

Patient-oriented pandemic influenza research

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The world is currently experiencing a pandemic of a novel influenza A (H1N1) strain, with a daily increasing number of confirmed cases (and a much larger, uncertain total number of infections) in many countries.¹ More than 160 deaths have been related to confirmed infection, but most cases have been mild and uncomplicated. The strategy has been to identify suspected patients early, to isolate them, and—in some countries—to offer treatment with oseltamivir for patients and their contacts. Production and initial testing of specific vaccines are underway. This rapid action has helped to vindicate the planning, preparation, and epidemiological modelling that has underpinned the global response. History will judge the real impact, but in many ways response to the pandemic has been a model of ensuring that the best available science informs policy and is implemented. The sharing of information and samples from the countries first affected, and the inclusivity and calm leadership from WHO, have been exemplary.

Yet the interventions used to date are not an option for most of the world. Viral diagnostic facilities remain limited, there is insufficient oseltamivir for all suspected and confirmed cases, and contact tracing is impossible. Inevitably, now that this highly transmissible virus has arrived in densely populated countries with limited resources and increased vulnerability related to malnutrition, chronic infections such as HIV and tuberculosis, and limited access to medical care, it will spread rapidly, and very large numbers of people will be infected.² The virus will then have far more chance of mutation or reassortment with circulating human seasonal influenza viruses or, in the worst-case scenario, with other animal viruses. In resource-limited countries, human beings and animals commonly live closely together and continue to experience transmission of influenza A (H5N1) and other avian influenza viruses in animals with sporadic infections in people. As the rich world orders, stockpiles, and deploys antiviral drugs and vaccines, who will ensure that less well off countries have equitable access to these crucial interventions?

There are two other immediate issues: antiviral drug resistance and clinical research. The world is badly prepared for influenza, with just a single widely

available oral drug (oseltamivir) that is not available to give intravenously to severely ill patients. Drug resistance is a single mutation away in a highly variable RNA virus, and has already resulted in global circulation of an oseltamivir-resistant human H1N1 virus.¹ Although active against most oseltamivir-resistant strains, zanamivir is not widely available, and the manufacturer has been painfully slow in developing it as an intravenous formulation because of the lack of perceived commercial opportunity and excessive regulatory hurdles for approval. Peramivir is still in clinical development and is given intravenously, but will probably be ineffective against N1-containing viruses resistant to oseltamivir. Many influenza viruses, including the new H1N1 virus, are already resistant to the M2 inhibitors amantadine and rimantadine. So we have a single class of drugs—and most parts of the world have a single drug—and we have no information on combinations of drugs to treat the new virus. If the pharmaceutical industry is not willing to develop these drugs then perhaps governments need to carry the burden of development to protect their citizens. The need is too important to leave to market forces.

Our major concern about the current response to H1N1 has been the dearth of any systematic, prospective, patient-oriented clinical research alongside the commendable public health response to the pandemic. Almost no patients with H1N1 have been

PREVENTION OF SWINE-FLU

World Health Organisation (WHO) has appealed to people across the world to follow a few precautions

SWINE-FLU: Do's	SWINE-FLU: Don'ts
<ul style="list-style-type: none"> ✓ Wash your hands regularly ✓ Avoid crowded places ✓ Maintain at least one arm distance from people suffering with SWINE-FLU ✓ Get plenty of sleep ✓ Drink plenty of water and eat nutritious food 	<ul style="list-style-type: none"> ✗ Do not shake hands or hug while greeting ✗ Do not spit in public places ✗ Do not take medicines without consulting a physician

IF YOU ARE SICK, PLEASE...

1. Stay at home and limit contact with others as much as possible	3. Cover your mouth and nose while coughing / sneezing
2. Take adequate rest and drink plenty of fluids	4. Seek your medical advice, if needed
	5. For further assistance, call 104

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recruited into clinical descriptive studies and, to our knowledge, none have been enrolled into randomised controlled trials. No comprehensive data on disease pathogenesis and viral replication patterns have emerged to date, and no randomisation or prospective qualitative research was done in the early phase to establish the benefits of public health responses. To what extent any interventions work in this setting remains unclear. Anecdotal reports suggest more severe disease in obese individuals, infants, pregnant women, and patients with comorbidities than in other people.^{3,4} There is no solid evidence on how to treat these patients, and historically such individuals have been excluded from trials. We lack assessments of: combinations of antiviral drugs; drugs that target the immune cascade in severely ill patients; intensive care interventions; pharmacokinetic and pharmacodynamic parameters; and viral dynamics. Furthermore, drug resistance has not been systematically assessed.

Public health officials, virologists, epidemiologists, and policy makers have done well in responding to a rapidly emerging and complex problem. By contrast, the clinical research community's response has been delayed and modest. While efforts are quickly moving forward for immunogenicity studies of candidate H1N1 vaccines, there is a lack of information on the pathogenesis, clinical spectrum and course, and response to treatment for this viral infection, especially in people with severe illness. Has the clinical research community responded better to this pandemic in 2009 than in 1918, 1957, 1968, or 1977? For example, in 1968, and 1977 controlled studies of the then available antiviral drugs were done.⁵ Learning what has and has not worked, preferably by randomised trials of clinical care, should have been at the forefront and integrated into today's public health response. But patient-oriented clinical research has become so complex and cumbersome that rapid responses are very difficult. Furthermore, clinical research has been divorced from public health. We need to be much more proactive and energetic in clinical research with generic protocols in place, pre-crisis in-principle ethics approvals, support laboratories identified, and studies ready to go within days of an epidemic starting. The establishment before a crisis of linked clinical research centres that are committed to working together would help. But these would need to be flexible, free of unnecessary bureaucracy, and

adequately funded. All of this is standard practice in public health. A change in attitude to patient-oriented research is required by the clinical community, by funding organisations, scientific journals, and national and international agencies. We have got to work more closely with the public to ensure their support, to reintegrate clinical research with public health, and to ensure both are part of emergency planning and response. Open access, iteratively designed, wiki-style protocols, and case record forms agreed by experts that can be freely downloaded in any language could help and save researchers from having to start from scratch every time an emergency arose (such a template would also facilitate research in endemic diseases). Such forms were provided by WHO in August, 2007, for reporting of data on patients with H5N1 and could have been rapidly adapted for use in the current outbreak.⁶ We, the clinical research community, need to catch up with the example set by our colleagues in public health, virology, epidemiology, and modelling and facilitate crucial patient-oriented clinical research. To do otherwise would be unethical.

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