Tackling the next influenza pandemic [from BMJ 2004;328:1391]

"Ring" prophylaxis of close contacts with antivirals may be an effective strategy

Recent efforts have been directed towards preparing rapid effective responses to epidemics of smallpox and severe acute respiratory syndrome (SARS). We must now hasten the preparations for another inevitable threat—the next global influenza pandemic. Currently contingency plans are largely based on rapid vaccination of susceptible populations; other measures, such as treatment with antiviral drugs, serve only as adjuncts.[1] In practice, however, technical constraints on vaccine production—foremost among these the time required to initiate mass vaccine production during a pandemic—will limit the effectiveness of this measure in the first stages of the pandemic.[2] Recently a systematic review by Cooper et al addressed the effectiveness of neuraminidase inhibitors in the treatment and prevention of influenza.[3] The authors concluded that the prophylactic use of these drugs can lead to a reduction of 70-90% in the risk of laboratory confirmed symptomatic flu, depending on the strategy adopted and the population studied. Neuraminidase inhibitors have also shown efficacy in preventing transmission of influenza in institutions and community settings.[3,4] The availability of a highly effective supplement to vaccination opens to debate the appropriate role of neuraminidase inhibitors and other antiviral drugs in the control of pandemic influenza.

Some authors argue that mass use of prophylactic antiviral drugs to suppress a pandemic is not feasible.[5] When considering large scale, long term, continuous prophylactic treatment, some challenges may indeed prove too difficult to overcome. Inadequate compliance with prolonged daily treatment may decrease its effectiveness and may lead to the emergence of resistant viral strains. Insufficient supplies and limited manufacturing ability present further difficulties. Currently in the United States, for example, only several million persons could receive continuous antiviral chemoprophylaxis each month during a pandemic.[6] Stockpiling of antiviral drugs is therefore necessary, but the cost of stockpiling in such magnitude looks to be prohibitively expensive. These limitations necessitate a search for novel strategies to effectively employ antivirals on a smaller scale, as was stressed by the World Health Organization in its global agenda on influenza surveillance and control and by the US Centers for Disease Control and Prevention in its pandemic contingency plan.[6,7]

We suggest an alternative strategy, borrowed from the lexicon of smallpox containment, where it is known as ring vaccination. This strategy, routinely used in the past to quell smallpox outbreaks, entailed post-exposure vaccination of the close contacts of a case. For smallpox, this approach provided a wide safety net of prevention, while focusing vaccination where it was needed most. This approach may be applicable to the initial management of an influenza pandemic: in the absence of a strain specific vaccine during the first stages of the outbreak, treatment of influenza cases and their contacts may decrease attack rates substantially while rationing the pharmacological treatment to where it is needed most.

Influenza possesses epidemiological characteristics markedly different from those of smallpox, such as a shorter incubation period, a higher attack rate, and a lack of disease specific symptoms. Together, these characteristics may impose difficulties in accurately identifying and rapidly treating contacts. Still this policy in conjunction with a strict regimen of isolation and quarantine can be expected to slow down dissemination of the disease, providing valuable time for production and distribution of a vaccine. This goal may thus be achieved in a more frugal manner in terms of costs and logistics than was previously described. Antiviral ring prophylaxis, which proved to be effective in family settings, requires

only short term daily treatment for a period of 5-10 days,[8 9] and targets a relatively limited proportion of the population, thus substantially reducing the amount of drug to be stockpiled and dispensed rapidly. Furthermore, contacts receiving antiviral prophylaxis may form protective antibodies due to subclinical infection, rendering them immune for the duration of the pandemic.[10] Finally, a short treatment period will probably help to increase compliance and to reduce the risk of emerging drug resistance.

Cost seems be the limiting factor in any strategy employing widespread use of neuraminidase inhibitors or other antiviral drugs in the context of an influenza pandemic. However, the projected costs of a major influenza pandemic are estimated to be high in terms of morbidity, mortality, and spending on hospitalisation. The economic impact of such an event in the United States is estimated to be over $100bn (£56bn; €80bn).[11] This cost may be decreased, however, through the use of an appropriate containment strategy during the first stages of the pandemic, which would make this expenditure a worthwhile investment.[2]

Although this strategy seems to be worthy of investigation, several issues must be addressed before it is adopted in practice. Not enough is known about the extent of transmission through subclinical infections during pandemics, and the effect of such transmission on the overall effectiveness of the proposed strategy is difficult to estimate. Furthermore, chemoprophylaxis would require large proportions of the healthy asymptomatic population to comply with daily treatment, but compliance in such extreme circumstances is difficult to predict. Finally, chemoprophylaxis will not suffice as a sole preventive measure in the case of a pandemic but rather must be supported by additional measures such as quarantine, isolation, and prevention of mass congregations. Public acceptance of such measures is unknown but is probably culture dependent and was proved surprisingly feasible during the recent SARS epidemic.

Some theoretical aspects of the suggested strategy may be established by using appropriate mathematical modelling or by testing this strategy during local epidemics. The work on such models is already under way, and the outcomes of these models may serve to strengthen the hypothesis we raise here. We believe that the use of this relatively frugal strategy of epidemiologically directed chemoprophylaxis will prove both effective and cost beneficial in the defence against an emerging threat to global public health.

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