# What's in the medicine cabinet?

**Drugs that could lessen the death toll in a flu pandemic do exist. But global stockpiles are too small, and the countries at most immediate risk are among the worst prepared. Alison Abbott reports.**

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Rows of antiviral flu drugs fill Roche's warehouse — but stocks would not meet demand in a pandemic.

The pharmaceutical company Roche didn't have huge commercial expectations for its influenza drug oseltamivir when it was licensed under the brand name Tamiflu in 1999. Flu is a fact of life, and doctors have been advising aspirin, hot lemon and bed-rest for generations. In most countries they continue to do so, reserving the drug for vulnerable groups such as the elderly.

But in the past year or so, Roche has quadrupled its Tamiflu production capacity. The reason: developed countries are now stockpiling the drug against the threat of a pandemic flu virus that could arise at any time. Given the difficulty of rapidly producing an effective vaccine (see page 404), drugs will be the first line of defence. But even after Roche's moves to boost Tamiflu production, experts say that global stockpiles are woefully inadequate.

What's more, no one knows for sure the answers to several key questions. How many deaths could antiviral drugs prevent? To what extent would they slow the spread of a pandemic? Could they, as some mathematical modellers claim, even stamp out the disease as it emerges? "There is a lot of uncertainty, but that is no reason not to plan their use," says Marc Lipsitch, an infectious-disease epidemiologist at the Harvard School of Public Health in Boston.

## Home guard

Although the pandemic will be global, defence plans are so far strictly national. Thanks mostly to prodding by the World Health Organization (WHO), about 50 countries have drawn up pandemic-preparedness plans. Most are still very sketchy, but include strategies for stockpiling antiviral drugs. Only a handful of nations, including Britain and Canada — but notably not the United States — have given their plans legal status.

Worryingly, the list of relatively well-prepared nations includes few of those countries in Asia where a pandemic strain is most likely to emerge. Historically, the WHO has found it hard to persuade even rich countries to produce a pandemic plan: many governments

have proved reluctant to pay for a stock of drugs that may not be used during their terms of office. Only now that the alarm bells are ringing about the H5N1 avian flu virus have official minds been focused.

Experts agree that Tamiflu is the best of the four currently available anti-influenza drugs. A course costs between US$10 and $30, but national stockpilers have negotiated prices in the lower range. Roche is also making the powdered active ingredient available at a cheaper price than tablets. The powder would be dissolved in water and drunk when needed — nasty-tasting but still effective, and stable in solution for several days.

Tamiflu, and the chemically related zanamivir, marketed by GlaxoSmithKline as Relenza, belong to a class of drugs called neuraminidase inhibitors. They do not eliminate the virus, but they reduce its release from infected cells by blocking a key viral enzyme. If taken within 48 hours of the onset of symptoms — the earlier, the better — they reduce the duration of symptoms by at least a day[1,2]. They also limit the severity of symptoms in non-pandemic flu: patients succumb less frequently to acute bronchitis or pneumonia[1]. That should be good news if the same applies to a pandemic strain, as patients who cough less will spread the virus less effectively.

Relenza is less helpful because it has to be taken by inhaler, which is not very practical if a patient's breathing is impaired. But both neuraminidase inhibitors have so far generated few problems with drug resistance: mutations in the flu virus that confer resistance seem rare, and generally seem to weaken it[3]. (But an H5N1 virus sample from one Vietnamese patient has recently been shown to be less susceptible to Tamiflu, so experts are not complacent.) Side effects are also mild, and the drugs can be kept on the shelf for at least ten years without losing their activity.

The older, off-patent drugs amantadine and rimantadine belong to a different class and interfere with a viral protein called M2, which stops the virus from entering its target cells. They seem to be as clinically effective as the neuraminidase inhibitors, but resistance arises very rapidly and the drugs can have disturbing side effects, including psychotic episodes. Although such reactions are rare, they would be highly unwelcome in the already panicky atmosphere of a flu pandemic.


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## Fair treatment?

Indeed, the potential for social unrest is a major concern for those laying pandemic plans. And demand for Tamiflu could exacerbate the problem. Who will, and who will not, be treated with this scarce but valuable resource? "It's not easy — we know there won't be enough for everyone," says Theresa Tam of the Public Health Agency of Canada. Britain, which is among the best-prepared countries, has ordered enough for about 25% of its population; Canada has stocks for just over 5% of its people; the United States currently cannot even cover 1%.

In practice, a significant proportion of supplies might be used for prophylaxis of health-care workers — for up to two months as the influenza wave passes through — leaving less for treating the sick. "It is not a happy situation," says Klaus Stöhr, the WHO's chief influenza expert. Canada, wary of the potential for a public backlash if health workers were perceived to be saving their own skins, included an ethicist on its Pandemic Influenza Committee.

The WHO recommends that antiviral drugs should be available for the early treatment and prophylaxis of "those groups at highest risk of infection" and "essential workers". But defining these people, and matching their number to the doses available, is difficult.

Ultimately, how you define your strategy depends on what you want to achieve, says clinical virologist Fred Hayden of the University of Virginia in Charlottesville. Most countries are aiming to keep the death toll as low as possible, but for others, maintaining the economy may be at least as high a priority. So the definition of essential workers will vary. Those deemed non-essential will be able to do little

## Masking our ignorance

When SARS, or severe acute respiratory syndrome, hit the cities of Asia in 2003, one product was in hot demand: the N95 face mask.

These cup-shaped masks fit snugly on the face and filter out particles smaller than a few hundred nanometres across. Flu viruses are smaller than this, but are often coughed or sneezed out in larger droplets. Official advice on whether N95 masks offer protection against flu is confusing, to say the least.

The World Health Organization (WHO) recommends that people at the highest risk — health-care workers and the families of those infected with the disease — wear N95 masks, which retail for about US$1 each. Many national health agencies are following this advice. Given that flu is largely transmitted in droplets, N95 masks should be of some value, suggests Klaus Stöhr, the WHO's chief flu expert. But the US Department of Health and Human Services takes the opposite view. Its pandemic plan, released in August 2004, states: "N95 respirators, which would be recommended for infections with airborne spread such as tuberculosis, are not required for influenza."

Experience with the SARS virus, which is roughly the same size as flu viruses, and seems to be spread in a similar manner, shows that N95 masks aren't completely reliable. Researchers in Canada reported that nine health-care workers developed SARS from a single patient despite using the masks and other recommended infection-control procedures[5].

And some experts worry that the emphasis on N95 masks, rather than simple polypropylene surgical masks that cost a few cents each, is misguided. Wing Hong Seto of the Queen Mary Hospital in Hong Kong led a study on health-care workers during the SARS outbreak, and showed that cheaper surgical masks were effective in helping to prevent transmission as part of a suite of infection-control measures[6].

Seto warns that all masks can pose a threat if reused or not disposed of carefully. "They could be contaminated with droplets that are then passed on to the hands," he says. "They should be used only once." In poorer countries, cheap surgical masks may be a more viable disposable option.

**David Cyranoski**

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**VIPs: in some countries, will drugs be earmarked for 'essential' construction workers?**

but don a protective face mask — which provides no guarantee of safety (see 'Masking our ignorance', opposite).

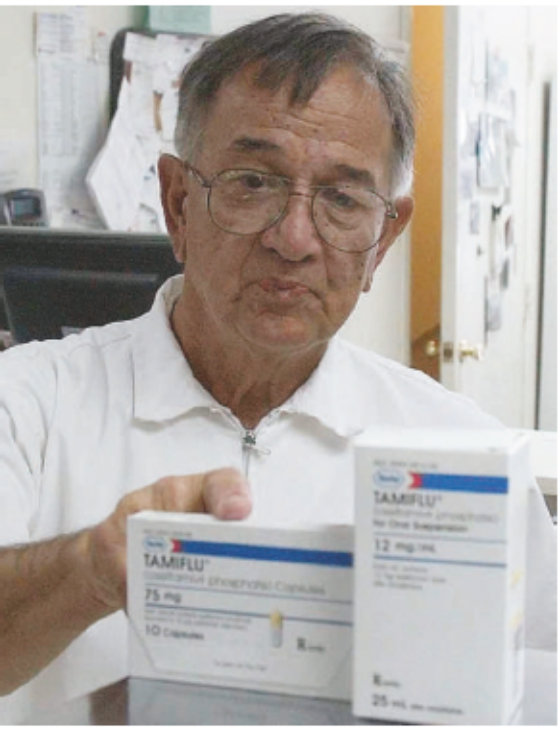
But the biggest challenge to any plan is the intrinsic biological uncertainty: just how nasty will a pandemic virus be? "We have so many unknowns — about how many people of what age groups would get ill, just how ill they would get, just how fast the virus would transmit — so it is hard to be firm about the best strategy for prioritizing treatment groups," Hayden says.

Of course, the larger the stockpiles, the easier the choices will be. This is why the WHO is using all its persuasive powers to get governments to place orders now. Once a pandemic breaks out, it will be too late. Roche has promised not to profiteer by hiking prices during a pandemic, but it is not simply a question of money. The firm has no spare production capacity and batches take up to a year to make.

In addition to encouraging stockpiling, experts are trying to find other ways of driving up the supply of antiviral drugs. They argue strongly, for example, for the wider prescription of antivirals against non-pandemic influenza. "This would allow companies to increase their routine manufacturing capacity without fear of losing money," says Stöhr. Other countries should follow the example of Japan, which consumes three-quarters of the Tamiflu prescribed each year, he argues. Most of the rest is used in the United States, with only 3% being prescribed in the rest of the world.

> "There are gaps in our knowledge that we need to fill so that physicians can use Tamiflu more effectively in a pandemic." — Fred Hayden

"It would be very good for physicians in these other countries to have experience with the drug before a pandemic arrives, so that they learn how best to treat patients," agrees Hayden. It's important for patients to be hit with the drug early, he says, but doctors may accept this only through clinical experience. The wider use of antivirals during annual flu epidemics would also stimulate companies to develop new drugs. This is currently not a priority for the pharmaceutical industry because the market is too small.




B. BRANCH-PRICE/AP

**Bitter pill: governments will have to make tough decisions about who should receive Tamiflu.**

## Unknown quantity

There is still of plenty of work to be done to further our understanding of Tamiflu's pharmacology. "There are gaps in our knowledge that we need to fill so that physicians can use it more effectively in a pandemic," says Hayden. For example, Tamiflu is not licensed for infants under one year old, because of the ethical difficulties of running trials in very young children — yet this age group proved exceptionally vulnerable in the severe pandemic of 1918.

Pharmacologists also want more biological data on patients who are treated with Tamiflu after being infected with the H5N1 virus now circulating in Asia. This will help them optimize dosing regimes. They complain that not enough is being done to gather these data from the relatively few patients who have so far been given the drug. Animal studies would also help, but this has similarly not yet been made an official priority.

Animal models could be used to investigate the use of Tamiflu in drug combinations, which may help avoid any problems with resistance. Pandemic planners are considering stockpiling amantadine and rimantadine as back-ups, despite their disadvantages, because they are cheap and were shown to have some prophylactic activity in the milder 1968 pandemic[4]. Now is the time to begin investigating the merits of using both major classes of anti-flu drugs together, says Hayden.

Finally, experts urge that the few new candidate drugs coming up should be given serious consideration, even if they don't seem ideal. For example, peramivir, another neuraminidase inhibitor was developed by BioCryst Pharmaceuticals of Birmingham, Alabama, but abandoned because it has to be injected. Nevertheless, its very long half-life in the body means that it needs to be given only once or twice a week and so might be useful prophylactically.

For most developing countries, meanwhile, creating a national stockpile would simply break the bank. So some public-health experts are calling for an international supply of Tamiflu that could be deployed by the WHO when a pandemic threatens. In unpublished work, Ira Longini, a biostatistician at Emory University in Atlanta, Georgia, has calculated that about 120,000 courses of Tamiflu, if deployed rapidly to treat the sick and protect their families — and if combined with strict quarantine of their houses — could even nip a pandemic in the bud at its point of origin.

Stöhr thinks the idea of ring-fencing outbreaks in this way is "well worth investigating". But Longini's model depends on assumptions about transmissibility and initial death rate that may prove to be wrong. And given the poor infrastructure in many of the Asian countries in which a pandemic virus is most likely to arise, such measures might prove hard to implement in practice. Before embarking on an effort to persuade sceptical governments to invest in such a plan, says Stöhr, there has to be much more confidence in the possibility that it could be made to work.

Uncertainty, unfortunately, is the name of the pandemic flu game. And the problem, for those trying to work out how to organize the first line of defence, is that politicians are averse to spending large sums of money when they don't know the odds — or even whether they'll still be in post when the bet comes in. ■

**Alison Abbott is *Nature*'s senior European correspondent.**

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