Minisymposium

Experience and lessons from surveillance and studies of the 2009 pandemic in Europe

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SUMMARY

Surveillance and studies in a pandemic is a complex topic including four distinct components: (1) early detection and investigation; (2) comprehensive early assessment; (3) monitoring; and (4) rapid investigation of the effectiveness and impact of countermeasures, including monitoring the safety of pharmaceutical countermeasures. In the 2009 pandemic, the prime early detection and investigation took place in the Americas, but Europe needed to undertake the other three components while remaining vigilant to new phenomenon such as the emergence of antiviral resistance and important viral mutation. Laboratory-based surveillance was essential and also integral to epidemiological and clinical surveillance. Early assessment was especially vital because of the many important strategic parameters of the pandemic that could not be anticipated (the ‘known unknowns’). Such assessment did not need to be undertaken in every country, and was done by the earliest affected European countries, particularly those with stronger surveillance. This was more successful than requiring countries to forward primary data for central analysis. However, it sometimes proved difficult to get even those analyses from European counties, and information from Southern hemisphere countries and North America proved equally valuable. These analyses informed which public health and clinical measures were most likely to be successful, and were summarized in a European risk assessment that was updated repeatedly. The estimate of the severity of the pandemic by the World Health Organization (WHO), and more detailed description by the European Centre for Disease Prevention and Control in the risk assessment along with revised planning assumptions were essential, as most national European plans envisaged triggering more disruptive interventions in the event of a severe pandemic. Setting up new surveillance systems in the midst of the pandemic and getting information from them was generally less successful. All European countries needed to perform monitoring (Component 3) for the proper management of their own healthcare systems and other services. The information that central authorities might like to have for monitoring was legion, and some countries found it difficult to limit this to what was essential for decisions and key communications. Monitoring should have been tested for feasibility in influenza seasons, but also needed to consider what surveillance systems will change or cease to deliver during a pandemic. International monitoring (reporting upwards to WHO and European
Objectives

This paper summarizes current thinking on surveillance and studies in a pandemic in Europe and the experience in 2009, taking a broad definition of surveillance to include early assessment, monitoring and investigation of effectiveness, and safety of pharmaceutical and other measures. Such an approach goes beyond what some authorities would term ‘surveillance’. This is deliberate as the same departments and staff are often expected to perform or oversee all these processes, and the most successful countries in 2009 were those that identified the extent of their tasks and were resourced accordingly.

This paper does not include clinical research, and does not include the vital work of monitoring public perceptions, following the media, nor studies after a pandemic determining which of the public health measures were effective.

Background

Since 2005, governments in European countries and international health bodies have intensified planning and preparations for the next pandemic, focusing on the threat from avian influenza A(H5N1). By the start of 2008, all European countries had pandemic plans, usually conforming to the original World Health Organization (WHO) 2005 health sector template. When the 2009 pandemic emerged, the template was in the process of being updated with a suite of supporting documentation. An important new component was draft standard operating procedures for surveillance and studies in a pandemic, which the European Centre for Disease Control and Prevention (ECDC) and WHO developed through expert consultations and papers from 2007 onwards. This work also included the vital contribution of modelling. It became apparent that this involved not just classical surveillance but also supporting studies, hence the phrase ‘surveillance and studies in a pandemic’ was adopted by ECDC.

Surveillance and studies in a pandemic is a complex topic. In their initial thinking, WHO and ECDC divided it into three areas: early detection and investigation; comprehensive early assessment; and monitoring. Laboratory-based surveillance is integral to all three, but there is a fourth related component: investigations concerning the effectiveness, safety and impact of pharmaceutical interventions. These four components have distinct features and functions; while they overlap, they are best considered as separate items within a broad envelope (Table 1 and Fig. 1).

Why pandemics represent exceptional challenges for surveillance

Four facts about the 2009 pandemic presented particular challenges, although these would have applied for any pandemic. Firstly, it has been stressful for those in the health sector, especially the essential contributors to surveillance: laboratories, clinicians and the public health workforce. Asking more than usual from surveillance processes in 2009 proved difficult unless it was pre-planned, well practised and resourced. The other three facts concerned the heterogeneity of pandemics. No two pandemics are the same, and some of the differences, what ECDC refers to as the ‘known unknowns’ (Table 2), are of crucial importance for effective mitigation. It was considered most likely that the next pandemic would emerge in the Far East (as three of the last four pandemics had done). However, this assumption proved wrong, with A(H1N1) 2009 emerging in the Americas. That said, uncertainty, unpredictability and idiosyncrasy are inherent to influenza. Recent detection of an abrupt increase in resistance to oseltamivir among circulating seasonal A(H1N1) influenza viruses in Europe during the Northern hemisphere influenza season 2007/2008 is another example of this type of uncertainty.

Component 1. Early detection and investigation

The objective of Component 1 is to detect and investigate the first emergence anywhere in the world of a novel pandemic influenza virus with a view to early containment. That means an influenza virus to which much of the population is non-immune and which is sufficiently adapted to humans to infect and cause some pathology and, crucially, to show susceptibility (Table 3). Although it is considered unlikely that
a pandemic virus will first emerge in Europe, it could happen and Europe would then have to mount rapid investigations supported by the International Health Regulations (2005) and European Decision 2119. If it was not too late, the WHO plan for rapid containment would apply in Europe as elsewhere. However, events occur regularly that might represent the start of a pandemic, so early detection and investigation is a continuous process, even if true pandemic strains only emerge a few times each century. However, the unexpected appearance of the virus in the Western hemisphere caught all authorities unawares, and by the time it was detected, early containment was obviously impossible. However, phenomenon such as the emergence of mutations in the virus and the appearance of transmitting antiviral-resistant virus in immunocompromised patients showed the need for continuing early detection and prompt investigation, including in Europe.

Component 2. Comprehensive early assessment: the strategic parameters

The objective of Component 2 is to characterize the important features of the new virus, its infection and the disease it causes, including virological, epidemiological and clinical characteristics. The prime objective is to guide and direct effective countermeasures. This is essentially determining the ‘known unknowns’ of the pandemic; the features that are known to differ from one pandemic to another (Table 2). There are many such features, but the most important are those that lead to specific and differing public health actions according to the findings. These are called the ‘strategic parameters’ by ECDC. A suggested list of the parameters and their linked actions is shown in Table 2. Two examples demonstrate their importance. Early laboratory surveillance is vital for isolation of the pandemic strain which, in turn, leads to identification of the virological phenotype and genotype (as well as development of diagnostics and pandemic vaccines). This will decide which antivirals are likely to be effective and whether to deploy any stockpiled human avian influenza vaccines. It is also crucial to starting the process of developing sensitive and specific tests and specific pandemic vaccines. The distribution of cases and transmission across age groups will help to determine where and how public health interventions should be directed. A pandemic that especially affects school-age children, like that of 2009 (equivalent to that of 1957), might justify school closure as an intervention, while such a measure would probably be ineffective in a pandemic such as that of 1968 which affected all age groups (Fig. 1).

Severity of the pandemic

This proved a most difficult parameter to determine, not least because no severity scale had been agreed before the pandemic.
pandemic. Equally, it was also one of the most important, since a number of European national plans stated that they would adopt more radical and disruptive measures if a pandemic is declared to be severe. There is no consensus on a definition of severity, but it is usually taken to mean some combination of the effect on individuals, societies and the intensity of transmission (Fig. 2). Severity is closely related to but subtly different from the impact of the pandemic on society, healthcare services and essential systems which, in turn, is also dependent on the level of preparedness. The US authorities had adopted a five-point severity scale based on case fatality ratio (CFR). The scale communicates well in America as it is based on a well-known national scale for hurricanes. WHO preferred a simpler three-point scale (mild, moderate and severe), roughly corresponding to the severity of observed pandemics (a theoretical mild pandemic, 1957 or 1968 and 1918). However, what had not been determined was how to assess severity. CFR estimates were one possible parameter, but these were not available early in the pandemic or were potentially misleading. CFR estimates only became stable later in the pandemic, well after decisions had had to be made by governments. However, what had not been determined was how to assess severity. CFR estimates were one possible parameter, but these were not available early in the pandemic or were potentially misleading. CFR estimates only became stable later in the pandemic, well after decisions had had to be made by governments. CFR estimates only became stable later in the pandemic, well after decisions had had to be made by governments.

A prior indication of the potential value of early assessment of severity in Europe in a pandemic had been shown in the 2008/9 seasonal influenza season. The early epidemics of European seasonal influenza were reported to be more severe than in the preceding few years when they first appeared in South and Western European countries. Based on this observation and the fact that seasonal epidemics tend to progress from West to East and/or South to North in Europe, ECDC alerted the rest of Europe of the need to prepare and finish routine immunization. Equally, early observations voiced by WHO in 1957 that the then pandemic was mild compared with its 1918/19 predecessor did much to prevent over-reaction in countries yet to be affected. This is what happened in 2009 when the WHO declaration that although this was truly a pandemic, it was moderate rather than severe had a steadying effect in Europe. However, this required considerable reminding of countries by WHO that pandemics could be less than severe.

It could not be assumed that viruses and estimates of the strategic parameters would be available from centres nearer to the starting point of a pandemic. However, with 21st century travel patterns, the 2009 pandemic spread more rapidly than any previous pandemics. A feature of the early assessment process (Component 2) is that all can benefit from it being undertaken, wherever the pandemic virus first takes

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b The proportion of all cases that die from the illness.

c Evidence for this comes from reviewing contemporary accounts in the Times of London.
important that a sample of currently transmitting viruses laboratory testing declined through work pressure, but it was needed for management decisions. As numbers built up, needed and demanded should not exceed the information useful principle that ECDC recommended was that the data monitoring is communicating the results (upward briefings). A often excessive central expectations in countries of what be monitored were legion and it was found that there were across multiple sectors for use in all crises. Lists of what can all-purpose emergency proforma for monitoring performance mostly within the health sector. Some also have pre-existing individual countries (national monitoring). Some European them (Table 1). It includes detecting established transmission in every European country and perhaps some localities within them (Table 1). It includes detecting established transmission in countries, demonstrating that they are ‘affected’ in WHO parlance for the final triggering of national pandemic plans; in countries, demonstrating that they are ‘affected’ in WHO parlance for the final triggering of national pandemic plans; (as early assessment as it will be needed in every European country and perhaps some localities within them (Table 1). It includes detecting established transmission in countries, demonstrating that they are ‘affected’ in WHO parlance for the final triggering of national pandemic plans; a local process akin to part of the early detection process.5 hold in Europe. It does not need to be done in every country, even if this was possible. It could be that it was impossible for any one country to determine all the strategic parameters and there was scope for local developments.

Component 3. Monitoring

The objective of Component 3 is to provide key information for communication, and for decision makers and managers to monitor and manage essential services including the health services. This differs from early assessment as it will be needed in every European country and perhaps some localities within them (Table 1). It includes detecting established transmission in countries, demonstrating that they are ‘affected’ in WHO parlance for the final triggering of national pandemic plans; a local process akin to part of the early detection process.5

Most monitoring is internal and for the benefit of individual countries (national monitoring). Some European countries have developed sophisticated systems for this, mostly within the health sector. Some also have pre-existing all-purpose emergency proforma for monitoring performance across multiple sectors for use in all crises. Lists of what can be monitored were legion and it was found that there were often excessive central expectations in countries of what could and should be delivered from local staff. Closely allied to monitoring is communicating the results (upward briefings). A useful principle that ECDC recommended was that the data needed and demanded should not exceed the information needed for management decisions. As numbers built up, laboratory testing declined through work pressure, but it was important that a sample of currently transmitting viruses should continue to be examined in order to detect expected virological change in the characteristics of the epidemic strain, such as the emergence of transmitting resistant viruses and pathogenicity markers. One European country (the UK) had developed a sophisticated modelling and surveillance method (now-casting and forecasting) for determining how the pandemic is progressing and is likely to develop, partially for managing its strategic stocks of antivirals.37,38 For monitoring systems such as combined clinical and microbiology monitoring in primary care, consideration needed to be given to how the extra stresses in a pandemic will affect them and how healthcare systems may undergo planned reconfiguration. These systems needed to be made as resilient as possible. In 2009, some systems were planned to reconfigure; for example, to divert people with suspected uncomplicated influenza away from primary care doctors which, in turn, distorted monitoring through primary care.

In addition, there was international monitoring and communication. For Europe, there are both the International Health Regulations and the pre-existing Early Warning and Response System mechanism under European Union Decision 2119.17–18 However, neither were intended for use once Europe was within a health crisis, when such formal early warning systems rapidly over-load. WHO had suggested some formal weekly data returns. However, the number of items was considerable and not necessarily compatible with the internal monitoring that countries were already planning. Numeric comparisons (numbers of cases) are likely to be difficult or misleading as they will probably reflect differences in surveillance systems. When considered by a working group at the ECDC’s Advisory Forum, the first WHO requirements were considered to be too complex by a number of European countries that could not collect such data routinely. Simplicity was felt to be key, with the most important international monitoring showing: where community transmission had started by country and, if available, by region in the country; whether transmission is rising, unchanging or falling; and, if possible, monitoring of the impact on the health services and, if any, other essential services. Subsequently, WHO produced a simpler mechanism.5 Within Europe, countries particularly wanted to know what their neighbouring countries are doing or planning to do in terms of measures, and to communicate their own intentions to ensure interoperability. This was

Table 2 – What can and cannot be assumed for the next pandemic.

<table>
<thead>
<tr>
<th>What probably can be assumed: the ‘known knowns’</th>
<th>What cannot be assumed: the ‘known unknowns’</th>
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<tbody>
<tr>
<td>• Modes of transmission (droplet, direct and indirect contact)</td>
<td>• Antigenic type and phenotype</td>
</tr>
<tr>
<td>• Broad incubation period and serial interval</td>
<td>• Susceptibility/resistance to antivirals</td>
</tr>
<tr>
<td>• At what stage a person is infectious</td>
<td>• Age groups most affected</td>
</tr>
<tr>
<td>• Broad clinical presentation and case definition (what influenza looks like)</td>
<td>• Clinical attack rates</td>
</tr>
<tr>
<td>• The general effectiveness of hygienic measures</td>
<td>• Pathogenicity (case fatality rates)</td>
</tr>
<tr>
<td>• That transmission will decline in the spring and summer in temperate zones</td>
<td>• Severity of the pandemic</td>
</tr>
<tr>
<td></td>
<td>• Precise parameters needed for modelling and forecasting (serial interval, R0)</td>
</tr>
<tr>
<td></td>
<td>• Precise clinical case definition</td>
</tr>
<tr>
<td></td>
<td>• The duration, shape and tempo of the waves of infection</td>
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<td></td>
<td>• Complicating conditions (superinfections)</td>
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<td></td>
<td>• The effectiveness of interventions and countermeasures</td>
</tr>
</tbody>
</table>

Table 3 – Early detection and investigation: the rationales.

| • Attempting the WHO early containment strategy if it is not too late               |
| • WHO Director General declaring a pandemic has started; this will trigger multiple international and national actions |
| • Early characterization of the strain and passing isolates to start development of specific |
| • Vaccine manufacturers switching from production of seasonal to pandemic vaccine   |

Table 3 – Early detection and investigation: the rationales.
achieved, to an extent, by frequent virtual meetings of the European Union Health Security Committee, chaired by the European Commission.

Component 4. Investigations of the effectiveness, safety and impact of countermeasures

The objective of Component 4 is to determine the effectiveness of the various proposed countermeasures and treatments intended to mitigate the pandemic.\textsuperscript{39,40} For the pharmaceutical measures (those involving antimicrobials and vaccines), the objective is to detect and assess any adverse effects as rapidly as possible. There were similarities with the process of early assessment in that systems needed to be pre-planned. Detecting and evaluating potential adverse effects of the pharmaceuticals was considered especially important for maintaining safety, as well as sustaining professional and public confidence. Antivirals are little used in Europe, and their mass deployment in a pandemic was thought likely to generate reports of adverse events by the chance coincidence of their use with severe illness.\textsuperscript{41,42} Similarly, the rapid deployment of specific pandemic vaccines would also make the likelihood of coincidental occurrences inevitable.\textsuperscript{23,24} Due to its previous reported association with one now historic vaccine (the 1976 swine flu incident in the USA), particular attention was paid to looking for Guillain Barré syndrome, which is more likely to occur in a pandemic due to its association with influenza infection.\textsuperscript{43,44}

In Europe, producers of vaccines and medicines bear a legal responsibility for monitoring and evaluating safety, but leaving this to the companies alone was considered to be unlikely to have credibility, especially in a crisis. Also, rapid evaluation of uncommon but plausible side-effects in the post-marketing phase requires special studies conducted by public authorities, such as through linking of large databases or population-based studies.\textsuperscript{45,46} This was not readily done in all Member States, but European added value will come from plausible side-effects being detected in one Member State and the hypothesized relationship being tested in others. In response to this, ECDC brought forward systems for rapidly assessing vaccine effectiveness (I-MOVE) and monitoring vaccine safety (VAESCO).\textsuperscript{47}

<table>
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<th>Table 4 – Early comprehensive assessment.</th>
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<tr>
<td>Strategic parameter</td>
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<tr>
<td>1. Identify and monitor changing phenotypic/genotypic characteristics of the pandemic strain in Europe, including antiviral resistance and pathogenicity markers</td>
</tr>
<tr>
<td>2. Broad estimate of severity of the pandemic, including age-related mortality and hospitalization rates for different influenza-related diagnoses</td>
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<tr>
<td>3. Confirm/determine case definition and its predictive value</td>
</tr>
<tr>
<td>4. Give estimates of incidence by age group or other risk parameters</td>
</tr>
<tr>
<td>5. Give estimates of disease and especially severe disease by age group or other risk parameters (e.g. those with chronic conditions, pregnant women)</td>
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<tr>
<td>6. Define pattern of disease for the pandemic strain</td>
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<tr>
<td>7. Determine if the modes of transmission conform to usual</td>
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<tr>
<td>8. Determine key parameters for modelling-reproductive number, serial interval</td>
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<tr>
<td>9. Monitoring of bacterial superinfection–bacterial type and resistance</td>
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WHO, World Health Organization.
What is meant by 'mild' and 'severe'?
Not a simple scale

- **Death ratio.** Expectation of an infected person dying (the Case Fatality Ratio).
- **Number of people falling ill with respiratory illnesses at one time — ‘winter pressures’**. Pressure on the health services' ability to deal with these — very related to preparedness and robustness.
- **Critical service functioning.** Peak prevalence of people off ill or caring for others.
- **Certain groups dying unexpectedly**, e.g. children, pregnant women, young healthy adults.
- **Public and media perception.**
- **Conclusions.** Not easy to come up with a single measure.
- May be better to state what interventions/countermeasures are useful and justifiable (and what are not).


whilst avoiding cross-reactions. Europe lagged behind the USA in producing and publishing relevant serological data. In addition, there was a need for more laboratory grounded work, such as looking for evidence of prior immunity, and monitoring for the emergence of antiviral resistance, pathogenicity markers and other evidence of change in the virus such as may occur when it meets other influenza viruses, both seasonal influenzas and the avian influenzas. Some countries, but not all, had developed surge capacity plans as per WHO and ECDC planning guidance.

### Operational consequences and planning
Performing comprehensive early assessment, monitoring and investigations of the effectiveness and safety of

<table>
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<th>Component 4—later studies and surveillance.</th>
<th>Rationale for determining the actions that follow</th>
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<tr>
<td>1. Serological determination of who was infected in the first wave</td>
<td>Inform preparedness for second and subsequent was and targeting vaccines</td>
</tr>
<tr>
<td>2. Determining the impact of non-pharmaceutical countermeasures</td>
<td>Amend and adjust interventions</td>
</tr>
<tr>
<td>3. Estimate antiviral effectiveness</td>
<td>Decide on or refine recommended use of antivirals for treatment Estimate the impact at population level (effect on transmissibility) and refine use for prophylaxis and early treatment</td>
</tr>
<tr>
<td>4. Estimate vaccine effectiveness</td>
<td>Decide on or refine recommendations for use of vaccine Trigger further investigations on pandemic vaccine (improve composition, adjuvants, boosters)</td>
</tr>
<tr>
<td>5. Monitor/study antiviral safety, and investigate and evaluate initial concerns</td>
<td>Proper investigation of credible adverse effects Decide on recommendations for antivirals Respond to possible safety concerns and minimize their impact on treatment programmes</td>
</tr>
<tr>
<td>6. Monitor/study vaccine safety, and investigate and evaluate initial concerns</td>
<td>Deal properly with possible safety concerns and avoid these adversely affecting immunization campaigns. Proper investigation of credible adverse effects. Decide on or refine recommendations for use of vaccine</td>
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</tbody>
</table>
countermeasures in European countries was a major task. At national level, the difficulty was that the same central staff were often expected to perform or at least co-ordinate all three. This is difficult in normal circumstances and proved impossible in some countries in a pandemic situation without pre-planning and, especially, reinforcement of staff.

Discussion

For ECDC and the WHO Regional Office for Europe, the main focus of the work in Europe in 2008/9 had been on the early assessment process, as that needed tackling at the European level. This was undertaken with WHO Headquarters who took global leadership. This process culminated for Europe in a meeting held in July 2009 with representatives from WHO and countries in other parts of the world that had already been affected (Australia, Canada and the USA). Working with European Union Member States/European Economic Area countries, especially those that were involved in analysing the features of cases of oseltamivir-resistant A(H1N1-H247Y) during the 2007/2008 Northern hemisphere influenza season in Europe, was a priority. The primary goals were to estimate the strategic parameters (Table 4), especially:

- infection incidence rates by age group;
- disease risk status by age and risk group, i.e. which chronic co-morbid conditions, pregnancy status, etc.;
- severity of disease (severity of symptoms, complication rates, CFRs etc.); and
- key data which would be used for modelling.

Web-based data collection platforms were developed or adapted in individual countries to speed up and facilitate work, with follow-up via telephone contacts. In addition to study design issues, there was an unresolved need to pro-actively address data sharing, confidentiality and informed consent issues. In relation to this, a major issue was whether to undertake central data analysis at the European Union or even global level, or whether to rely on more local country data analysis to answer the questions suggested by the strategic parameters (Table 4). To an extent, both approaches were less than successful. Information on strategic parameters was collected and analysed in individual country investigations, but those analyses were not always passed on to international authorities or shared with other countries in a timely manner. Equally, data on severely affected individuals and deaths, for example, were not passed on. Most useful analyses were done at the country or more local level, and these were gathered together in a European Union risk assessment that was repeatedly refreshed. Facilitating this, the independent journal Euro-surveillance provided a venue for very rapid peer review and publishing of original articles and reports on the pandemic at a rate of more than two per week from April onwards. Therefore, in practice, the most value came from learning from the counties affected earliest in Europe and elsewhere. An example of this arose from an early inclination to attempt containment of the pandemic in the summer months of 2009. This proved impossible without very intensive commitment of staff and resources, even in June and July when transmission was low (Table 5). A meeting organized under the Swedish Presidency in early July was crucial in sharing the
early experience in the first affected countries, so that the others did not feel that they needed to repeat the intensive process in the autumn.\textsuperscript{54,55}

In summary, Europe has been most fortunate in the pandemic that it has experienced (Fig. 3). This was a pandemic strain that emerged in the Americas. Although it was detected too late for rapid containment, there was immediate virus sharing so a rapid risk assessment was possible along with immediate commencement of development of diagnostic tests and vaccines. The basis of the pandemic was an A(H1N1) virus that currently is much less pathogenic that had been anticipated with an A(H5N1) virus and with residual immunity in much of a large group (older people). The virus has shown sustained susceptibility to oseltamivir, and Europe has benefitted from good data and information from North America and the Southern hemisphere. It is difficult to imagine a better pandemic, and it will be important to learn from this experience for something that could be considerably worse.

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Competing interests

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