by adopting a technology that can protect against safety breakdowns during production, preparation, or cooking: routine irradiation of the final commercial product in the case of poultry and hamburger, processed foods containing eggs or milk, and selected leafy and other vegetables eaten raw could greatly reduce the incidence of bacterial foodborne disease. Research has shown that irradiation kills pathogens or markedly reduces pathogen counts without impairing the nutritional value of food or making it toxic, carcinogenic, or radioactive. Food irradiation has been endorsed by the World Health Organization, the CDC, the FDA, the USDA, the American Medical Association, and the European Commission’s Scientific Committee on Food and is already used in many other countries. In the United States, irradiation of fresh meat has been allowed since 1997; last August, the FDA approved the irradiation of iceberg lettuce and spinach. The CDC has estimated that irradiation of high-risk foods could prevent up to a million cases of bacterial foodborne disease each year in North America. I believe it is time to launch a major effort to gain public acceptance of irradiation of high-risk foods. It is time to stop reliving history.

No potential conflict of interest relevant to this article was reported.

Dr. Maki is a professor of medicine at the University of Wisconsin School of Medicine and Public Health and a hospital epidemiologist at the University of Wisconsin Hospital and Clinics — both in Madison.

This article (10.1056/NEJMmp0806573) was published at NEJM.org on February 11, 2009.


Copyright © 2009 Massachusetts Medical Society.

Global Transmission of Oseltamivir-Resistant Influenza
Anne Moscona, M.D.

Seemingly from one influenza season to the next, we have lost the use of our leading antiviral influenza drug because of resistance. This winter, the circulating strain of seasonal influenza A virus (H1N1) is resistant to the neuraminidase inhibitor oseltamivir. Moreover, rather than emerging under selective pressure of drug use, as many antibiotic-resistant bacteria do and as has been the concern for influenza, this resistant strain seems to be a natural, spontaneously arising variant. Nevertheless, science has given us the tools with which to anticipate these events — and should allow us to develop new clinical solutions that build on our knowledge of the biology of RNA viruses.

Neuraminidase cleaves sialic acid residues on the cellular receptor that bind the newly formed virions to the cell and to one another, enabling infection to spread to new host cells and ongoing infection to be established. The neuraminidase inhibitors mimic neuraminidase’s natural substrate and bind to the active site, preventing the enzyme from cleaving host-cell receptors, thereby preventing infection of new host cells and halting the spread of infection. The two licensed neuraminidase inhibitors, zanamivir (Relenza) and oseltamivir (Tamiflu), have very little toxicity and are effective against all neuraminidase subtypes and, therefore, against all strains of influenza virus.

But the possibility of widespread oseltamivir resistance has been a concern for several years. Structural analysis of the influenza neuraminidase predicted that resistance to oseltamivir would be feasible — and more likely to arise than resistance to zanamivir. Although the concern was focused on the emergence of resistance under the selective pressure of drug treatment, the same principles apply to natural variants: mutations could arise that would inhibit oseltamivir’s action while leaving viral fitness and zanamivir activity unaffected. These predictions were borne out by clinical data during the past several years, as resistance to oseltamivir in influenza A isolates from treated patients, especially children, has grown more common. However, some complacency about the clinical significance of
neuraminidase-inhibitor–resistant influenza was based on the belief that such viruses would be less infectious and less transmissible in humans. Clearly, this complacency was not warranted. H1N1 influenza viruses containing a mutation conferring resistance to oseltamivir — one of the most common resistance mutations seen in treated patients since 2004 — have now circled the globe.

The mechanism of the development of resistance to oseltamivir is illustrated in the diagram. For oseltamivir to fit into the neuraminidase active site, the amino acids must undergo a conformational change to accommodate oseltamivir’s hydrophobic side chain; mutations that prevent this rearrangement may lead to resistance. Since zanamivir is more structurally similar to the natural substrate of neuraminidase and fits directly into the active site, the mutations that prevent the rearrangement do not bring about resistance to zanamivir. Three sets of mutations have been identified that prevent this rearrangement — Arg292Lys, Asn294Ser, and His274Tyr — and the presence of any of them confers oseltamivir resistance in H1N1 influenza viruses. The mutations identified in clinical isolates have been in the exact amino acids predicted by this molecular analysis, and it is the His274Tyr mutation that confers oseltamivir resistance on the currently circulating H1N1 strain.

H1N1 viruses containing the His274Tyr resistance mutation became widespread beginning with...
the 2007–2008 influenza season in the Northern Hemisphere, with a prevalence of about 10% in the United States and about 25% in Europe (except for an astonishing prevalence of about 70% in Norway). These resistant viruses then predominated during the Southern Hemisphere’s 2008 influenza season. In the United States today, H1N1 is the dominant circulating strain and is virtually 100% oseltamivir-resistant. The urgency of the situation is tempered by the fact that this season’s oseltamivir-resistant viruses are sensitive to zanamivir and by the tendency for the H1N1 strain of viruses to cause milder disease and fewer deaths than the H3N2 strain. However, H1N1 viruses can cause serious complications, and recent data from Norway’s 2007–2008 influenza season suggest that patients infected with the resistant virus may be more likely to develop pneumonia or sinusitis than those infected with wild-type virus, although this finding did not reach statistical significance.3

The surprise element of the circulating resistant virus is its apparently spontaneous emergence since 2007. Though unpredicted, this occurrence is consistent both with the idea that a mutation that is apparently harmless to the virus can confer resistance and with previous evidence that genetic variations lead to degrees of oseltamivir resistance in vitro, without selective pressure. RNA viruses such as influenza virus adapt nimblly to changes in the host, driven by the immune response, and rapidly escape any intervention targeting only one point in the life cycle. The influenza life cycle depends on a precise balance between the functions of the neuraminidase (cleaving receptor moieties) and the hemagglutinin (receptor binding), and mutations in one can be counteracted by mutations in the other. The spontaneous emergence of the H1N1 strain may have resulted from a coselection of the mutation with a compensatory hemagglutinin mutation, which maintained the balance and yielded a fit, transmissible virus.

Could a resistant strain of H3N2 influenza — the virus more commonly associated with death — persist and be transmitted like the current H1N1 strain? In principle, it could, although it would most likely result from different resistance mutations on a different genetic background, given the structural differences between N1 and N2 neuraminidases. These differences mean, for example, that the His274Tyr mutation disrupts the oseltamivir-binding site on N1 but not on N2 and that the Arg292Lys mutation confers more resistance on N2 than N1.2,4

We cannot yet anticipate the precise combination of mutations that might enable fitness and persistence of a neuraminidase-inhibitor–resistant H3N2 strain.

Faced with this season’s influenza viruses, we do have therapeutic options, but they are complicated and likely to change. H1N1, the major circulating influenza strain in the United States, is still sensitive to zanamivir, the inhaled neuraminidase inhibitor, and to the adamantanes, an older class of compounds. H3N2, which has been isolated less frequently in the United States this year than in the past, is sensitive to both neuraminidase inhibitors but resistant to the adamantanes, which elicit rapid emergence during treatment of drug-resistant variants that are then easily transmissible. The rapidity with which the adamantanes elicit resistance — 30% of treated patients shed resistant, transmissible viruses within 3 days after beginning treatment — limits their usefulness for the treatment of seasonal influenza. In fact, since 2005, virtually all circulating H3N2 strains have been resistant to the adamantanes. The use of these drugs was curtailed in an effort to allow adamantine-susceptible strains to reemerge. However, most strains of H1N1 are still sensitive to these drugs, which are providing benefit this influenza season.

Therapy with neuraminidase inhibitors or prophylaxis in contacts to avert disease transmission is effective if it is initiated soon after the onset of symptoms, but the benefit diminishes over time.1 Therefore, prompt identification of illness and early initiation of treatment are essential. Unfortunately, in the United States this season, the appropriate drug depends on the infecting strain, and it may be difficult to identify the subtype sufficiently quickly to guide clinical decisions. Since rapid tests do not distinguish be-
A Multidrug Strategy for the Future.

Over time, influenza viruses will probably develop resistance to any single antiviral agent. Treatment with several compounds that act at different stages of the viral life cycle would be more effective and make it less likely that any single mutation could confer resistance. This strategy may become feasible as new agents, such as the following, become available:

**Intravenous zanamivir:** A therapy for patients hospitalized with severe influenza and for those in whom neither oral nor inhaled routes are an option.

**Peramivir:** An as-yet-unlicensed neuraminidase inhibitor that is being developed in intravenous and intramuscular formulations.

**Long-acting inhaled neuraminidase inhibitors:** A therapy based on the enhanced potency of dimeric derivatives of zanamivir that will probably be available in the next few years; administration may be possible in a single dose for treatment or once a week for prophylaxis.

**Fludase (DAS181):** A sialidase fusion construct that cleaves the sialic acid receptors that influenza viruses use for attachment, removing influenza receptors from the airway epithelium and preventing infection of lung cells.

**Cyanovirin-N:** A hemagglutinin inhibitor that may block viral entry.

**Short interfering RNAs:** A therapy that may hold promise for influenza.

**T-705:** A substituted pyrazine compound that is active against neuraminidase-inhibitor–resistant and amantadine-resistant viruses and that probably inhibits the RNA polymerase.

The recent discovery of the active site of a key endonuclease activity in the PA subunit of the influenza polymerase molecule could lead to a new class of drugs targeting the essential polymerase function of “cap-snatching.” Other promising antiviral avenues under investigation include signal transduction inhibitors, interferon inducers, and molecules targeting the interaction between the influenza NS1A protein and the 30-kD subunit of cleavage and polyadenylation specificity factor.

Between H1N1 and H3N2 subtypes, clinicians will need to remain informed about the locally circulating influenza strains and subtypes. Difficult treatment decisions must be made to contend with resistance. Patient characteristics, together with either actual data on antiviral susceptibility or the best guess, must be weighed in individual cases. Zanamivir is indicated when either the infecting virus or the locally circulating virus is known to be H1N1 or is unknown. However, zanamivir is an option only for patients who can actively use an inhaled drug and thus cannot be used in children under 5 years of age, impaired older adults, or persons with underlying airway disease — groups of patients who are particularly vulnerable to serious complications from influenza infection. The recommended alternative is combining an adamantane (preferably rimantadine) with oseltamivir, which provides coverage for either strain and may enhance efficacy while reducing the likelihood of resistance. In the future, as additional antiviral agents are developed, an enhanced multidrug strategy targeting various stages of the viral life cycle might become possible (see box).

The startling news about oseltamivir resistance should unite the global medical and scientific communities in an effort to cope with this rapidly evolving pathogen. For years, we have seen warning signals that highly oseltamivir-resistant influenza viruses could emerge and spread, disabling our defenses against this pathogen. Now the alarm has been sounded, and it is time to act.

Dr. Moscona reports serving on advisory boards for or receiving consulting fees from MedImmune, GlaxoSmithKline, and Roche, receiving lecture fees from Medimmune, Merck, and GlaxoSmithKline, and receiving grant support from NexBio and Shaklee. No other potential conflict of interest relevant to this article was reported.

Dr. Moscona is a professor in the Department of Pediatrics and Microbiology and Immunology at Weill Medical College of Cornell University, New York.


Copyright © 2009 Massachusetts Medical Society.