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Prevention and control of emerging infections: a challenge for the 3rd millennium

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SUMMARY

In the last 30 years, several emerging infections due to novel viruses have been identified, from haemorrhagic fever viruses to HIV, from the SARS-Coronavirus to Avian influenza viruses. Ecological and genetic changes are important determinants of the emergence of new viral infections, driving to an increase of R0 (the basic reproductive number) through increasing the probability of transmission. The current H5N1 epidemic may be considered a pre-pandemic paradigm that needs thorough investigation.

KEY WORDS: Emerging infections, Pandemic threat, Avian influenza

In the last 30 years, several emerging infections due to novel viruses have been identified, from Ebola/Marburg haemorrhagic fever to the human immunodeficiency virus (HIV), to the severe acute respiratory syndrome (SARS)-related Coronavirus, to avian influenza viruses. Moreover, changes in the ecosystem and technological advancement have favoured both the re-emergence of viruses bacteria, and the detection of previously unidentified agents. Improving knowledge on mechanisms of pathogens emergence and on early identification of initial chains of transmission is important to implement appropriate interventions.

HOW DO NOVEL VIRUSES EMERGE?

The successful emergence of a pathogen in a new host requires that the average number of secondary infections arising from one infected individual in a completely susceptible population exceeds one. This "number" is defined as the "basic reproductive number" or "R_0".

When the R_0 of a new virus is above one, an epidemic may start (i.e., an avian influenza virus "humanised" after reassortment). When R_0 is initially less than one, infection will inevitably die out and there will be no epidemic., unless ecological or genetic changes drive R_0 above one (i.e., non reassortant avian virus "waiting for" humanisation). There are a number of ways in which R_0 may increase:

1) Ecological changes (i.e., changes in host density or behaviour);
2) Genetic changes (i.e., adaptive evolution).

Ecological changes are mainly represented by changes in host density or behaviour that may lead to increased opportunity of interhuman contact with consequent amplification of viral circulation. Genetic changes, such as adaptive mutations or recombination or rearrangement (as in the case of influenza viruses) are even more important in our perspective, since they may drive to an increase of R_0 through increasing the probability of infection transmission (Antia *et al.,* 2003). Introductions of a novel virus from a reservoir may occur stochastically and are followed by probabilistic chains of transmission in the

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human population. For example, after rearrangement, a new influenza virus with R_0 >1 may be introduced and spread in the human population. However, infections with the introduced strain may have a basic reproductive number less than one (R_0 <1); in this case, after a short chain of transmission or no interhuman transmission at all, if the virus has no chance evolve R_0 remains below one thus leading to extinction of the infection. If the virus evolves during the stochastic chains of transmissions, pathogen evolution may generate an evolved strain with R_0 >1 through adaptive mutations. The infection caused by the evolved strain can go on to cause an epidemic.

AVIAN INFLUENZA H5N1 VIRUS AS A POTENTIAL PANDEMIC AGENT: A PRE-PANDEMIC PARADIGM?

The avian influenza virus H5N1 is now considered the most threatening emerging agent in terms of epidemic potential. Yet we do not know whether there will be a new pandemic although this is a very likely scenario, when it will occur, whether it will be due to H5, and whether it will be very aggressive. What we do know is that to have a new pandemic we do need a pandemic virus, but so far H5N1 is (still) not efficiently transmitted and is causing only sporadic cases of disease. The trend of new cases of H5N1 disease in humans is shown in Table 1. There is not a clear increase in all the affected countries. The main remarks are:

i) peaks during the winter season, whose determinants are different from those of seasonal flu, and
ii) a turnover in the most affected countries. Furthermore, the worldwide distribution of human cases, most of whom are reported in south-east Asia (i.e., Vietnam, Indonesia, China) and in the middle east (i.e., Egypt) emphasizes that H5 is behaving as a poverty-related disease, which affects countries with a subsistence economy based on domestic poultry breeding.

Although limited information is still available, seroprevalence studies show low prevalence of

TABLE 1 - *Cumulative number of confirmed human cases of avian influenza A/(H5N1) reported to WHO (15 June 2007).*

Country	*2003*	*2004*	*2005*	*2006*	*2007*	*Total*
Azerbaijan	0		0	8	0	8
Cambodia	0	0	4	2	1	7
China	1	0	8	13	3	25
Djibouti	0	0	0	1	0	1
Egypt	0	0	0	18	18	36
Indonesia	0	0	20	55	25	100
Iraq	0	0	0	3	0	3
Laos	0	0	0	0	2	2
Nigeria	0	0	0	0	1	1
Thailand	0	17	5	3	0	25
Turkey	0	0	0	12	0	12
Viet Nam	3	29	61	0	0	93
Total	4	46	98	115	50	313

anti-H5 antibodies, suggesting that asymptomatic infection may occur but seems to be a relatively rare event. Prevalence rates range from 0 and 0.7% among health care workers and neighbours of an index case up to 2 to 3.7% among exposed health care workers, thus remaining below 1% among non-exposed individuals (Saw *et al.,* 1998; Liem *et al.,* 2004; Vong *et al.,* 2006; Buxton Bridges *et al.,* 2000).
The heterogeneity in the results of different studies may be explained, at least in part, by the characteristics of the serological tests (i.e., low specificity?). In summary, it can be affirmed that human-to-human transmission may occur but appears to be rare. However, a cluster of human cases has been reported in North Sumatra, Indonesia, where at least 2 generations of secondary cases occurred in an enlarged family. Five or 6 cases were generated by the index case, and another family member was infected through close contact with a secondary case (Anonymous).
Thus, it can be assumed that we are in a situation where short chains of transmission may eventually occur but no major mutants capable to be efficiently transmitted from human-to-human have been generated yet. Whether it will occur in the near future is unpredictable.

CONTAINMENT AND MITIGATION OF AN EPIDEMIC

Let us now design a scenario where an animal virus has evolved into a humanised virus capable to be efficiently transmitted between human beings. If this occur, is it possible to contain an initial outbreak?
There are several interventions that may be implemented to contain an initial outbreak, such as isolation or quarantine, the use of antiviral drugs, pre-vaccination with a low efficacy vaccine.
Results of mathematical models suggest that, to put an outbreak under control, the R_0 of the infection should be no higher than 1.8 when using antiviral drugs in combination with quarantine, and lower than 2.4 combining antivirals and quarantine with pre-vaccination (i.e., a low efficacy vaccine) (Longini *et al.,* 2005; Ferguson *et al.,* 2005).

TABLE 2 - *Influenza vs SARS*

R_0	*2-3 vs 2-4*
Incubation time	2 vs 5 days
Serial interval between disease onset in two consecutive cases	2 vs 8-10 days
Peak of viral shedding	1-3 vs >7 days

Again, when we consider the population effect of antiviral drugs, we have to rely on assumptions, since we do not have any evidence of the efficacy of these drugs against a potential pandemic virus (i.e., a humanised form of H5) and have to consider possible determinants of effect modification, such as the rate of acquisition of drug resistance.
The effect of quarantine is also difficult to predict. In fact, we know that quarantine has been extremely successful against SARS, but also that influenza behaves in a different way. As shown in Table 2, although R_0 of influenza and SARS appears not to greatly differ, other parameters as the incubation time, the serial interval between cases, and the virus excretion peak, are much more faster for influenza than for SARS. This makes quarantine likely to be less efficient for influenza than it was for SARS (Lipsitch *et al.,* 2003; Riley *et al.,* 2003; Rezza, 2004).
If the initial outbreak is not contained, it may be important to slower the course of the epidemic to prepare and implement possible control measures. This is what we call mitigation of the epidemic. Recent models applied to a virtual epidemic suggest that the higher the number of interventions (i.e., isolation and quarantine, increased social distance, chemoprophylaxis, and pre-vaccination) the higher the number of spared cases of disease (Wu *et al.,* 2006).
Containing, mitigating, and slowing down the progression of an influenza pandemic is of paramount importance. Firstly, because morbidity and mortality can be reduced, and secondly because the window of opportunity for more efficient interventions, such as vaccination, may be expanded. In this regard, we learnt from past experience that the Asian influenza virus took less than six months to spread from its initial focus in China to the rest of the world. In fact, without intervention, influenza may spread very rap-

idly, and even travel restriction may not be very efficient to in slowing down the epidemic.
In conclusion, it is expected that novel agents may emerge and possibly cause life-threatening pandemics. Thus, it is essential to strengthen communicable disease surveillance in order to implement prevention and control activities.

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