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Pandemic Influenza: An Inconvenient Mutation

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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

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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 recon-firm 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, 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.

References and Notes

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