EVIDENCE BASED PUBLIC HEALTH POLICY AND PRACTICE

Influenza pandemic preparedness in France: modelling the impact of interventions

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J Epidemiol Community Health 2006;**60**:399–404. doi: 10.1136/jech.2005.034082

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Accepted 1 January 2006

Background: Influenza pandemics result in excess mortality and social disruption. To assist health authorities update the French pandemic plan, the authors estimated the number of health events (cases, hospitalisations, and deaths) in a pandemic and compared interventions in terms of impact and efficiency.
Method: A Monte Carlo simulation model, incorporating probability distributions of key variables, provided estimates of health events (HE) by age and risk group. Input variables were set after literature and expert consultation. The impact of targeted influenza vaccination and antiviral prophylaxis/treatment (oseltamivir) in high risk groups (elderly, chronic diseases), priority (essential professionals), and total populations was compared. Outcome measures were HE avoided, number of doses needed, and direct cost per HE avoided.
Results: Without intervention, an influenza pandemic could result in 14.9 million cases, 0.12 million deaths, and 0.6 million hospitalisations in France. Twenty four per cent of deaths and 40% of hospitalisations would be among high risk groups. With a 25% attack rate, 2000–86 000 deaths could be avoided, depending on population targeted and intervention. If available initially, vaccination of the total population is preferred. If not, for priority populations, seasonal prophylaxis seems the best strategy. For high risk groups, antiviral treatment, although less effective, seems more feasible and cost effective than prophylaxis (respectively 29% deaths avoided; 1800 doses/death avoided and 56% deaths avoided; 18 500 doses/death avoided) and should be chosen, especially if limited drug availability.
Conclusion: The results suggest a strong role for antivirals in an influenza pandemic. While this model can compare the impact of different intervention strategies, there remains uncertainty surrounding key variables.

Influenza pandemics, which occur three to four times each century, have a number of characteristics differentiating them from regular influenza epidemics. By definition a pandemic affects a large number of countries worldwide. A pandemic virus has usually not been previously encountered by the population and succeeds in causing a large number of cases and high associated mortality. The novelty of the virus also makes prevention and control measures difficult as existing vaccines are not effective and production of new vaccine can take four to six months.[1] Antiviral drugs will be the only virus specific intervention during the initial response. They have the advantage of conferring almost immediate protection and their use does not interfere with response to inactivated influenza vaccine.[2] It is well recognised that countries must prepare for the next pandemic[3] but uncertainty regarding the characteristics of the virus, the populations that will be most seriously affected, and the most appropriate interventions make preparation difficult.

The most important questions that health planners are asking are ''What are the most appropriate interventions during an influenza pandemic in terms of number of cases, hospitalisations and deaths prevented? What resources are needed and how much will the intervention cost?'' This work was undertaken, in the context of the preparation of the French pandemic preparedness plan, in an attempt to provide the Ministry of Health with some answers to these questions.

A number of countries have already attempted to estimate the burden of an influenza pandemic[4–8] and some have investigated the impact of interventions.[5–7] These studies used scenario analysis[5–7] or more sophisticated mathematical modelling[6] to investigate the epidemiological and economic impact of influenza vaccination,[6] antiviral treatment,[5 7] and antiviral prophylaxis.[5] Van Genugten *et al* suggest pneumococcal vaccination for risk groups and therapeutic treatment for all cases. Meltzer *et al*, who defined target groups for vaccination, concluded that the decision will depend on the criteria for prioritisation: high risk ⩾65 years are at highest risk of death but if interested in preventing the largest proportion of deaths or having the best returns to vaccination then the high risk 20–64 year olds should be vaccinated.[6]

Post-exposure antiviral prophylaxis has been suggested by Longini *et al* with the aim of limiting the transmission of the virus in the initial phase.[9] Despite the growing consensus that the prophylactic or therapeutic use of antiviral drugs will be essential in the public health management of a pandemic[10 11] there have been few attempts to investigate the impact of their use once the pandemic has taken hold (widespread human to human transmission). We created a mathematical model, specific to the French population structure, defined risk and priority populations and drug recommendations. This model permitted detailed exploration of the options for the use of antiviral drugs and influenza vaccination in three target populations. We focused on the comparison of interventions and in contrast with previous studies have introduced probability distributions for the key intervention parameter (effectiveness).

METHODS

A Monte Carlo simulation model, similar to that used by Meltzer,[6] was used to estimate the impact of interventions during an influenza pandemic. Probability distributions were assigned to uncertain intervention variables in the model and 10 000 simulations were used to generate probability distributions for output variables using the package S Plus. All outcomes were evaluated at the end of the hypothesised

Table 1 Input variables for model of pandemic influenza in France: population and proportion of cases, admissions to hospital, and deaths

	Total	0–19 years	20–64 years	⩾65 years
Population*	59.6 million	15.0 million	34.9 million	9.7 million
Number (%) at ''high risk''†	8.7 million (14.5%)	2.0 million (13.5%)	1.8 million (5%)	4.9 million (50%)
Number (%) to be prioritised for protection‡	3.64 million (6%)	0. 04 million (0.2%)	3.6 million (10%)	0 million (0%)
Clinical attack rate§	25%			
Distribution of cases¶	100%	40%	50%	10%
Lethality				
Standard risk		0.5%	0.75%	1.5%
High risk		1.0%	1.5%	2.0%
% of cases hospitalised				
Standard risk		2.0%	3.0%	5.0%
High risk		10.0%	12.5%	15.0%

*Total population of France metropole on 1 January 2003. Source: INSEE (provisional evaluation based on results of 1999 census). †Persons with medical or social characteristics rendering them at high risk of complications from influenza: 50% of those aged 65 years and over; all those <65 years of age with a long term illnesses listed in the French national vaccination recommendations 2003[13]: all those <65 years who live in an institution; pregnant women; infants <2 years of age. ‡Essential healthcare and public service personnel as defined in French pandemic preparedness plan.[12] §Nguyen 2003.[14] Clinical case is symptomatic case of influenza regardless of whether they consult a doctor or not. ¶Based on Meltzers[6] estimates using data from 1918, 1928–29, and 1957 epidemic and pandemics (distribution A: 0–19 40%, 20–64 53.1%, 65+6.8%).

pandemic and we did not attempt to model the impact of interventions over time.

The population of France metropole, estimated on 1 January 2003 to be 59.6 million (INSEE, 1999 census), was divided into three age groups (0–19 years, 20–64 years, and ⩾65 years). We further divided each age group into those at high risk and average risk of complications after influenza infection (table 1). All analysis was carried out stratified by these six age risk groups and outcomes summed for presentation purposes. The French pandemic preparedness plan proposes to prioritise for protection personnel working in the following sectors: health (1.3 million), security and emergency (600 000), essential public services (45 000), transport and communications (1.2 million), and industry (500 000).[12 16]

Key input variables for pandemic situation were set after a review of the data on previous pandemics, in particular the 1918–19 pandemic,[14 15] and discussion with clinicians, virologists, and epidemiologists sitting on the National Influenza Pandemic Preparedness Committee. The clinical attack rate was fixed at 25%, the proportion hospitalised between 2% and 15% of cases and case fatality between 0.5% and 2% depending on age and risk group (table 1). The distribution of cases in the different age groups was estimated based on previous pandemics (table 1). These pandemic parameters were varied in previous work[16] but for ease of interpretation of this model we only introduced probability distributions for specific intervention input parameters. We hypothesised that the pandemic would have two waves, each lasting 10 weeks.

Consultation with experts led to the selection of specific medical interventions that could be considered in the context of French pandemic planning (table 2). Vaccination with a vaccine specific to the pandemic strain and therapeutic treatment with the neuraminidase inhibitor oseltamivir were considered for all populations. Prophylactic treatment with oseltamivir was not considered feasible for the whole population. For the population ''at risk'' post-exposition prophylaxis would be feasible if this population also reduced movement outside of their households. A reduction in mobility seems feasible for this population and could reduce the number of times that this population is exposed to a case. We considered three episodes of exposure to a case per wave for this population. The essential healthcare and service workers that are to be prioritised for protection are likely to be exposed throughout the pandemic and so seasonal prophylaxis (treatment with oseltamivir throughout the pandemic) was selected.

The treatment/vaccination coverage and compliance were set at 100% for the target age groups. For each intervention a target population(s) was specified and a range of values for the effectiveness of each intervention was defined based on a literature review[5 17–24] and consultation with experts (table 3). Post-exposition prophylaxis was considered to have a lower effectiveness because of the probable delay between exposure and start of treatment.

The main outcome variable was proportion of health events (cases, hospitalisations, deaths) avoided for each intervention. This measure of efficacy is calculated using two different denominators (a) the events expected in the

Table 2 Interventions to be considered during an influenza pandemic in France

	Influenza vaccination	Therapeutic treatment with oseltamivir	Prophylactic treatment with oseltamivir
Target age group*	⩾6 months	⩾1 year	⩾5 years
Number of doses per person	2 doses	10 doses†	7 doses‡
Cost per dose§	6 euros	1 euro	1 euro
''At risk'' population	Yes	Yes	Post-exposition (6 treatments)¶
Priority population	Yes	Yes	Seasonal prophylaxis (20 weeks)¶
Total population	Yes	Yes	No

*French national recommendations for use during influenza pandemic. †Four doses for those aged 1–3 years, six doses for 4–6 year olds, eight doses for 7–12 year olds, 10 doses (two doses/day for five days) for over 12 years old. ‡Post-exposition prophylaxis consists of four doses for those aged 5–6 years, six doses for 7–12 year olds, seven doses (one dose/day for sevendays) for those over 12 years. Seasonal prophylaxis consists of one dose/day for 20 weeks. §French Ministry of Health. ¶Pandemic hypothesised to have two waves, each lasting 10 weeks. At risk population to be exposed to a case three times during each wave of the pandemic.

Table 3 Input variables for model of pandemic influenza in France: effectiveness of selected interventions to prevent cases, admissions to hospital, and deaths

Intervention		Probability distribution	Effectiveness* (lower limit, ''most probable'', upper limit)		
			Case	Hospitalisation	Death
Oseltamivir	Seasonal prophylaxis	Triangular	0.60, 0.70, 0.80	0.70, 0.75, 0.85	0.75, 0.80, 0.90
	Post-exposition prophylaxis	Triangular	0.50, 0.60, 0.70	0.60, 0.65, 0.75	0.65, 0.70, 0.80
	Therapeutic treatment	Uniform	NA	0.25, 0.30	0.30, 0.35
Vaccination with vaccine specific to pandemic virus	0-19 years	Triangular	0.40, 0.60, 0.80	0.50, 0.70, 0.85	0.60, 0.80, 0.90
	20-64 years	Triangular	0.40, 0.55, 0.75	0.50, 0.65, 0.80	0.60, 0.75, 0.85
	⩾65 years	Triangular	0.40, 0.45, 0.60	0.45, 0.55, 0.70	0.60, 0.70, 0.80

*Effectiveness is defined as the reduction in the number of cases and values are based on a literature review[5 17–24] and consultation with experts. For uniform distribution the lower limit and upper limit values are provided.

population of intervention and (b) the events expected in the total population.

The number and cost of doses of drug/vaccine required for each intervention was also calculated. Finally, as a measure of efficiency, we calculated the number of doses and cost per death and hospitalisation avoided.

RESULTS

In France, with an attack rate of 25%, 15 million cases, 593 000 hospitalisations and 119 000 deaths can occur.

About 28% of deaths would occur in those less than 20 years, 50% in 20–64 year olds, and 22% in those ⩾65 years (table 4). Twenty four per cent of the deaths and 40% of the hospitalisations would be among those at high risk of complications. Half of these ''high risk'' deaths and hospitalisations would be among those ⩾65 years.

The proportion of total cases that can be avoided ranges from 3% to 57% depending on the target population and intervention chosen (table 5). Similarly the proportion of total hospitalisations and deaths that can be avoided range from 1% to 62% and 2% to 73% respectively. The direct cost of each avoided health event varies greatly. Although a dose of influenza vaccine would cost 6 euros, six times as expensive as a dose of oseltamivir, prophylaxis with oseltamivir, requiring a large number of doses, has the highest cost/health event avoided (table 5).

In the total population influenza vaccination prevents, on average, 368 500 hospitalisations and 86 000 deaths, about 2.5 times as many as therapeutic treatment with oseltamivir (table 5). However, the direct cost of preventing a death by vaccination is twice as high (8500 compared with 3500 euros).

Influenza vaccination is also the most effective intervention in the population ''at risk'', with 68% of deaths in this target group prevented. Prophylaxis with oseltamivir can prevent 56% of deaths and its overall impact in terms of the number of health events avoided in the total population is comparable to that of influenza vaccination. The cost per death avoided with oseltamivir prophylaxis is almost four times higher than that for influenza vaccination. Therapeutic use of oseltamivir prevents less than 30% of deaths in the population ''at risk'' but the cost per death avoided is 10 times lower than that for prophylaxis (1800 compared with 18 500 euros).

Seasonal prophylaxis with oseltamivir of the priority population could prevent slightly more health events than influenza vaccination but will be 10 times as expensive. Therapeutic use of oseltamivir in this target group, although the most efficient of all the interventions, has a very low effectiveness with only 8500 (1%) hospitalisations and 2000 (2%) of deaths prevented

DISCUSSION

Future influenza pandemics are likely to cause large numbers of hospitalisations and deaths in France. If an effective vaccine is available before a pandemic reaches France then the results confirm that the best option is to give the vaccine to the general population. The effectiveness of vaccination seems to be similar to that of the prophylactic use of the antiviral, oseltamivir, but has the advantages of being more efficient, more feasible, suitable for young children, does not rely on adherence, and confers longlasting immunity. If there is a limited supply of vaccine then vaccination will be targeted at priority or ''at risk'' populations. In the most probable scenario, the vaccine will not be available in time and this is where our comparison of the use of antiviral drugs will be important to consider.

For the priority population, post-exposure prophylaxis was not considered feasible because this population will not be able to limit their contact with the general population and are likely to be exposed continuously during the course of the pandemic. Seasonal prophylaxis was found to be twice as effective as treatment but with a cost per event avoided that was 25 greater. If sufficient antivirals are available then

Table 4 Health outcomes per age group and risk category, modelled influenza pandemic with 25% attack rate, France

Age group	Risk category	Hospitalisations		Deaths	
		Number*	%	Number*	%
0–19 years	High risk	81000	13.6	8000	6.8
	Standard risk	103000	17.4	26000	21.7
20–64 years	High risk	48000	8.1	6000	4.8
	Standard risk	212000	35.8	53000	44.7
⩾65 years	High risk	112000	18.8	15000	12.6
	Standard risk	37000	6.3	11000	9.4
All ages	High risk	241000	40.5	29000	24.2
	Standard risk	352000	59.5	90000	75.8
	Total	593000	100	119000	100

*Numbers rounded to the nearest 1000.

Table 5 Impact of different interventions during modelled influenza pandemic in France: health events (HE: case, death, hospitalisation) avoided and efficiency (number of doses and cost of intervention) for interventions in total population and two target populations

		Health events prevented			
		Number	% (number/target population)	% (number/total population)	Cost/HE avoided
		Mean	Mean % (5th, 95th centiles)	Mean %	Mean
Total population					
Oseltamivir—therapeutic					
131.6 million doses (1 €/dose)	Hospitalisation	155000	26 (24, 28)	26	850
	Death	38 000	32 (29, 34)	32	3500
Influenza vaccination					
119.2 million doses (6 €/dose)	Case	8440000	57 (49, 65)	57	85
	Hospitalisation	368500	62 (56, 68)	62	2000
	Death	86000	73 (67, 78)	73	8500
Population ''at risk''	**(represent 13% of all expected cases, 41% of hospitalisations, and 24% of deaths)**				
Oseltamivir—post-exposition prophylaxis					
295.3 million doses (1 €/dose)	Case	779000	40 (36, 45)	5	400
	Hospitalisation	118000	49 (45, 53)	20	2500
	Death	16000	56 (52, 61)	14	18500
Oseltamivir—therapeutic					
15.2 million dose (1 €/dose)	Hospitalisation	58000	24 (22, 26)	10	250
	Death	8500	29 (27, 31)	7	1800
Influenza vaccination					
17.4 million doses (6 €/dose)	Case	968000	50 (44, 56)	6	100
	Hospitalisation	139500	58 (52, 63)	24	750
	Death	19500	68 (64, 73)	16	5500
Priority population	**(expected to represent 5% of all cases, hospitalisations and deaths)**				
Oseltamivir- seasonal prophylaxis					
510.3 million doses (1 €/dose)	Case	550000	70 (63, 77)	4	900
	Hospitalisation	23500	76 (71, 82)	4	21500
	Death	5000	83 (77, 88)	4	96000
Oseltamivir- therapeutic					
7.85 million doses (1€/dose)	Hospitalisation	8500	27 (25, 30)	1	900
	Death	2000	31 (30, 34)	2	3900
Influenza vaccination					
7.3 million doses (6 €/dose))	Case	446000	57 (45, 69)	3	100
	Hospitalisation	20000	65 (54, 75)	3	2200
	Death	5000	73 (63, 82)	4	9300

seasonal prophylaxis of priority groups is to be recommended. It is uncertain, however, as to whether the high levels of adherence required could be achieved and maintained throughout the pandemic. For the ''at risk'' population, post-exposure prophylaxis was twice as effective as therapeutic treatment but cost 10 times more for each event avoided. Limited stocks of antivirals and difficulty in defining exposure in groups ''at risk'' may result in therapeutic treatment being chosen for this population. This will also be the only option for those aged 1–4 years. In the event of limited stocks of antivirals a balance will need to be found between the need to protect priority groups, an intervention with low epidemiological impact but high social desirability, and treatment of the groups at highest risk of complications. It is sobering to note that in the absence of a vaccine our model predicts that none of the strategies considered will avoid more than 32% of the total expected deaths.

What this paper adds

- Individual countries are drawing up influenza pandemic preparedness plans to help to minimise morbidity, mortality, and disruption during the next pandemic.
- A vaccine specific to the pandemic strain would be the best preventative intervention but it is unlikely that such a vaccine will be available at the beginning of the pandemic.
- The prophylactic and therapeutic use of antiviral drugs is also being considered but the relative benefits of each approach have not been explored in detail.
- This study modelled the impact (effectiveness and efficiency) of vaccination, antiviral treatment, and prophylaxis during an influenza pandemic in France.
- Once a pandemic is established in France, therapeutic use of antiviral drugs for the subpopulation at higher risk of complications and, if the stockpile is large enough, prophylactic use for the subpopulation of essential workers is recommended.

Policy implications

- Our findings were useful to the French Ministry of Health for decisions regarding the antiviral strategies to adopt and the amount of antiviral drugs to order.
- The control strategies within the pandemic plan were adjusted, taking into account the limited availability of these drugs and the theoretical needs as estimated by our simulations.
- The French Influenza Pandemic Preparedness plan is available at: http://www.sante.gouv.fr/htm/dossiers/grippe_pandemie/sommaire.htm (in French language only).

In parallel with previous studies, we made some strong assumptions about the characteristics of the next pandemic (attack rates and proportion of health outcomes). Extensive sensitivity analyses carried by van Genugten *et al* showed that varying the age specific attack rates, for a given value of the gross attack rate, does not lead to a big difference in the proportion of deaths and hospitalisations that can be avoided by each intervention.[25] However, studies have also shown results to be sensitive to changes in the gross attack rate and in the complication rates for each age/risk group.[6 7 26] We used the most probable figure for the clinical attack rate, based on previous pandemics. Some authors have chosen to extrapolate hospitalisation and death rates during a regular epidemic.[7] We based our rates on those reported in previous pandemics. It is probable that medical advances, especially in the field of antibiotic therapy will result in lower rates of deaths and hospitalisations attributable to bacterial complications. On the other hand, the aging of the population and the higher prevalence of immunocompromised persons may lead to an increase in the number of complications. In addition, although possibly biased towards identification of the most severe cases, the data available to date regarding the case fatality rate of recent human cases of H5N1 infections in Asia are not reassuring.[1] Our worst case scenario may have led to an overestimation of the number of health outcomes but this should not affect the comparison of the interventions.

One concern is that the burden of disease in each subpopulation may not have been appropriately assigned. Meltzer's model suggests that 84% of all deaths will be among patients at high risk. The lower proportion in our model (24%) can be explained by different definitions of ''at risk'' groups and the 10-fold difference in death rates between the risk groups in Meltzers model compared with a twofold difference in our model. It is precisely the distribution of complications that is impossible to predict as it will depend on susceptibility of each subpopulation.

More important to our analysis is variation in the intervention input variables of vaccine and treatment effectiveness. We used a slightly lower value for oseltamivir therapeutic treatment effectiveness than other studies as we considered it unlikely that all cases would receive treatment within 48 hours of symptoms.[7] All values for vaccine and oseltamivir efficacy are based on studies carried out inter-pandemic and it is unclear if they will be as effective with a pandemic strain

Our model, similar to models previously published, is static and we considered this the biggest constraint in our work. The creation of a dynamic model, however, based on current lack of knowledge of the characteristics of the next pandemic would be difficult and require many more assumptions to be made. It is certain that transmission of a pandemic virus will be efficient but how efficient and how quickly will it spread? The impact of non-medical interventions (prevention of public gatherings, closure of schools, quarantine of cases, wearing of masks, etc) is unknown and their simultaneous implementation may have an impact on the effectiveness of the interventions that we have considered here. The real number of contacts with those infected is unclear and the number and dynamics of the different waves of the pandemic unknown.

Our results will help in deciding on the most appropriate interventions but the ultimate decisions will require a pragmatic approach based on the dynamic of the epidemic and resources available. Despite the greater epidemiological impact of treatment of the ''at risk'' population it will be difficult to deny essential workers access to antiviral drugs when they have been asked to be exposed by carrying out essential duties. Those at highest risk of complications may be asked to limit their movements to avoid exposure and maximise the use of limited drug supplies. Recent evidence of the emergence of resistance to oseltamivir is a concern[27] and will have to be taken into account, if this becomes a significant problem.

Our findings were useful to the Ministry of Health for decisions regarding the antiviral strategies to adopt and the amount of antiviral drugs to order. The control strategies within the pandemic plan were adjusted, taking into account the limited availability of these drugs when compared with the theoretical needs as estimated by our simulations. Ideally, information on the epidemiological characteristics of the influenza pandemic would become available before a pandemic strain of influenza is identified in France allowing us to refine our model and make a more informed decision on the most appropriate interventions. If we take into consideration the speed and frequency of travel between countries, with SARS as an example, little time is likely to be given to us and it is imperative that adequate policies and programmes are put in place now. Nevertheless, as the pandemic progresses we will be able to adjust our definition of the ''at risk'' population. From a decision makers point of view, this model is useful as it shows the relative effectiveness and efficiency of different intervention options and enables decisions to be made on stockpiling of resources. These findings will be of interest to other countries currently revising their pandemic plans. However, it is important to note that any differences in the age distribution or the size of the various subpopulations will have an impact on resource requirements. That said, it seems unlikely, at least in developed countries, that the relative benefits of each intervention would be substantially modified. Our ability to limit the impact of the next pandemic will ultimately depend on availability and effectiveness of antivirals and the time taken to produce a vaccine relative to the speed of diffusion of the virus.

ACKNOWLEDGEMENTS

We thank Martin Meltzer (US), the Robert Koch Institute (Germany) and RIVM (Netherlands) who shared their models with us. Thanks also to the European Programme for Intervention Epidemiology Training (EPIET) for their support and the EPIET coordinators for their helpful comments.

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Funding: none.

Competing interests: none declared.

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