

## LETTERS

edited by Jennifer Sills

## Pandemic Influenza: An Inconvenient Mutation

SEASONAL INFLUENZA AFFECTS 10% OF THE POPULATION ANNUALLY, KILLING UP TO ONE million persons worldwide. Pandemic viruses have even greater potential for mortality. We have several defenses, including personal and public health protective measures, vaccines immunologically matched to circulating strains, and two classes of antiviral drugs (neuraminidase inhibitors and adamantane ion-channel blockers). Our preventive options are limited by viral genetic diversity and a rapid viral mutation rate. Currently, two human influenza A subtypes (H1N1 and H3N2) and two influenza type B lineages cocirculate. About 425 million doses of trivalent influenza vaccine are produced annually, enough to protect less than 7% of the world's population. In the event of a pandemic, well-matched protective vaccines against a novel agent would not be available for at least several months, highlighting the importance of therapeutic options.

By 2009, however, 98% of circulating influenza A/H1N1 strains in North America have become resistant to the frequently prescribed and widely stockpiled neuraminidase inhibitor oseltamivir (Tamiflu), and 98% of A/H3N2 strains are resistant to the adamantanes. The alternative neuraminidase inhibitor zanamivir and the two approved adamantanes—amantadine

and rimantadine—are all in short supply, and the adamantanes have substantial side effects. Influenza therapeutic options are clearly unraveling at a time when public health officials are appropriately concerned about pandemic emergence.

The spread of high-level oseltamivir resistance in A/H1N1 strains is puzzling, as it appears to have occurred without antiviral selective pressure (1). Whether such levels of resistance will continue or diminish is unknown. Is high-level resistance an unfortunate byproduct of (still unknown) polygenic factors that confer viral fitness, such as balancing hemagglutinin and neuraminidase activity? Does resistance in influenza A/H1N1 imply a chance that resistance will develop in highly pathogenic avian A/H5N1 viruses, which bear the same neuraminidase subtype? Two past pandemic viruses (1957 and 1968) emerged after circulating human viruses reassorted with avian influenza viruses; emergence of a future pandemic strain by the same mechanism, but incorporating either an antiviral-resistant H1N1 neuraminidase or A/H3N2 matrix gene, is a possibility that cannot be ignored.

Pandemic planning envisions that if a virus with pandemic potential emerges, initial human-to-human transmission can be spotted quickly and contained by nonpharmaceutical interventions and by rapid community administration of antiviral agents and vaccines (2, 3). If this strategy fails, a

conceivable consequence, however unlikely, is accidental creation of a drug-resistant pandemic strain, a manmade analog of the feared naturally arising reassortant alluded to above.

Most national stockpiles have appropriately favored neuraminidase inhibitors (mainly orally administered oseltamivir) over ion-channel blockers (oral adamantanes) for pandemic preparedness, given the well-recognized rapid emergence of resistance to the latter when used in treatment (4). Now, as noted, transmissible oseltamivir resistance in human A/H1N1 strains makes this strategy problematic on many levels, including concern about efficacy in a pandemic, as well as emergence of a pandemic reassortant containing resistance genes (1). A complicating factor is increasing appreciation that secondary bacterial pneumonias have caused most deaths in past pandemics (5). Circulation of clinically aggressive community-acquired methicillin-resistant *Staphylococcus aureus* is an additional factor to be considered in planning for pandemic response. Taken together, these several developments suggest a need to continually examine and periodically reconfirm or update pandemic response strategies.

Whatever strategies are adopted, it is clear that additional anti-influenza therapeutics are urgently needed. So far, vaccines and antivirals have targeted three influenza envelope proteins: hemagglutinin, neuraminidase, and the matrix 2 ion channel protein. We need new classes of antivirals that interfere with other necessary viral processes (e.g., polymerase complex activity, interferon antagonist activity, and viral assembly). The desired outcomes of existing and future therapies (reduced severity, mortality,



Preparing for a virus storm.

## Letters to the Editor

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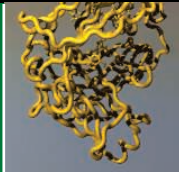
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Building in flexibility

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Closer to combination therapies

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viral shedding, and transmission) should be considered with respect to both seasonal and pandemic influenza.

The unpredictable nature of influenza presents a challenge for both research and pandemic preparedness planning. Our ability to anticipate pandemic events is poor, and our anti-pandemic armamentarium is weak. In an ever-shifting landscape of influenza evolution, we need to be farsighted and forceful in optimizing pandemic response capacity.

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2. M. E. Halloran *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **105**, 4639 (2008).
3. A. S. Monto, *Clin. Infect. Dis.* **48**, 397 (2009).
4. The United States has stockpiled 81 million doses of oseltamivir—one dose each for 25% of the population.
5. D. M. Morens, J. K. Taubenberger, A. S. Fauci, *J. Infect. Dis.* **198**, 962 (2008).
6. This research was supported in part by the Intramural Research Program of the NIAID and the NIH.

## Romanian Expatriates Face Career Obstacles

IN HIS NEWS FOCUS STORY “REACHING FOR the stars in Romania” (21 November 2008, p. 1183), M. Enserink gives a realistic description of some important problems of Romanian science. I would like to add another important issue: Successful expatriated Romanian scientists should be encouraged to return to Romania to hold important positions, and they should be appropriately compensated for doing so. In theory, expatriated scientists are encouraged to return and take leadership roles. In practice, these scientists have trouble securing their place in the applicant pool. To qualify for consideration, the expatriated scientists must demonstrate that the position they

hold abroad is equivalent to the Romanian position immediately subordinate to the open position. The legal process to determine equivalency is cumbersome, and there is no definite authority who can certify equivalence. These ambiguous requirements often serve as an obstruction to expatriated scientists.

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## Reversible Exploration Not Worth the Cost

C. P. MCKAY (“BIOLOGICALLY REVERSIBLE exploration,” Policy Forum, 6 February, p. 718) makes an impassioned case for so-called biologically reversible exploration of Mars. However, such a strategy will impose additional costs on an already strained program (1), and it is neither feasible in the context of a robust Mars exploration program nor necessary to ensure the fidelity of future in situ scientific endeavors. The concept of biologically reversible exploration is focused on potential effects of forward contamination—the transport of terrestrial microorganisms to other planetary bodies. Using real options theory (2), we can evaluate the ability to preserve future decision paths (such as the ability to

“reverse” biological incursions) with present investments [such as spacecraft sterilization and constraints put in place on “special regions” (3)]. An accounting of present and future scientific costs and benefits must be made to critically assess this idea. In the near term, additional costs will result from spacecraft preparation regimes, compliance, and possibly reduced mission capability due to constraints on instrumentation and landing site restrictions. The suggestion that even human exploration should achieve “biological reversibility” will impose an enormous burden on such missions in terms of both direct costs and curtailed science from restrictions on access to the subsurface. In contrast, the supposed benefits are only potential benefits, mostly in the event of terraforming, and extremely long-term in nature. The exchange of meteorite material between Earth and Mars (4), the flotilla of existing landed missions, and the fleet of orbiters that will eventually crash into the surface already determine both the past and near-future two-way exchange of biological material between Earth and Mars. Special regions of scientific interest on Mars do call for prudent measures to reduce contamination, but the extreme measures advocated by McKay will not yield sufficient benefits to justify their high costs.

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## CORRECTIONS AND CLARIFICATIONS

**News of the Week:** “NSF restores data on minority Ph.D.s” by J. Mervis (27 February, p. 1161). The National Science Foundation estimates that its new policy on reporting small numbers of minorities will suppress data on 3.7% of the new Ph.D.s in the Survey of Earned Doctorates. The original story incorrectly reported that 4% of the 280 subfields would be affected.

**News Focus:** “Tales of a prehistoric human genome” by E. Pennisi (13 February, p. 866). The story mischaracterized James P. Noonan’s mouse experiment that used an enhancer showing human-specific activity. In that study (published in the 5 September 2008 issue of *Science*, p. 1346), the enhancer drove the expression of a reporter gene in the mice, but the researchers did not examine its effect on thumb development.

**News Focus:** “On the origin of art and symbolism” by M. Balter (6 February, p. 709). Ochre expert Ian Watts was cited as saying that there was little sign that ochre found at Twin Rivers, Zambia, was ground into powder, as needed for decoration. This incorrectly states Watts’s view. Although only a small percentage of the approximately 300 pieces of ochre found at Twin Rivers show signs of grinding or other use, nearly all those that do are a dark, sparkly red. This leads Watts to conclude that they might have been preferentially chosen for symbolic purposes, although that is not certain.

**Reviews:** “Darwin’s originality” by P. J. Bowler (9 January, p. 223). On page 226, reference 8 should read as follows: J. Browne, *Charles Darwin: The Power of Place* (Jonathan Cape, London, 2002). In reference 22, *Transmutation Notebook D* should have been *Notebook B*. Also in reference 22, two page numbers were missing: *Natural Selection*, p. 36, and *Charles Darwin’s Notebooks*, p. 180.

**Reports:** “Observation of pulsed  $\gamma$ -rays above 25 GeV from the Crab pulsar with MAGIC” by The MAGIC Collaboration (21 November 2008, p. 1221). The e-mail address for N. Otte was incorrect. The correct address is nepomuk@scipp.ucsc.edu.