

Essential Elements of a Plan To Reduce the Risk of an Influenza Pandemic and Limit its Impact

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I. Goal

Limit replication of H5 N1 in general

Minimize the replication of H5N1 in mammalian hosts

Rationale:

Viral replication is associated with mutation events. More replication means more opportunities for mutation or other change in the virus.

Most avian influenza viruses are well adapted to aquatic birds and show little change in them over time (evolutionary stasis). They replicate to high titer and are shed in feces but do not cause illness. Highly pathogenic avian viruses, such as H5N1, have high lethality for domestically raised chickens and several other avian species. Some avian species (especially ducks) can carry highly pathogenic H5N1 virus, shed it over days to weeks, and do not appear ill. H5N1 has also been documented to infect several non-avian species, including cats, leopards, tigers, pigs, and dogs, among others.

Influenza viruses, in general, have a wide host range, though specific influenza types tend to infect specific species, in a pattern that is reasonably stable over time. Only influenza viruses with 3 hemagglutinins (H1, H2, H3) of the 16 that exist and 2 of the neuraminidases (of the 9 that have been described) have caused pandemics in humans. Viruses with all 16 hemagglutinins infect avian species.

Influenza virus infection in a mammalian host (not the natural reservoir host for influenza viruses) is associated with more rapid evolution of the virus, more pressure for adaptation. If a mammalian cell is simultaneously infected with an avian and a mammalian influenza virus, reassortment (swapping of segments of the viruses) can occur, and the resulting virus may have different biological characteristics. These can determine cellular receptors (which cells are infected), level of replication, and other characteristics that influence which tissues are involved, how virus is shed from the body, pathophysiology of infection, and clinical expression and outcome.

Questions for discussion

What are the potential ways to limit replication of H5N1 and minimize infection of mammalian hosts?

What are the barriers? How can these be overcome?

What specific measures can be undertaken to achieve this goal?

II. Goal: Rapid, reliable diagnostic test that can identify H5N1 infection locally (without need to send specimen to specialized laboratory).

Rationale:

It is necessary to identify presence of virus in avian species before intervening with mass culling and other interventions that are expensive and disruptive. In humans, infection with H5N1 can resemble many other infectious diseases. Drugs and vaccines are currently limited in supply; ideally interventions should be targeted to populations with infection (confirmed or highly likely based on specific tests). Current tests have limited availability; confirmatory testing can be done only in specialized laboratories.

Problems in achieving rapid diagnosis include obtaining specimens that will yield useful results and getting them to appropriate laboratory. At present, lag time to confirmation of H5N1 infection often exceeds a week.

Questions for discussion

What are the potential ways to do develop rapid, reliable diagnostic test for H5N1?

What are the hurdles? How can these be overcome?

What specific measures can be undertaken to achieve that goal?

III. Goal: Capability to produce vaccine with new influenza antigen within 3 months in large volume (100 million doses in US; x billion globally) using technology that is not egg based.

Rationale: The H5N1 virus will not be eliminated from the reservoir host (avian species), which means the risk for repeated introductions into the human population will persist. Antiviral drugs for treatment and prophylaxis are not a viable longterm single strategy for preventing human disease. Resistance to available antivirals has already been documented in a few isolates. Vaccination offers the potential for protecting large populations prior to exposure or repeated exposures. Current vaccine technology lacks flexibility to rapidly change to a new antigen and capacity to produce the large number of doses needed. One must assume that the virus will continue to undergo genetic change.

Desired vaccine attributes and capacity:

Rapid production; capacity to scale up rapidly

Flexibility to add new antigens

Not egg based

Easy to deliver (ideally without need for injections and maintenance of cold chain)

Immunogenic with single dose; durable immunity

Safe and effective in all populations, including pediatric, elderly, immunocompromised

Note: Would not have to produce sterilizing immunity. Vaccine would still be valuable if it could reduce disease severity, prevent death; reduce viral replication and duration of viral shedding; reduce spread in a population.

Questions for discussion

What are the potential ways to reach these vaccine goals?

What are the hurdles?

What specific measures can be undertaken to achieve that goal?