FLU’S UNEXPECTED BONUS

As governments stockpile oseltamivir Andrew Jack assesses who has benefited from pandemic flu

Former US defence secretary Donald Rumsfeld was talking about weapons of mass destruction and the war in Iraq when he referred to “unknown unknowns” in 2002, but he could just as easily have been explaining why drug companies have been able to make money out of the global flu pandemic. Within a few months of his comments, a series of events began to fuel growing international concern about a new pandemic. The mixture of fear and ignorance over its timing, nature, and severity soon sparked an unexpected bonanza for the manufacturers.

Since the emergence of swine flu in Mexico this spring finally triggered the first pandemic in four decades, J P Morgan, the investment bank, estimates that governments have made fresh orders for antiviral drugs of $3bn (£1.8bn; €2bn) and that recent or potential sales of vaccines are $7bn.1 All that despite signs that the virus is proving relatively mild, with potentially less impact than a standard seasonal flu outbreak.

One beneficiary has been Gilead, a fast growing US biotech business that initially developed the antiviral medicine oseltamivir (Tamiflu). In the three months to June this year alone it reported $52m in royalties on its drug. Another who gained was Rumsfeld, Gilead’s former chairman and continuing shareholder, who stressed that he disqualiﬁed himself from decisions that could have caused conflicts of interest.2

Roche, the Swiss giant that licensed, commercialised, and manufactured the drug from Gilead, has beneﬁted most of all. In its most recent ﬁnancial quarter, it generated SFr1.6bn in 2005, long before the pandemic began. In fact, the drug became the world’s ﬁrst “virtual” blockbuster, earning ten digit revenues to treat a virus that did not yet exist.3

Such commercial success was far from inevitable. When the drug was launched to treat seasonal ﬂu in 1999, it—and the slightly older, ﬁrst in class sister drug zanamivir (Relenza)—flopped. Zanamivir was judged not cost effective by the UK’s National Institute for Health and Clinical Excellence, ruling out its use in the National Health Service. Japan was among the few large countries to prescribe oseltamivir on any scale. Elsewhere, seasonal ﬂu was widely dismissed as little more harmful than the common cold, although it kills up to 500 000 people globally each year. But in 2003, the mood began to change. Severe acute respiratory syndrome (SARS) reminded people how fast and far lethal new viruses could spread with plane travel. Then the spread of H5N1, including to birds across Europe and human deaths in Turkey, switched attention to ﬂu.

Already in 2004, the government’s exercise to assess security threats had identiﬁed ﬂu as a greater risk than terrorism

Oseltamivir provided only a partial solution to a pandemic, offering a modest reduction in the length and severity of ﬂu symptoms. But it was far more effective than the older class of antiviral drugs, now rendered largely obsolete by resistance. And it was far easier to take than zanamivir, which patients have to inhale.

And while the lengthy production of a ﬂu vaccine could not even begin until the speciﬁc pandemic strain emerged, oseltamivir allowed politicians to show that they were doing something.

There was a chance for the first time to treat and even potentially prevent a ﬂu pandemic. At the least, a containment strategy to slow the spread of the virus and reduce its intensity would ease pressure on overworked general practitioners and hospital intensive care units while buying time for vaccine production.

Roche has traditionally worked closely with public relations advisers to stoke media interest, adding to political pressure. As its public adviser Edelman wrote at the time of initial US launch of oseltamivir for seasonal ﬂu in 1999, it worked with the company to create “a hybrid network of twelve local public relations agencies to take advantage of ﬂu as a breaking news story and launch Tamiflu in the top 100 local markets when ﬂu was in the area . . . The Roche local business units and sales force identiﬁed local physicians who were interested in participating in our media campaign to add the clinical angle to the Tamiflu story . . . We partnered with consumer and professional organizations in an effort to educate their members and
constituents on influenza and Tamiflu... We leveraged these relationships by enlisting our third-party partners to serve as spokespeople and increase awareness of Tamiflu and its benefits.”

Earlier this year, research supported by Roche showing the widely varied levels of stockpiles in different countries put pressure on the laggards to catch up.4 As a pandemic of conferences got underway, drug stockpiles were an easy box to tick in efforts to show that governments were doing something. To date, Roche has provided more than 270 million doses to 96 governments.

Exploiting opportunity
Over time, Roche has expanded the uses of the drug, winning regulatory approval for its use in children and pregnant women and providing lower dose and easier to swallow liquid paediatric versions. Today, it is studying oseltamivir’s use in combination with other medicines, over longer durations, and in intravenous form.

It has offered to reprocess older stocks of the drug. Even a highly unusual recent extension by regulators of the shelf life from five to seven years, which postpones any need to replace expired stock, may perversely tempt some governments to add to their stockpiles, knowing that they will now last longer.

With the pandemic underway, it was soon clear that using oseltamivir as a “fire blanket” to prevent localised flu outbreaks escalating into a global pandemic would not work. Some doctors raised concerns about side effects of the drug. Even so, in the UK and elsewhere, conferences got underway, drug stockpiles from the World Health Organization were an easy box to tick in efforts to show that governments were doing something. To date, Roche has provided more than 270 million doses to 96 governments.

Oseltamivir’s rise has not been without drawbacks. A number of seasonal flu viruses in circulation began to show resistance to the drug. The enormous gap between demand and supply, and its relatively high cost for the poor, triggered calls to overturn the patents and let rival companies make it more cheaply. But Roche defended its brand, expanding production capacity while donating 11 million treatments to WHO; offering to license manufacturing to generic rivals; waiving patent rights in the poorest countries; and providing deeper discounts and deferred payment terms to others.

Future directions
The peak may soon be over. Today, Roche’s former dominance is under threat. Biota, the Australian biotech company which first developed zanamivir, and GlaxoSmithKline, which commercialised it, have seen more modest sales, partly because the drug is more difficult to take. But as governments have sought to diversify from a single drug, and some resistance has emerged, they have complemented their oseltamivir stockpiles with supplies of zanamivir. The drug contributed A$45m (£23m; €26m; $39m) in the past year to Biota; and £60m in the second quarter of this year alone to GlaxoSmithKline—up from just £3m in the second quarter last year.

Oseltamivir’s patents expire in 2016, and newer experimental antiviral drugs pose a competitive threat even before then. These include peramivir, which is being developed by BioCryst with Green Cross Pharmaceuticals and Shionogi and lanainamivir, by Biota and Daichi Sankyo.

Although antiviral drugs have provided a stop-gap for prevention, government planners hope that vaccination will provide still greater reassurance against a returning, second pandemic wave. Vaccine manufacturers have been much more coy about providing figures on their pandemic sales, partly because they have yet to produce, test, and deliver the vaccines. There are still regulatory hurdles over the use of adjuvants and other antigen sparing techniques.

But more than a dozen companies—including Sanofi-Aventis, GlaxoSmithKline, Novartis, Baxter, CSL, and AstraZeneca—all stand to gain and are already receiving substantial funding from governments to reserve scarce capacity, invest in research, and launch production. Many are already indulging in a public relations war stressing the relative advantages of their vaccines.

Despite the sales now being generated by the pandemic, neither the main flu drugs nor the vaccines have become a primary source of profits for the large companies. As William Burns, Roche’s head of pharmaceuticals, said in a presentation in early September, Tamiflu was a “hidden surprise,” but even now it is only the fourth bestselling medicine.

Other companies also stress that they have risked substantial sums in development—$2bn so far for GlaxoSmithKline alone. And the head of Sanofi-Aventis asserts that although pandemic vaccine orders represent a “nice one-off,” they are not sustainable.2 What the current response is doing is creating a stronger future range of tools for tackling seasonal flu.

There is little doubt that several drug companies and their shareholders have benefited strongly from flu. But they have also contributed to easing its ill effects. Whether the money has been justified will ultimately depend on the final toll once the pandemic has passed, and how far its impact could have been known in advance.

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EUROPE’S KNOWLEDGE BROKER

The European Observatory on Health Systems and Policies provides evidence to help Europe’s health ministers develop their policies. Tessa Richards looks at its work.

next week policy makers, researchers, and clinicians from across Europe will meet at the annual European Health Forum in Bad Gastein, Austria. Debate will focus on the effect of the financial crisis on Europe’s health systems and strategies to rein in costs, improve efficiency, and meet rising demand for services.

Let’s hope the discussions prove more productive than recent ones in the US. There, a summer of well orchestrated attacks on Barack Obama’s proposed health reforms and scare stories about Britain’s “dreaded NHS” all but drowned rational dialogue. This is regrettable, not least because policy experts on both sides of the Atlantic agree that the US could learn useful lessons not only from the NHS but from several of Europe’s cheaper, equally effective, and more equitable health systems.

One organisation committed to furthering such cross country learning and using it to promote evidence based policy making is the European Observatory on Health Systems and Policies, a major contributor to the agenda and background information for the Gastein meeting.

From small beginnings

The idea of setting up an independent organisation to look at the different ways countries in Europe provide health care, extract policy lessons from their experience, and flag up examples of good practice, germinated in the corridors of two academic centres in London in the early 1990s. Chance brought together a small group of health researchers with a commitment to public health and an interest in policy analysis at the London School of Hygiene and Tropical Medicine and the London School of Economics and Political Science. They included Josep Figueras, the observatory’s full time director; codirector Elias Mossialos, who is also director of LSE Health; and Martin McKee, who heads the observatory’s research arm alongside his job as director of the European Centre on Health Societies in Transition. Professor McKee explained to me how the organisation developed.

“In the 1990s, the newly independent states in central and eastern Europe were attempting to shake off the legacy of the Soviet era and introduce new health reforms. Unsurprisingly, they looked to their Western neighbours and noted the enthusiasm for market reforms. When they sought information about the nature and impact of these reforms, it became obvious to us (and many others) that there was little available, and what there was, was hard to find and of poor quality. Policy was being influenced by ideology as much or more than evidence.

“We concluded that a new body was needed to bridge the divide between politicians on short tenures seeking quick simple fixes to complex problems and academics, who spend their working lives examining the same health issues but from a wholly different perspective—one oriented more towards advancing knowledge than informing current policy.”

The way to bring the two camps closer together, the group decided, would be to talk to health ministers to identify what they thought were the pressing problems and policy questions and then to harness the skills of academics to mount a “rapid response” to them. The academics’ role, facilitated by the observatory, would be to conduct secondary research (mostly in the form of cross country analyses) and present ministers with the best evidence available on policy options and impact relevant to their concerns.

The group first collaborated to inform discussions at the WHO European health ministerial conference in Ljubljana, Slovenia, in 1996. At that meeting 53 health ministers from the WHO European region pledged to provide sustainable, universally accessible, and equitable health services oriented towards primary care—and to exchange experience on implementing health reform. It was this last commitment that led to the formal establishment of the observatory in 1999.

Since its inception the organisation has accepted requests from health ministers and their advisers for reports to support discussions at a wide variety of national and European health policy meetings. It has also developed a role in anticipating and stimulating the wider European health agenda. One of the regular policy forums to which it contributes background reports is the rotating six monthly presidency meeting of the EU Health Council. Sweden is currently in the driving seat, and one of its priorities is tackling antibiotic resistance. At its request the observatory compiled a report on stimulating research and development of new antibiotics, which fed into last week’s ministerial meeting on the topic. Last year it provided a raft of background papers to support the WHO European region’s second ministerial conference on health systems...
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in Tallinn, Estonia. Ministers at the meeting signed another charter encapsulating the tenet that investing in health systems not only improves health but also the economy. Focus was also put on the need to measure the performance of health systems.

Output and influence

The observatory’s output is diverse and extensive. It includes analyses of individual countries’ health systems and publications that collate information on the nature and impact of the varied policies countries have implemented to tackle common problems—for example, financing health care and strategies to tackle communicable and chronic diseases. Recent titles look at how countries use health technology assessment to try to “improve value for money in health care” and maintaining Europe’s health workforce. It also publishes short policy briefs, a regular ebulletin, and a monthly magazine. All publications can be downloaded (free of charge) from its website (www.euro.int/observatory).

The organisation is run from a modest base in Brussels by Dr Figueras and Lynchnpin Suzi Lessof, the director of management. The two work closely with a handful of full time staff and hubs in London, Berlin, and Atlanta, Georgia. Many of the requests it gets for reports (and the funding to commission and produce them) come from its partners. These currently include WHO Europe, the World Bank, the European Investment Bank, and the governments of Belgium, Finland, Norway, Slovenia, Spain, Sweden, and the Veneto region of Italy. The European Commission and the governments of France and Ireland are likely to join the partnership soon.

When I asked Professor Mossialos why the UK was not listed as a partner, he paused, looked quizzical, and expressed the hope that it “would be in the future,” before going on to talk about the reach, influence, and future of the organisation.

“Because our goal is to respond speedily to requests for evidence and advice on policy issues we commission most of our reports and ‘synthesise’ them in house. As a result we have established strong links (aided by a listserv) with over 300 researchers and academic centres throughout Europe and beyond including the US, Japan, Australia, New Zealand, and South Korea. Demand for our publication has grown steadily, and it’s laid the ground for the development of several European Commission programmes, including one on mental health and wellbeing.” The observatory’s website, which is hosted by WHO, has been WHO’s most accessed site for the past five years, although it was recently overtaken by the one on swine flu.

Dr Figueras considers influence from another perspective. “It is not just how many people we reach but who they are and whether we influence their thinking. That’s why we hold our regular national policy dialogues with small groups of high level decision makers.” Some are more successful than others, he admits disarmingly, but cites examples (in confidence) where ministers bent on one course of action have been swayed to take another after discussion of the evidence. He also refers to a recent statement from Marc Danzon, regional director of WHO Europe, in which he describes the observatory as a “fine example of a cooperative structure” which has “supported (health) reforms programmes in numerous countries.”

The observatory is not without critics, however. David Hunter, professor of health policy and management at Durham University, says that “To outsiders, it appears a bit elitist and it is not clear how it works or how it sets its agenda. I also wonder how much it permeates health systems at sub-national level. Policy making, innovation, and organisational change go on at many levels and often the most interesting occur at ground level. While its publications are useful to academics, I am not sure how much impact they have on real-time policy makers and managers, or in getting research into practice.”

Both Dr Figueras and Professor Mossialos acknowledge that the observatory needs to consider how to reach a broader constituency, including health professionals and the public, and it is currently in the throes of developing a new media and dissemination strategy.

Looking to the future, there are proposals to emulate the organisation’s work elsewhere. The US Agency for International Development has just asked Dr Figueras and his colleagues to assess the feasibility of setting up an African observatory on health systems and plans are also underway to set one up in Asia and possibly the Middle East.

In the face of these developments and what Professor Mossialos describes as “a spiralling demand for new reports” the observatory is grappling with the challenge of how to grow. Its staff have spent years working closely together and honing the diplomatic skills that are needed to work effectively with a wide range of politicians, academics, and different organisations. Finding the right people to engage, and in time pass the baton to, may not be easy; but is arguably no harder than persuading politicians to think long term and act on sound evidence.

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