Perspectives

EUROPE'S INITIAL EXPERIENCE WITH PANDEMIC (H1N1) 2009 - MITIGATION AND DELAYING POLICIES AND PRACTICES

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Europe has experienced more than two months of the first transmissions and outbreak of the 2009 pandemic of A(H1N1)v. This article summarises some of the experience to date and looks towards the expected autumn increases of influenza activity that will affect every country. To date the distribution of transmission has been highly heterogenous between and within countries, with one country the United Kingdom (UK) experiencing the most cases and the highest transmission rates. Most infections are mild but there are steadily increasing numbers of people needing hospital care and more deaths are being reported. An initial difference in practice between Europe and North America was over case-finding and treatment with some authorities in Europe using active case-finding, contact tracing and treatment/prophylaxis with antivirals to try and delay transmission. This article details the history of this practice in the past two months and explains how and why countries are moving to mitigation, especially treating with antivirals those at higher risk of experiencing severe disease.

The current situation in the United States and Europe

In the three months since its first recognition the pandemic strain of influenza A(H1N1)v virus has spread to all six continents [1]. So many people are being infected that the World Health Organization (WHO) considers counting cases of little value in the more affected countries and hence it has advised to stop testing and reporting individual cases and to move on to other surveillance strategies [2]. In the temperate areas of the southern hemisphere, where it is winter, the first pandemic wave is in progress. In the northern hemisphere most countries are in the initiation phase (Figure).

The United States Centers for Disease Control and Prevention (CDC) broadly estimates that at least a million people have been infected with the pandemic virus in the United States, a large figure, but representing only 0.3% of the US population compared to the 20-30% that is anticipated to be affected in the first wave in the winter season [3]. The picture is also heterogeneous geographically as is often the case with both seasonal and pandemic influenza. Up to 7% of the population may have been infected in New York city in May, while other places are reporting only a few infections [4,5]. CDC expects the virus to keep spreading in the US through the summer and then transmission to accelerate in the autumn [6].

In the European Union all countries have now reported cases and the picture is even more heterogeneous than in the US [1]. Two countries, Spain and the UK account for more than four fifths

of the reported cases and France and Germany have recently also reported significant numbers [1,7]. Hospitalisations and deaths are mounting up and the most affected country (UK) has revised its planning assumptions for a major first wave in the light of its particular experience (Table 1) [8].

Reported case numbers will become increasingly meaningless as countries abandon trying to test all cases and stop being able to count cases. However the initial analyses give important information. Initially case reports in Europe were dominated by imported (travel-related) cases [9]. These now represent ever decreasing proportions. In the latest cumulative analysis they accounted for only 13% (1,946 of 14,146) reported cases and the countries that have reported substantial numbers have all observed a strong trend of predominating domestically-acquired infections [7].

The most affected country is the UK and its experience gives useful indications of what is to come. Again the picture is one of heterogeneity with some parts of the UK experiencing intense transmission indicating the start of an acceleration phase with numbers of primary care consultations several times higher than

FIGURE

Idealised national curve for planning, Europe 2009 (reality is never so smooth and simple)

Single-wave profile showing the proportion of new clinical cases, consultations, hospitalisations or deaths by week. Based on influenza pandemic in London in 1918, second wave.

those experienced at the peak of last winter (when seasonal influenza was the worst in some years) [10]. However other parts are relatively unaffected [10]. The most recent numbers (as of 23 July) are available at the website of the Health Protection Agency: http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1247816558780?p=1231252394302

Overall the modelled estimated rate of new infections for the week of 23 July of 0.2% (100,000 in the week) in the UK is still somewhat down the acceleration phase but according to the UK's planning assumptions it might be expected to peak at about 6.5% or around 800,000 clinical infections per week (Table 1) [8].

Severity of the disease and risk groups

It remains the case that most people who are infected in Europe experience a mild illness that does not require treatment. However this in itself is making surveillance more difficult since most people will not need to seek medical attention when infected [11]. For example in a New York city survey very few of the people reporting illness thought it was sufficiently serious to seek medical care (I Weisfuse, personal communication). Certainly many cases are also not coming to the attention of surveillance in Europe.

TABLE 1

United Kingdom revised planning assumptions for the pandemic – first wave A(H1N1) 2009

Clinical attack rate	30%
Peak clinical attack rate	6.5% (local planning assumption 4.5% to 8%) per week
Complication rate	15% of clinical cases
Hospitalisation rate	2% of clinical cases
Case fatality rate	0.1–0.35% of clinical cases
Peak absence rate	12% of workforce

Source: United Kingdom Department of Health: http://www.dh.gov.uk/en/Publicationsandstatistics/publications/PublicationsPolicyAndGuidance/DH_102892

TABLE 2

Risk groups for the pandemic (H1N1) 2009

The following groups are considered more at risk of experiencing severe disease than the general population should they become infected with the pandemic A(H1N1)v virus 2009:

People with chronic conditions in the following categories:

- chronic respiratory diseases;
- chronic cardiovascular diseases (though not isolated mild hypertension);
- chronic metabolic disorders (notably diabetes);
- chronic renal and hepatic diseases;
- persons with deficient immunity (congenital or acquired);
- chronic neurological or neuromuscular conditions; and
- any other condition that impairs a person's immunity or prejudices their respiratory (breathing) function, including severe or morbid obesity.

Note: These categories will be subject to amendment and development as more data become available. These are very similar underlying conditions that serve as risk factors for seasonal influenza. What is especially different from seasonal influenza is that the older age groups (over the age of 60 years) without underlying conditions are relatively unaffected by the pandemic strain.

Pregnant women

Young children (especially those under two years)

Crucial information is being published on the *higher risk groups* (those who are more likely to experience severe disease). The conclusions are still preliminary but the initial data from North America and Europe on who is affected by severe symptoms indicate risk groups similar to those for seasonal influenza, though with some important differences, notably the relative absence of cases in older people [12] (Table 2).

Expectations for the autumn in Europe

The European Centre for Disease Prevention and Control (ECDC) expects that in autumn European countries will experience a major first wave well beyond anything that has been experienced to date in this pandemic (Figure) [11]. However it is not possible to predict exactly what percentage of the population will be infected in the autumn wave and when it will come for individual countries. It is unlikely to occur at once and there will be heterogeneity within countries. Even if the experience of the UK is that the first acceleration phase of the pandemic truncates in the summer (perhaps as schools close), ECDC considers it important to prepare for an earlier start in autumn than the time when seasonal influenza usually takes off. Based on the initial surveillance results the UK has revised its planning assumptions for up to 30% of the population to be affected in the first wave [8] (Note: It is important here to distinguish between planning assumptions and predictions. Planning assumptions represent the reasonable worst case scenario for a first major pandemic wave).

Hence Europe should be prepared to experience a very large number of cases in the coming months with inevitable strain on the health services because of a proportion of cases requiring primary or secondary care [11,13–15] (Table 1). A new approach to surveillance, building on what is already there will be needed and that is being developed by ECDC with Member States and WHO.

Initial differences in practises between North America and Europe

An area of differing practice or even policy between countries has been how to manage the initial cases and transmissions of influenza A(H1N1)v virus. In North America the approach from the start was of mitigation, essentially following WHO's early advice (Table 3) [16]. This includes applying standard guidance on the management of influenza cases and outbreaks similar to those for seasonal influenza, not treating the majority of cases who experience a mild self-limiting illness but offering antivirals to those who are considered at higher risk of experiencing severe disease [17,18]. Prophylaxis is being reserved for these groups when they are thought to have been exposed.

In Europe the initial approach was different from North America with some countries starting by attempting *containment* (trying to stop influenza spread beyond initial outbreaks) with energetic case-finding, treatment, contact-tracing and chemoprophylaxis of contacts (Table 3). Cases were isolated in hospital and quarantine was practised. A country that typified this approach was the UK which practised active finding and treatment of cases and contacts in schools and families, although not isolation in hospital or quarantine [19]. Though the word containment was used this was better described as *delaying* (Table 3). Despite great efforts in May and June daily reports of new laboratory confirmed cases rose to over 500 a day in late June. Hence, the UK found it difficult to sustain the intensive case-finding and contact-tracing strategy and on 2 July announced it was moving to a mitigation strategy which it called a *treatment* approach [20]. The principle is to make

antivirals available for all, but focusing especially on the early treatment of those in risk groups and to limit the use of prophylaxis to protect those at higher risk of severe disease [20]. Some other European countries have also treated all cases and contacts [21] but as their numbers of detected cases are small they were initially able to manage this more readily.

The question therefore was which practise should all European countries follow when they are inevitably affected, either over the summer or sometime in the autumn? Following a request from EU member states for guidance, in June ECDC published the arguments for and against these approaches, which this article will now summarise [22,23].

WHO's position on containment

When announcing pandemic phase 4, WHO indicated that the epidemic had already started to spread beyond a level justifying attempts at containment and a mitigation approach was recommended [16]. Two days later, on 29 April, WHO escalated to phase 5 and then on 11 June to phase 6. According to WHO guidance, under phases 5 and 6, measures differ between affected and not yet affected countries but containment attempts are no longer recommended, the guidance advises member states to implement a mitigation strategy, including considering measures for reducing the spread of infection [16,24]. This includes applying standard guidance on the management of influenza cases and outbreaks similar to those for seasonal influenza (Table 3). This

entails not treating the majority of cases who experience a mild self-limiting illness but offering antivirals to those who are considered at higher risk of experiencing severe disease [16-18]. Neither ECDC nor WHO recommend the use of the word 'containment' for influenza outside of the theoretical context of place and time where a pandemic strain first emerges somewhere in the world [25]. Previous modelling work has suggested that containment will be both impractical and unsuccessful once there is extensive community transmission and certainly once the pandemic has entered its acceleration phase [26]. Apart from some very isolated settings, history dictates that European communities will not be able to contain the pandemic strain or isolate themselves from it [27].

The experience with delaying and containment

The 'delaying' strategy was certainly legitimate to attempt, especially in the EU where the initiation phase started at the very end of the seasonal influenza period when influenza transmission would be expected to be low. The delaying strategy is therefore appealing when a pandemic starts in the spring or early summer. The rationale is that an aggressive approach could decrease the effective reproduction number (R) and delay the inevitable acceleration of the pandemic until autumn allowing more time for preparations and for vaccines to be developed and licensed. Besides, identifying the first cases and documenting their clinical presentation has proven to be important at the early stages of a pandemic to gather information needed for the *early assessment* to steer the strategy for response [14,15,28].

Operational aspects

The main issues around the debate on mitigation versus delaying are operational and concern the *opportunity costs* of aggressive case-finding, contact tracing and management (Table 3). The question is whether there are staff available who can deliver the necessary response seven days a week and what else cannot be done because the human and other resources are fully engaged on case-finding, contact-tracing, testing and treating. In the UK delivering the delaying strategy was initially possible because the Health Protection Agency and Health Protection Scotland led the work and combined effectively with local public health and primary care staff to focus massive effort on the initially affected communities. At the same time central authorities concentrated on making final preparations especially readying the health services for the autumn wave. Even so the intense work involving many schools and families was unsustainable. This has demonstrated that where there is active influenza transmission the strain on the work-force from attempting delaying is considerable. Probably only countries with national public health workforces who can be moved around the country could implement such a policy at the population level during initiation. Once into the acceleration phase in the autumn the task will be impossible in any country given what is known now about the effective reproductive number [29]. Australia and New Zealand are unusual in having formal containment phases in their pandemic plans. Their current experience is telling for what Europe could expect in the autumn. Both these countries moved through and beyond containment rapidly into mitigation [30,31].

Communication challenges

Besides burden on staff there are major communication challenges from an initial delaying approach. These arise from starting on a delaying tactic and treating everyone with what may seem a very mild disease, plus their contacts. Then having to move back to mitigation with only offering antivirals to those in the risk

TABLE 3

Mitigation, containment and delaying – the definitions

<p>Mitigation is a collective term recommended by WHO for actions in affected countries in phases 5 and 6 of pandemic alert, essentially reducing the impact of a pandemic.</p> <p>In the health sector, the aims of mitigation include:</p> <ul style="list-style-type: none"> • reducing the overall number of people affected; • reducing transmission; • ensuring healthcare for those who may be infected; • maximising care for those with disease; • protecting the most vulnerable; and • more general interventions.
<p>Containment</p> <p>Containment means preventing spread of a infection in a defined areas or areas by:</p> <ul style="list-style-type: none"> • case-finding: detecting imported infections and first generation transmissions; and • taking actions to prevent their turning into chains of transmission and outbreaks, notably through vigorous contact tracing, treatment and/or quarantine of contacts. <p>The objective is to stop as many transmissions as possible and eventually the outbreak 'burns out'.</p> <p>The term 'containment' is not recommended in this context by WHO or ECDC as it raises expectations that a pandemic virus can be contained once it has got beyond the initial outbreak, as was the case with the 2009 virus because, when it was discovered, transmission was already well beyond a delimited area.</p> <p>DeLaying is a less complete form of containment where the aim is not to contain the pandemic but rather to simply slow down transmission.</p>
<p>Differences</p> <p>It is important to note that many of the actions and messages being undertaken or promulgated are the same for delaying and mitigation strategies.</p> <p>What is different between the two is that in delaying there is special emphasis put on:</p> <ol style="list-style-type: none"> 1. Vigorous case-finding and tracing of contact-persons and giving antivirals or alerting them to watch for symptoms; 2. Putting contact-persons or even all travellers from areas with community transmission under quarantine.

groups [8,10]. Explaining this to professionals and the public may not be easy. It is also not clear how it is possible to get patients, especially children to take antivirals and complete course when they are only experiencing mild disease or are contacts of cases [32].

Differences between mitigation and containment

It should be appreciated that looked at overall mitigation and delaying strategies have a lot in common. They only differ in the emphasis in delaying on finding as many infectious cases as possible and treating them and their contacts (Table 3) However that difference is very important as the UK found the work is very demanding on human resources in the field and in the laboratory. This is especially so with using antivirals because of the evidence that to be effective treatment has to be given early, within 48 hours of symptoms starting [33,34].

Exit strategies

If a country decides to adopt delaying it needs to have a very clear exit strategy and triggers for giving up. ECDC does not recommend delaying but if a country does adopt the policy then it could consider the ECDC criteria for being 'affected' as the sign it is time to change to mitigation in all parts of the country [35]. Once policy makers adopt delaying or containment as a formal policy rather than an operational practice it can be especially difficult to change policy in a timely manner and so it is best to keep decisions at the technical level. An additional factor influencing the choice of strategy is that if a number of countries in Europe started on delaying or containment then others might have felt they had to follow. Unlike in the United States and Canada there are no cross-European agreed recommendations on the use of antivirals (although there is an ECDC guidance) [34]. It is therefore difficult to explain why delaying is being done in one country and not in others and this problem will arise again (i.e. in the autumn). Some solution was offered by meetings that took place in early July where experts met to discuss this topic and advised ministers at an informal EU Health Council to allow a degree of coordination. There was also broad agreement based on the UK example that mitigation should be adopted either in the initiation phase or when acceleration starts (Figure) in individual countries [36,37].

Has delaying been effective?

Have attempts at case-finding, contact tracing and treatment of all cases and contacts been effective in Europe so far? The

answer depends on whether effectiveness is considered at the individual or population level. For those infected and treated within 24 to 48 hours the answer is almost certainly 'yes'. Trials of both the neuraminidase inhibitors, oseltamivir and zanamivir against seasonal influenza have shown benefit in otherwise healthy adults [33,34] although it must be appreciated that antivirals are not 'magic bullets'. Even if given in time they only shorten the illness by one or two days and do not stop a person being infectious [33,34]. There may be more benefit when antivirals are given to those developing severe illness [34]. There are no such data for the pandemic strain as yet but since only a handful of viruses have shown genetic markers of resistance to either drug (they do have markers of resistance to the adamantanes) a reasonable default assumption is that they should be effective for treatment of infected individual [34,40]. The arguments around prophylaxis are more complicated. Certainly many episodes of illnesses will have been prevented but we do not know how successful prophylaxis is in preventing actual infection rather than just preventing the onset of symptoms. A sophisticated view, not supported by ECDC, recalls the accounts of the 1918-19 pandemic, which was also the last A(H1N1)-based pandemic. Then a lower pathogenicity wave in the spring in Europe was followed by a much higher pathogenicity wave in the autumn [41]. So the logic goes it may be better to be infected now by this mild A(H1N1)v virus rather than later by one causing more severe disease.

At a population level it is harder to determine the success of the delaying tactic. Delaying can appear to work by chance alone. Pandemics of influenza, like seasonal influenza each autumn, take an uncertain time to move from initiation to acceleration (contrary to popular belief influenza is only 'infectious' not 'highly infectious' (Table 4)) Considering the United States since April the heterogeneity of transmission has been striking [5]. If relatively pandemic-spared cities like those on the West Coast had attempted delaying they might now be congratulating themselves while cities like Chicago and New York would be wondering what they did wrong. It is highly possible that the efforts made by the UK and other European countries delayed the progression of transmission in May and June. Indeed given the scale of the effort in the UK it seems hard to imagine there has not been some benefit but a final verdict on how much delaying was achieved will have to await the results of considered evaluations which will take some time.

What to do?

In conclusion, what should a European country do when confronted by first cases? It can be difficult when there are only a handful of cases to offer no treatment except to individuals in risk groups. But that may be what national policies dictate, what WHO recommends and what is being done in North America [16-18]. It would also seem to be in line with the ECDC documents [22,23].

When confronted with more cases countries should consider whether to attempt delaying at all, what the advantages are of any time it might buy and the opportunity costs from what else will not be done as a consequence. The conclusion of the Swedish Presidency meeting was that countries should move to mitigation [36,37], and at least two more countries report having taken this decision [38,39].

However that does not mean that the first cases and transmissions in a country do not deserve special attention. There are very legitimate reasons for undertaking enhanced surveillance and working closely with those first affected to determine some of the

TABLE 4

Infectiousness of some communicable diseases

Infection	Effective (R) or basic reproductive rate (Ro)	Notes
Seasonal influenza	R around 1.1 – 1.2	Higher in crowded communities
Pandemic influenzas	R = 1.5 to 2.5	Higher in crowded communities
Pandemic (H1N1) 2009	R = 1.5 to 2	Presumed higher in crowded communities
Measles	Ro > 10	
Mumps	Ro 4 to 7	

R = effective reproductive rate = the average actual number of people that are observed to be infected by one infected person
Ro = basic reproductive rate = a theoretical concept of the average number of people that one person infects in a wholly susceptible population

known unknowns of the pandemic – for example: what proportions of people in a family are affected, are most older people really immune, how long are people infectious, do those who choose to take antivirals stop excreting virus and do they develop immunity [14,15,40-45] A number of countries are undertaking such work in Europe and ECDC and WHO are working with them to ensure the rapid sharing of protocols and data.

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