



The drug Tamiflu is prescribed as the front-line treatment for serious cases of influenza.

## Tamiflu report comes under fire

Conclusions on stockpiling of antiviral drugs challenged.

## **BY DECLAN BUTLER**

A study that calls into question the stockpiling of billions of dollars' worth of antiviral drugs to mitigate the threat of influenza pandemics has been criticized by flu researchers.

The analysis of Tamiflu and Relenza, drugs known as neuraminidase inhibitors, was published on 10 April by the Cochrane Collaboration<sup>1</sup>, a group that reviews the effectiveness of health-care measures. It concluded that the medicines were of little use. At the same time, the journal *BMJ* published a series of articles, including two that summarize the Cochrane findings<sup>2,3</sup>, and several editorials that focus on the five-year campaign by Cochrane and the *BMJ* to obtain the unpublished drug-company clinical-trial data later used in the review.

The results "challenge the historical assumption that neuraminidase inhibitors are effective

in combating influenza", declared a joint *BMJ*– Cochrane news release on the findings. The drugs have had their "effectiveness overplayed, and harms underplayed", said Fiona Godlee, the *BMJ*'s editor-in-chief, at a press conference. The study generated worldwide media coverage, including headlines labelling Tamiflu as "useless" and "ineffective".

But the review and its bottom line are vigorously contested by many flu researchers. They argue that the analysis — an update by Cochrane — is based on randomized clinical trials (RCTs) of the drugs that lack sufficient statistical power to allow reliable conclusions to be drawn about the effects on flu complications and hospitalizations. These are the key outcomes of interest during a flu pandemic.

The critics say that the review also excluded many observational studies that have found the drugs to be helpful in normal clinical settings.

Tamiflu is prescribed as the main treatment

for serious cases of flu, and researchers worry that the media storm risks undermining public confidence in this class of drug. "We risk losing one of the few weapons we have, because of overly negative publicity," says Peter Openshaw, director of the Centre for Respiratory Infection at Imperial College London.

The review by Cochrane, a non-profit organization in London, considered both Tamiflu (oseltamivir), produced by the drug company Roche in Basel, Switzerland, and Relenza (zanamivir), marketed by GlaxoSmithKline in Brentford, UK. It is one of the first analyses to review clinical-study reports — documents that companies submit to regulators and that contain fuller trial data than published RCTs.

Both drugs have been found to shorten the duration of flu-like symptoms, and to be effective in treating severe disease; what is in dispute is whether they reduce hospitalizations and severe complications. The Cochrane authors and the BMJ claim that there was no evidence for such gains. They also say that the findings bring into question the decision by governments in the mid-2000s to stockpile the drugs against the threat of a pandemic of the H5N1 avian-flu virus, which has a mortality rate of around 60%. Carl Heneghan of the University of Oxford, UK, a co-author of the review, said that there was "no credible way these drugs could prevent a pandemic" and that stockpiles were "money thrown down the drain".

But a dozen experts contacted by *Nature*'s News team said that the clinical-study reports, although they allow more detailed analyses, offer no substantial fresh findings.

"The Cochrane authors have done a thorough review, and deserve credit for their efforts to obtain raw clinical data from Roche and regulatory authorities, but ultimately its findings are not surprising," says Peter Horby, a flu researcher at the University of Oxford Clinical Research Unit in Hanoi, Vietnam.

Jody Lanard and Peter Sandman, independent risk-communication experts in New York, say that the press release on the review omits findings that in their opinion are key. For example, it rounds down Tamiflu's reported 17-hour reduction in symptom duration in adults to "just half a day", and describes the reduction as "small". It also does not report the 29-hour reduction in children. Lanard and Sandman claim that there has been "cherry-picking of the results to make them look worse for antivirals".

Horby's view is that the *BMJ*–Cochrane



press release and public statements have contributed to media misinterpretation of what the study does and does not say. "The review does not state the drugs are 'ineffective' or 'useless," as was reported in some media stories, he says.

In a joint response to *Nature*, *BMJ*– Cochrane said that they felt the press release did "a good job of presenting the main findings". They defend its presentation of the reduction in duration of symptoms as justified, and note that the fuller outcomes were included in the review's summary of its findings. The press coverage, they say, was "not bad in terms of balance and accuracy".

The two organizations agree that the limited statistical power of the trial data on the numbers of hospitalizations and complications makes it difficult to draw reliable conclusions on these. But they argue that their findings of no evidence for any effects challenge past analyses of trials that found that the drugs reduced complications and hospitalizations. They claim that the review did show new findings, for example data on side effects.

RCTs are considered the gold standard for establishing the effectiveness of drugs, and Cochrane restricts itself to meta-analyses of these in its review. But critics note that these small clinical trials were carried out to gain regulatory approval for Tamiflu as treatment and prophylaxis for seasonal flu, which in most cases is mild. This meant that the healthy trial subjects rarely developed complications. In other words, the trials were not designed to test for the severe outcomes that are most relevant to pandemics.

The critics add that observational studies of how large numbers of people respond to treatments under normal medical care can also provide important information on the effectiveness of drugs. In March, for example, an observational study<sup>4</sup> of 30,000 people hospitalized during the 2009–10 swine-flu pandemic reported that neuraminidase inhibitors reduced mortality by 25%.

But because of its policy of reviewing only RCTs, Cochrane did not include observational data. "Given the limited number of RCTs, and the considerable evidence base on the effectiveness of neuraminidase inhibitors over the past ten years or more, it is difficult to justify exclusion of the observational evidence," says Ben Cowling, a flu epidemiologist at the University of Hong Kong.

*BMJ*–Cochrane said they exclude all observational studies because they are "unreliable for establishing treatment effects". ■

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People walk along a road damaged in the 1 April Chilean earthquake.

# Chile quake defies expectations

Smaller - than - expected tremor has scientists scrambling to redefine rules for areas of extreme seismic stress.

### **BY ALEXANDRA WITZE**

Monika Sobiesiak wasn't expecting the morning of 2 April to start with such an adrenaline jolt. But as she scrolled through a list of earthquakes on her mobile phone, she saw that overnight a series of quakes had rocked the coast of northern Chile — almost exactly where she had installed a seismometer network a few years earlier. "I saw the 8.2," says the geophysicist, who works at the University of Kiel in Germany, "and I rushed to get to my desk."

That 1 April quake, which struck offshore near the village of Pisagua, was the largest in Chile since a magnitude-8.8 quake hit farther south in 2010. Although the Pisagua quake was not as big and not particularly damaging, it will still go down in the annals of seismology — as an intensively studied earthquake that upends some assumptions about how and when big quakes happen.

In one sense, seismologists knew it was coming. Northern Chile, near the border with Peru, was the only stretch of the country's coastline that had not broken in a large earthquake in the past century (see 'Under pressure'). In 2006, expecting it to go, a German– French–Chilean collaboration blanketed the region with seismometers, tiltmeters and other ground-measuring instruments, creating the Integrated Plate boundary Observatory Chile (IPOC). It captured the Pisagua quake in action, as did Sobiesiak's network.

But the earthquake was not the 'Big One' that seismologists had expected. Only a monstrous earthquake, of around magnitude 9, would have relieved all the geological stress built up in the region. More quakes, on the order of

## "A lot of energy remains to be released in north Chile."

magnitude 8, are still possible, but when they might strike is a mystery. More broadly, the Pisagua event has seismolo-

gists rethinking some basic ideas about the risk of earthquakes in similar geological settings elsewhere — places with deep-diving crustal plates, such as Japan and Indonesia.

Over time, earthquakes rupture particular portions of a long fault zone; the unbroken portions are 'seismic gaps' considered ripe for future quakes. Officials in these areas are often told to prepare for the worst-case scenario the biggest possible earthquake in a given seismic gap. But the Pisagua quake shows that this does not always happen, says Susan Beck, a seismologist at the University of Arizona in