VIROLOGY

# Flu surveillance lacking

*Nature analysis highlights need for international strategy to watch for pandemic threats.*

BY DECLAN BUTLER

When researchers created strains of the H5N1 avian influenza virus that could spread easily between mammals, they argued that their work would aid in surveillance, by identifying mutations to watch for in the wild.

But an analysis by *Nature* paints a dire picture of how animal flu viruses are being monitored. In 2010, the world's poultry population was estimated at 21 billion, yet only around 1,000 flu sequences from 400 avian virus isolates were collected — and many countries that are home to billions of farmed chickens, ducks and pigs contributed few or none.

In addition, the surveillance is typically not sustained, but instead is ad hoc and reactive, and is largely in response to disease outbreaks or temporary research projects. But a flu virus that emerges anywhere, at any time, can threaten the entire planet. The *Nature* analysis "highlights a global problem: lack of data", says Ian Brown, head of avian virology and mammalian influenza at the Animal Health and Veterinary Laboratories Agency lab in Weybridge, UK.

Timely global surveillance of animal flu viruses is crucial not just for identifying pandemic threats, but also for detecting outbreaks, monitoring how viruses are evolving, understanding risk factors that enable them to spread and keeping animal vaccines and diagnostics up to date.

To assess trends in global genetic surveillance, *Nature* analysed the records of non-identical sequences from all subtypes of avian and pig flu deposited in the US National Center for Biotechnology Information's Influenza Virus Sequence Database between 2003 and 2011. The database contains sequences from GenBank and several large flu sequencing projects, including the Influenza Genome Sequencing Project — a major initiative run by the National Institute of Allergy and Infectious Diseases (NIAID) to boost the sequencing of existing isolates. The analysis covered all subtypes of flu virus, not just H5N1. That's important, says Malik Peiris, a flu virologist and surveillance expert at the University of Hong Kong, because "H5N1 is not the sole pandemic candidate, and low pathogenic viruses are just as likely, if not more likely, to become pandemic".

The number of avian flu sequences deposited in the database skyrocketed between 2003 and 2010, before dropping off in 2011. The number of pig sequences deposited remained relatively flat from 2003 to 2010, before jumping dramatically in 2011.

However, few contemporary data are available. The number of avian flu sequences from isolates collected in each year peaks in 2007 and plummets thereafter. The jump in the number of pig sequences also disappears (see 'Delayed sequencing').

Roughly 30% of the sequences are from isolates collected before 2003. The 2007 peak in avian viral sampling was largely the result of surveys of more than 100,000 wild birds to monitor for the arrival of H5N1 in the Americas[1,2]. Also contributing was the sequencing of the H5N1 viral flare that moved from Asia into Europe and Africa in 2005 and 2006 (refs 3, 4). The older sequences can inform surveillance by showing how the viruses have evolved, says Peiris, but contemporary data are important "for real-time surveillance", such as spotting changes that might herald dangerous strains.

Many years can pass between the collection and sequencing of isolates, says Sylvie van der Werf, head of the Molecular Genetics of RNA Viruses lab at the Pasteur Institute in Paris. One reason is that many of the virus samples

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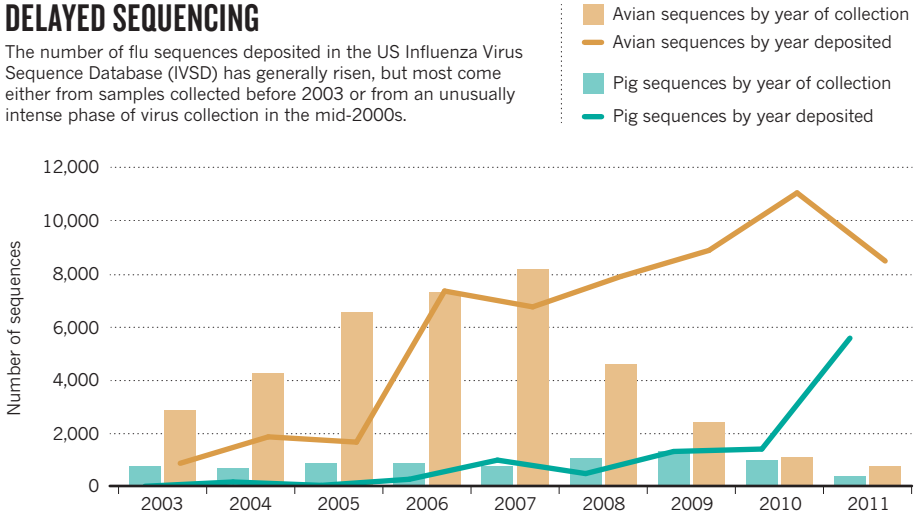
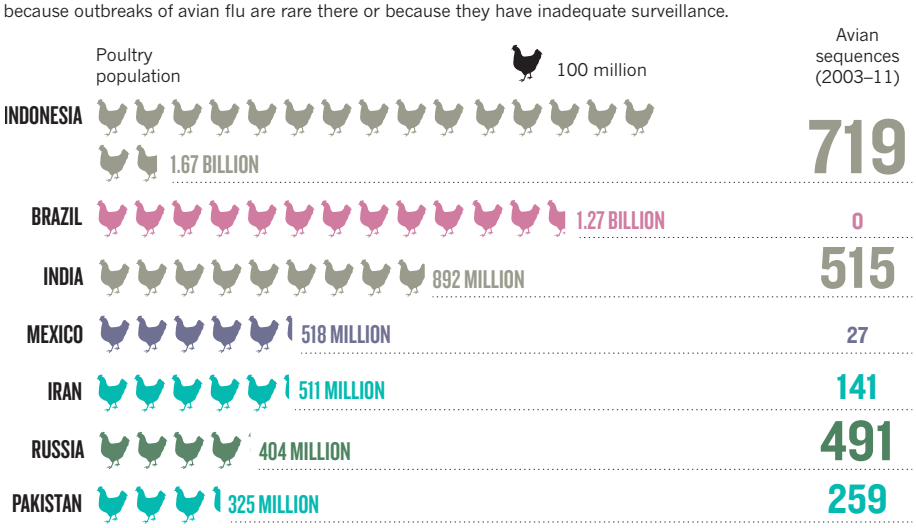
## DELAYED SEQUENCING

The number of flu sequences deposited in the US Influenza Virus Sequence Database (IVSD) has generally risen, but most come either from samples collected before 2003 or from an unusually intense phase of virus collection in the mid-2000s.



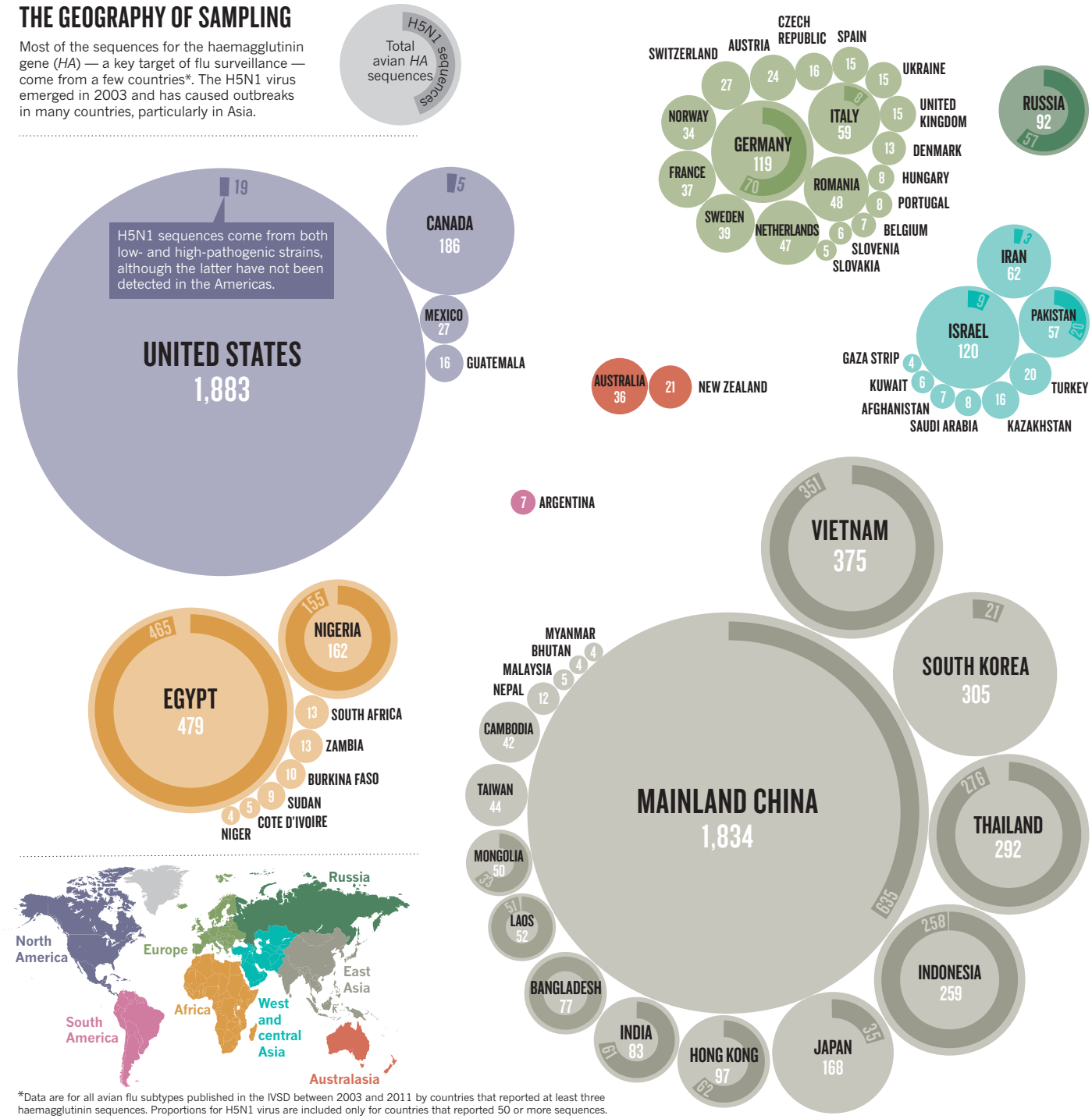

## MANY BIRDS, FEW SAMPLES

Some countries with large poultry populations have generated only a small number of sequences, either because outbreaks of avian flu are rare there or because they have inadequate surveillance.



## THE GEOGRAPHY OF SAMPLING

Most of the sequences for the haemagglutinin gene (*HA*) — a key target of flu surveillance — come from a few countries*. The H5N1 virus emerged in 2003 and has caused outbreaks in many countries, particularly in Asia.




*Data are for all avian flu subtypes published in the IVSD between 2003 and 2011 by countries that reported at least three haemagglutinin sequences. Proportions for H5N1 virus are included only for countries that reported 50 or more sequences.

are sequenced in retrospective research studies. Another is a lack of funding for sequencing, although falling sequencing costs are easing this bottleneck. The Influenza Genome Sequencing Project is also helping by generating vast quantities of sequences — it now accounts for half of all avian and pig sequences — but it is aimed at increasing the genomic knowledge base, rather than real-time surveillance.

Researchers, too, are contributing to the lag, because many do not share their sequences until after the data have been published. An exception is the Centers of Excellence for Influenza Research and Surveillance — a network created by the NIAID in 2007 to boost flu surveillance — which has a policy of releasing all sequence data within 45 days of its collection.

The two agencies responsible for monitoring disease outbreaks in animals — the Food and Agriculture Organization (FAO) of the United Nations and the World Organisation for Animal Health (OIE) — stipulate that sequences of potentially zoonotic viruses should be deposited in public databases within 3 months, but few researchers do so, says Ilaria Capua an avian-flu researcher at the Veterinary Public Health Institute in Legnaro, Italy, who champions greater availability of sequences[5].

*Nature* also looked at where the sequences come from (see 'The geography of sampling'). The picture that emerges is worse than some experts had thought. Almost all come from just a handful of countries — most countries have little or no genetic surveillance in place.

Just 7 of the 39 countries with more than 100 million poultry in 2010 collected more than 1,000 avian flu samples between 2003 and 2011. Eight countries — Brazil, Morocco, the Philippines, Colombia, Ecuador, Algeria, Venezuela and the Dominican Republic — collected none at all; 13 collected between 1 and 100; and 11 collected between 100 and ▶

1,000. Even fewer pig sequences were collected, with one-third of the countries that are home to more than 4 million pigs depositing none at all.

The size of a country's poultry population is no predictor of how many samples that country will generate (see 'Many birds, few samples'). Countries that have well-developed veterinary services and a well-structured and hygienic farming industry inevitably have fewer flu sequences to report, as disease levels tend to be low, says Brown. However, many of the countries that have contributed few or no sequences have poor veterinary systems and flu-prone farming systems, such as backyard farms and mixed poultry and pig farms, which are often close to wild ducks and other flu reservoirs.

"Proper geographic representation is lacking," says van der Werf, as is sustained surveillance. This results in large gaps in data, she says, because "many consecutive years of surveillance are needed to see trends" (see page 535). Poorer countries tend to have inadequate surveillance resources, and farmers often have little incentive to report outbreaks because they will not receive any compensation for culled livestock. Countries sometimes also fail to look for, or report, outbreaks so that they can claim they are free of infection and so avoid trade problems.

Flu experts say that the dire state of surveillance could be rapidly turned around by, for example, creating a network of sentinel sites, focusing on the countries and regions most at risk, that would collect isolates and sequence them in real time. Such a network would probably even cost less than the fragmented and uncoordinated surveillance efforts in place today, says Jeremy Farrar, director of the Oxford University Clinical Research Unit in Ho Chi Minh City, Vietnam (see page 534).

The problem is that no global body has overall responsibility for flu surveillance. The World Health Organization (WHO) runs a global network of labs for human flu surveillance and selects human strains to be included in vaccines for seasonal flu. Monitoring animals falls to the FAO, which tends to focus on food security, and the OIE, which looks mostly at animal health and trade.

What is needed is international leadership, says Farrar. "If, say, the WHO and the FAO were to construct an advisory framework, surveillance could probably be done much more systematically and efficiently."

■ SEE EDITORIAL P. 509

1. Butler, D. & Ruttimann, J. *Nature* **441,** 137–139 (2006).
2. Check, E. *Nature* **442,** 348–350 (2006).
3. Butler, D. *Nature* http://dx.doi.org/10.1038/news050801-1 (2005).
4. Butler. D. *Nature* http://dx.doi.org/10.1038/news060206-7 (2006).
5. *Nature* **440,** 255–256 (2006).

Italy's National Galileo Telescope in the Canary Islands will host the HARPS-North planet finder.

INAF

SPACE

# North set for mass analysis of planets

*Spectrograph will review results from Kepler telescope.*

BY ERIC HAND

How many extrasolar planets has NASA's Kepler mission discovered? That depends on how you count. Last month, the mission team published a catalogue that lists a staggering 2,321 candidate planets, amassed since May 2009 as the space-based telescope watches stars for the shadow of planets passing over their faces. Yet only 69 of them are considered confirmed planets. Astronomers have fretted over the growing backlog, but help is on its way.

For a Kepler planet to ascend from candidate to confirmed, a second method has to vouch for it: for example, a ground-based spectrograph must report signs that the planet's gravity is tugging its star back and forth. Yet Kepler looks north, whereas the instrument most sensitive to stellar wobbles, the European Southern Observatory's High Accuracy Radial Velocity Planet Searcher (HARPS), is located at the La Silla Observatory in Chile and can only observe the southern sky. On 1 April, however, the Northern Hemisphere will get a near-clone of HARPS when HARPS-North achieves first light at the Italian 3.6-metre National Galileo Telescope (TNG) on La Palma in the Canary Islands.

The instrument has been a long time coming. Conceived in 2005, the project was originally led by Harvard University in Cambridge, Massachusetts. But in 2010, after Harvard's endowment fell during the financial crisis, the University of Geneva in Switzerland took charge. Financial problems forced the group to switch from the 4.2-metre William Herschel Telescope, also on La Palma, to the TNG, which will give the HARPS-North team 80 nights of dedicated time per year for five years.

That should help to alleviate the bottleneck for Kepler candidates. Many astronomers, however, are looking to HARPS-North less for confirmation of the candidate planets than for insight into their properties. The false-positive rate for Kepler, after all, has already been shown to be less than 10% (T. D. Morton and J. A. Johnson *Astrophys. J.* (in the press) Preprint at http://arxiv.org/abs/1101.5630; 2011). "It has become acceptable to do a statistical analysis and say, 'They are planets'," says Joshua Winn, an astronomer at the Massachusetts Institute of Technology in Cambridge.

What Winn and

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