resources
- all users agree to analyze findings jointly and publish results collaboratively
- all users agree to maintain common access to technology derived from the data so that it can be used not only for research but for development of products such as diagnostics and vaccines.

This is different from many publicly funded databases, where there is no agreement to share the capability to use the data and to collaborate on it.

However, under the agreement all the sequence data are also made available to a variety of publicly funded databases with a maximum delay of six months

WHY is this so important?

Because it can serve as a model for future epidemics threatening mankind – we would have a system in place to react promptly and maximise the outcome of research efforts

GISAID- where are we?

- Created a foundation (www.gisaid.org)
- Sourced software, currently upscaling to satisfy number of users
- Drafted user access agreement
- Obtained worldwide consensus
- WE NEED FUNDS!!!

“One Health”

Birds of a feather should flock together… a little more

Istituto Zooprofilattico Sperimentale delle Venezie