



## And Now, a Few Words about Antivirals for Pandemic Flu

By John E. Calfee

*Antivirals could save thousands or even millions of lives in the event of a truly lethal swine flu epidemic. Governments worldwide have stockpiled significant quantities of two of them: Tamiflu and Relenza. The development of these essential drugs provides important insights into the pharmaceutical industry's ability to advance public health.*

The worldwide furor over the emergence of the H1N1 flu virus that combines DNA from human, pig, and avian influenza viruses—“swine flu”—has focused attention on two classes of medical technology. One is vaccines, for which the chief concern is the lack of a vaccine against what has turned out to be a pandemic flu (meaning that this virus has gained an intercontinental foothold through human-to-human transmission). Popular, regulatory, and scientific thinking has naturally concentrated on surmounting the technological and regulatory barriers that stand in the way of quick, large-scale production of an appropriate H1N1 vaccine.

The second class of medical products is antivirals, meaning drugs that attack a virus directly rather than prepare the immune system to repel it when it arrives. For the flu, the most useful antivirals are Tamiflu (oseltamivir) and Relenza (zanamivir). Tamiflu, taken as a pill or solution, is more widely used than Relenza, which must be inhaled and is more expensive to stockpile and distribute. Both were quickly determined to be effective against the swine flu now being transmitted around the world. Hundreds of millions of courses of Tamiflu and lesser quantities of Relenza had already been stockpiled by many nations in

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the aftermath of the threatened avian flu epidemic in 2005.

Tamiflu and Relenza are of great value because they would probably be an essential tool for keeping pandemic swine flu from becoming a public health disaster if it should evolve into a more lethal form while retaining its ability to be easily transmitted among humans. Tamiflu and Relenza do three things: they shorten the course of a flu episode by about one to two days; they dramatically reduce the probability of unvaccinated persons getting infected with the flu; and they similarly reduce the probability that an infected

### Key points in this *Outlook*:

- Vaccines and antivirals are two classes of products to deal with the flu.
- Antivirals such as Tamiflu and Relenza reduce the scope and lethality of outbreaks.
- Their development illustrates the role of serendipity in drug development, the massive uncertainties in bringing a new drug to market, and the importance of marketing.

person will spread the disease to someone else, thus acting somewhat like an improvised vaccine (Couzin-Frankel 2009). In short, antivirals can substantially and perhaps decisively reduce the scope and lethality of this or similar outbreaks.

This spring's swine flu will likely crest and recede as summer approaches (in northern latitudes), but it might return in a far more dangerous form in winter, just as the 1918–19 flu returned in a second wave that caused far more damage than the first. The fact that this flu has disproportionately targeted the relatively young (those under fifty and especially under eighteen) is frighteningly reminiscent of the events of 1918–19 (Virus Investigation Team 2009). We may well have a good swine flu vaccine to deal with that second wave (Gottlieb 2009). But even if we do, limited supplies will keep most of the world's population from being vaccinated, and vaccination is never 100 percent complete, even when supplies are adequate. Thus, in the unfortunate event of a truly lethal swine flu pandemic, antivirals could save thousands or even millions of lives through treatment and prevention. As nations ponder this scenario, we may see substantial additions to worldwide antiviral stockpiles. The European Medicines Agency (EMA) has declared that antivirals can be used for at least a few years beyond their labeled expiration dates, so current stockpiles remain useful (DIA Daily 2009), and it seems likely that the U.S. Food and Drug Administration will issue a similar statement. In the meantime, the Centers for Disease Control and Prevention (CDC) has updated its recommendation that emergency personnel take a daily antiviral when dealing with an outbreak and that hospitals and similar institutions maintain sufficient supplies.

## How Tamiflu and Relenza Work in a Pandemic

This immensely valuable pair of drugs has a rather odd history that illustrates some basic truths about the economics and science of drug development in general. Relenza was approved in July 1999 and Tamiflu three months later. There were already antivirals on the market (rimantadine and amantadine), but they worked for only one of the two main types of flu (type A, but not type B), and resistance to antivirals for type A was growing. In fact, the CDC has not recommended their use since at least 2005 (Derlat et al. 2009). Tamiflu and Relenza were the first neuraminidase inhibitors, meaning that they suppress a protein on the surface of

infected cells that the virus uses to spread within a human host. Both Relenza and Tamiflu have been the subject of criticism, however. There have been some safety worries: rare but severe breathing problems for Relenza and, for both drugs, psychiatric side effects that were found primarily in Japan, where flu mass vaccination was temporarily discontinued and where flu is treated aggressively with Tamiflu (Usdin 2007). The drug labels warn about both problems, but the drugs are nonetheless widely viewed as very safe, as evidenced by expert recommendations for quick and widespread use. (A dissenting view comes from Sidney Wolfe of the advocacy group Public Citizen, who says Relenza should not have been approved and patients would suffer no loss through its removal [WebMD 2000].) Critics have most often focused on costs, however, because antivirals can cost \$100 or more per treatment to treat

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a condition that could have been prevented by a much cheaper flu shot. Demand has accordingly been modest (except in Japan), but we should remember that a calculation of an average financial benefit disguises the very large benefits that some users could gain from, say, being at work for a day or two in a highly paid activity or having milder flu symptoms while fighting another serious illness at the same time.

But all this assumes that a vaccine is available. For the flu, that cannot be taken for granted. Most vaccines (such as that for measles, for example) can be used more or less unchanged for decades. But flu viruses mutate very rapidly, and, as a general rule, mutated flu viruses require different vaccine formulations. The seasonal flu vaccine typically addresses three strains and practically never the same three as the year before. A special threat is a virus that originates in other species, especially birds and pigs (in both of which flu is common). These viruses may differ so much from what the human immune system has faced that resistance to them is weak. Fortunately, when animal-borne flu

viruses mutate in ways that make them easily transmissible among humans, the result is usually a relatively mild version of the flu—perhaps as mild as or milder than seasonal flu. Even in ordinary years, however, the seasonal flu contributes to tens of thousands of deaths annually in the United States alone (CDC 2009). With that as a baseline, we can be thankful that we rarely encounter animal-borne viruses that are both lethal and easily transmissible among humans. But, if one arrives, it would be extraordinarily dangerous and could cause millions of deaths. That is what happened in 1918–19, and that is the threat posed by the avian flu in 2005 and H1N1 today.

The 2005 avian flu episode seems to have made public health authorities worldwide acutely aware of the benefits of antivirals, prompting governments worldwide to stockpile about 250 million courses, with even more likely to come soon (Couzin-Frankel 2009). Most public health authorities think Tamiflu and Relenza will play a crucial role in the event of a virulent pandemic flu, especially for emergency health care workers and others on the front lines in dealing with the pandemic. These antivirals are expected to serve as both treatments and makeshift preventatives in dealing with a lethal pandemic flu (Miller et al. 2009). This is true not only for the United States. In explaining its policy toward the emerging pandemic flu, the EMEA noted that its “recommendations resulted from a study of how to prevent shortages of antiviral medicines such as Tamiflu, which were key in managing flu pandemics because appropriate vaccines were not normally available during an outbreak’s early stages” (DIA Daily 2009). A general rule is that the faster a pandemic flu spreads and the more lethal it is, the more useful the antivirals will be.

## The Origins of the Unexpected Blockbusters

These evolving circumstances offer useful insights into the pharmaceutical industry and how it can advance public health. First, note the element of serendipity. With so much criticism of safety problems that pop up after drugs are approved (something that is bound to happen occasionally), there is far less attention to the unexpected benefits that pop up far more often. Some of these are legendary, such as the therapeutic revolution that was unexpectedly launched by Prozac, the first modern antidepressant, and the ever-expanding orbit of benefits from the statin class of cholesterol-reducing drugs introduced by Mevacor and Zocor two decades or so ago.

Antivirals for influenza are just one more item on what is a pretty long list of unexpected financial and medical blockbusters.

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Second, antivirals are indicative of the economics of drug development, which is characterized by mammoth financial and scientific uncertainties. The decision to launch expensive late-stage clinical trials is typically driven by the prospect of serving a narrow, well-defined market. Broader opportunities may be pleasant to contemplate, but the list of postapproval disappointments in the marketplace is far longer than the list of serendipitous successes. This is true even in the flu vaccine market, in which the first oral vaccine—MedImmune’s FluMist—has been a major disappointment thus far. A certain form of economic stubbornness usually comes into play both in sticking with the research agenda when a small but clear market is in sight, and in dropping expensive projects when prospects are nebulous, however enticing. Fortunately for us, a couple of small biotech R&D firms (Gilead Sciences for Tamiflu and Australia’s Biota for Relenza) persisted in antiviral development programs, even when the main therapeutic benefit was likely to be only a day or two of flu symptom relief. When Tamiflu was still new on the market, flu epidemics did not seem threatening, and there was little government interest in stockpiling. According to the CEO of Roche at the time, Tamiflu was “a drug which was very difficult to commercialize. We sat there with a drug in which we had invested a significant amount of development and where we had sales that were less than exciting” (Pollack 2005). Competing firms such as Johnson & Johnson, in partnership with the biotech firm BioCryst Pharmaceuticals, curtailed and drastically slowed down their own antiviral projects in the face of slim demand, as did the Japanese firm Sankyo (Pollack 2005). It was from this bleak market prospect that our two essential antivirals emerged.

The marketing of these antivirals deserves a cheer. The small pioneer firms that developed Tamiflu and Relenza licensed the manufacturing and marketing rights to large established pharmaceutical firms (Roche and GlaxoSmithKline, respectively). They were able to har-

ness marketing staffs to the task of matching these drugs with the relatively narrow patient base for whom they provided real value—those for whom one or two fewer days off work while fighting a dangerous illness was a large benefit.

In the meantime, while the flu antiviral market remained sedate, the ever-shifting worldwide assortment of flu viruses was generating the possibility of mammoth health crises in which these modest drugs could become life-saving tools on an unprecedented scale. We can be glad that we have two good antivirals. And we should hope that the new ones in early-stage development at firms like GlaxoSmithKline and BioCryst (NIH 2006) will meet success if and when Tamiflu and Relenza are overcome by drug resistance on the part of a dangerous new variant of the flu.

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