



## **TECHNICAL** REPORT

# Surveillance and studies in a pandemic in Europe

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ECDC TECHNICAL REPORT

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Françoise Guillaume  
Mira Kojouharova  
Chryso Gregoriadou  
Silke Buda  
Steffen Glismann  
Natalia Kerbo  
Amparo Larrauri  
Luke Perera  
Theodoros Lytras  
Agnes Portne Csohan  
Joan Mary O'Donnell  
Sandro Bonfigli  
Pierre Weicherding  
Greta Amasenkoviate  
Antonia Melillo Fenech  
Willem van der Hoek  
Karin Rønning  
Magda Rosinska  
Maria da Graça Gregorio de Freitas  
Amalia Canton  
Maja Sočan  
Ivan Bakoss  
Anne Mazick  
Jim McMenamin  
John Watson  
Colin Hawkins  
Franz Karcher  
Caroline Brown  
Tony Mounts  
Sylvie Briand  
Katelijn Vandemaele  
Andrea Ammon  
Andrew Amato  
Flaviu Plata  
Phillip Zucs  
Angus Nicoll  
Tommi Asikainen  
Vicente Lopez  
Todd Weber  
Piotr Kramarz  
Bruno Ciancio  
Rene Snacken  
Maroussia Bojkova  
Isabelle Bonmarin  
Peter Grove  
Ian Hall  
Steve Leach  
Baltazar Nunes  
Bohumír Procházka  
Andrea Pugliese  
Caterina Rizzo  
Jacco Wallinga  
Matthias an der Heiden  
Tom Britton

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## Summary

Surveillance and Studies in a Pandemic (SSiaP) is a complex topic including, as defined here, 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 the safety of pharmaceutical countermeasures) in achieving mitigation.

A pandemic is unlikely to emerge in Europe, and so early detection and investigation will probably take place elsewhere, but Europe will need to undertake the other three processes. Laboratory-based (microbiological) surveillance will be essential to all components but usually will be integrated with epidemiological and clinical surveillance. Early assessment (component 2) is vital because of the number of important parameters of the next pandemic that cannot be anticipated. However, early assessment does not need to be undertaken in every country. Optimally, it will be best done by the earliest affected European countries, with support from the European Centre of Disease Prevention and Control (ECDC) and the World Health Organization (WHO), and confined to determining the 'strategic parameters'. The values for these represent which is the information that will determine which public health and clinical measures are most likely to be successful. The results from a few countries would then be immediately conveyed to all other countries.

An estimate of the severity of the pandemic will be part of the early assessment. It will be difficult but is essential as some national European plans envisage triggering more disruptive interventions in the event of a severe pandemic. WHO leadership is anticipated for this assessment. However, the detail will require a European view tied to a risk assessment because the complexity of the concept of severity makes it difficult to reduce to a single measure. All European countries will need to perform monitoring (component 3) for the proper management of their own healthcare systems and other services. The information that central authorities in countries might like to have for monitoring is legion but should be limited to what is essential for decisions and key communications. Monitoring should be tested for feasibility in influenza seasons, but also will need to consider how routine surveillance systems will change or cease to deliver during a pandemic. International monitoring (reporting upwards to WHO and European authorities) should be kept simple, as many countries will find it difficult to provide routine information to international bodies as well as undertaking internal processes. Also, not every country will be able to supply the detail that European authorities might like to have.

Investigations of the impact of public health measures (and the safety of pharmaceutical countermeasures) (component 4) is another process that only needs to be undertaken in some countries. It is unlikely that it will become clear whether and which public health measures have been effective during the pandemic itself.

WHO and ECDC has been working with European Member States to develop procedures and 'mock-up protocols' for component 2, the early assessment process, and it was planned that these will be tested for acceptability in exercises and field tested in the 2009–2010 influenza season. The emergence of the novel influenza A(H1N1) means that these will be tested against a real pandemic strain. Piloting of methods of estimating influenza vaccine effectiveness (part of component 4) in Europe is underway. At the national level, it is important that authorities plan how they will undertake components 2 to 4, including working with academic bodies and staff, and resource them realistically in the pandemic itself.

## Background

Since at least 2005, governments in industrialised countries and a number of international health bodies have intensified planning and preparations for the next pandemic (WHO 2005, European Commission 2005, Mounier-Jack 2006). All European countries now have pandemic plans, usually conforming to the original WHO 2005 health sector template which has been updated with a suite of supporting documentation this year (WHOa 2009).

An important new component of suite are draft standard operating procedures for SSiaP, which WHO has been developing through expert consultations (WHO 2009b). In turn, ECDC has been developing European thinking with EU/EEA Member States through a series of meeting and papers going back to 2006 (ECDC 2007, Nicoll & ECDC Flu team 2007), which have also included the important contribution of modelling (ECDC 2008). It has become apparent that this involves not just classical surveillance but also supporting studies, hence the phrase Surveillance and Studies in a Pandemic and the acronym SSiaP.

## Objective

The objective of this paper is to summarise current thinking on SSiaP in Europe taking a broad definition to include early assessment, monitoring and the investigation of impact and safety of public health countermeasures (including the use of antivirals and vaccines). Such a broad approach goes beyond what some authorities would term surveillance. This is deliberate as often the same departments and staff are expected to perform or oversee all three processes and it is important to identify the extent of their tasks.

## Limitations

The paper does not include clinical research, for example, evaluating the impact of treatments outside their public health role, or antivirals and human avian influenza vaccines (HAIVs) in reducing transmission (Ferguson 2006, Jennings 2008). Neither does it include the vital work of monitoring public perceptions nor working with the media or work after a pandemic to finally determine which of the public health measures were effective (ECDC 2007).

## Introduction

Surveillance and studies in a pandemic is a complex topic. WHO has divided it into three components: 1) early detection and investigation, 2) early comprehensive assessment, and 3) monitoring. Laboratory-based (microbiological) surveillance is integral to all three. ECDC has introduced a fourth component related to investigations concerning the impact and safety of countermeasures, including pharmaceutical interventions. These four components have distinct features and functions and while they overlap to an extent they are best considered as separate items within a broad envelope of SSiAP (Table 1 and Figure 1).

### Why pandemics represent a special challenge

Four facts about pandemics present special challenges for SSiAP. Firstly, they are stressful for everyone, including the essential contributors to surveillance, laboratories, clinicians and the public health workforce. Hence wanting more than usual from surveillance processes will be difficult unless it is pre-planned, well practised and resourced. The three other relevant facts concern heterogeneity (Lipsitch 2009). No two pandemics are the same and some of the differences, the 'known unknowns' (Table 2), are crucial to both their impact and what countermeasures can best be applied to achieve mitigation. There is also the variability within each pandemic, so that severity and impact can differ even within a country and some of the features also change over time. Finally, there is the effect of serendipity, stochastic elements in pandemics. While it was considered most likely that the next pandemic will emerge in the Far East, as three of the last four have done, even this is not certain and events in 2009 with a new A(H1N1) virus have confounded this assumption (CDC 2009, Russell 2008, Smith 1995, Kilbourne 2006, Lipsitch 2009). Where a pandemic will first appear globally and then in Europe, and so how it will then spread, is almost unknowable. Recent detection of 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 (WHO/ECDC Writing Committee 2009).

## Component 1 – Early detection and investigation

The objective is to detect and investigate the first emergence anywhere in the world of a novel pandemic influenza virus. That means an influenza virus to which much of the population is non-immune to and is sufficiently adapted to humans to infect and cause pathology and to show sustained transmission from person to person (WHO 2005a). In WHO parlance, this is trying to detect Pandemic Phase 4 (or Phases 5 or 6, if earlier phases have been missed or were too short to be detectable) (WHO 2009a). There are at least four rationales for early detection (Table 3). These rationales are independent of each other, i.e. you can have one or more components without the whole package (WHO 2009a). Even though it is unlikely that a pandemic virus will first emerge in Europe, it could happen, and Europe would then mount rapid investigations supported by the International Health Regulations (2005) and European Decision 2119 (1998) (WHO 2005b, European Parliament & Council 1998)<sup>1</sup>. If it was not too late, the WHO Plan for Rapid Containment would apply in Europe (WHO 2007), of course. 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 (Kadun 2005, Kilbourne 2006).

## Component 2 – Comprehensive early assessment: the strategic parameters

The objective is to characterise the important features of the new virus, its infection and the disease it causes, including their 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) (ECDC 2007). There are many such features but the important ones 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 in Table 4. 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. This will decide which antivirals are likely to be effective (Hayden 2006, WHO/ECDC 2009) and whether to deploy any stockpiled human avian influenza vaccines (Jennings 2008). It is also crucial to starting the process of developing sensitive and specific tests and specific pandemic vaccines (WHO 2004).

The distribution of cases and transmission across age groups will help determine where and how public health interventions should be directed. A pandemic that especially affects school-age children like that of 1957, which focused in those ages, might justify school closure<sup>2</sup> as an intervention while such a measure would probably be ineffective in a pandemic like that of 1968, which affected all age groups (Figure 1) (Cauchemez 2009). The methodology for estimating the strategic parameters will depend heavily on the countries’ surveillance systems and availability of developed modelling work. The parameters may be determined in a variety of ways. The microbiological parameters will need careful and repeated sampling and laboratory investigation throughout a pandemic, essentially continuing under difficult circumstances what usually takes place in the inter-pandemic period, including rapid virus sharing (CDSC 2008). Most other parameters seem unlikely to be determined through routine systems. One or two European countries have developed centralised systems for gathering data from early cases. In Europe, the best known is the UK’s ‘First Few Hundreds’ mechanism (McMenamin 2008), but there are also pertinent developments in Germany and the Netherlands, and perhaps in other countries. However, determining features like relative age distribution and case fatality rate seems likely to require rapid field

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<sup>1</sup> It is important to note that in most European settings once a pandemic has emerged somewhere in a world, attempts to contain it when it then appears in European countries would be doomed to failure. This is because of continuous re-seeding from abroad. It would also be a waste of resources (Ferguson 2006) and there are significant ‘exit issues’ (how and when do you abandon the practice). It is possible to think of exceptions to this statement (e.g. isolatable islands), but these would involve only a small proportion of the European population.

<sup>2</sup> This is also called ‘class dismissal’ by some authorities. It assumes the mixing of children outside of school will also be reduced.



investigations including serology, since any system relying on central data referral from identified cases will be vulnerable to selection bias (ECDC/WHO EURO 2008). This could be a serious defect if it led to a declaration that a pandemic was more severe than it was in reality. Detecting changes in mortality could be useful if it is delivered in real time, and especially if it detects differences between age groups and can operate in many countries. A pan-European project, European Monitoring of Excess Mortality for Public Health Action ([EuroMoMo](#)), is attempting to stimulate and coordinate the development of such national systems. However, mortality monitoring will not necessarily be able to show at which age groups the transmission is taking place.

## Severity of the pandemic

This is probably the most difficult strategic parameter to determine. Equally, it is also one of the most important, since a number of European national plans state that they will adopt more radical and disruptive measures if a pandemic is declared to be severe. As yet, 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 (WHO 2009c) (Figure 2). Severity is closely related, but subtly different, from the impact of the pandemic on society, healthcare services and essential systems, which is also dependent on the level of preparedness. The United States authorities adopted a five-point severity scale based on case fatality ratio (CFR)<sup>3</sup> (US HHS/CDC 2006). The scale communicates well in that country as it is based on the well-known national scale for hurricanes. However, it suffers from the difficulty that CFR is especially difficult to determine until late in a pandemic, or even afterwards. The WHO 2009 plan prefers a simpler three-point scale (mild, moderate and severe), roughly corresponding to the severity of observed pandemics — a theoretical mild pandemic, 1957 or 1968 (moderate), and 1918 (severe) (WHO 2009a). What has yet to be determined is how to assess severity. CFR estimates are one possible parameter but may not be available until after a severity declaration is ready. They will also require serology to detect asymptomatic and mild infections, and, anyway, influenza can have a low CFR and still present large numbers of cases and result in high peak absenteeism with crippling effects on services. Seasonal influenza shows how the impact of an epidemic or pandemic can differ from intensity (new cases per unit of population). Impact will vary from setting to setting because of differences in populations and robustness of services and the level of preparedness in the same way that seasonal influenza can. If primary care services are unavailable, for example during a public holiday, epidemics of influenza may test hospital services that might be coped with at other times.

An indication of the potential value of early assessment of severity in a pandemic was shown in the 2008–2009 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 the South and Western European countries. Based on this observation and the fact that seasonal epidemics tend to progress from West to East or South to North in Europe, ECDC alerted the rest of Europe of the need to prepare and finish routine immunisation (Paget 2007, ECDC 2009). Equally, early observations voiced repeatedly by WHO that 1957 pandemic was mild compared to its 1918–1919 predecessor did much to prevent overreaction in countries yet to be affected<sup>4</sup>.

It cannot be assumed that viruses and estimates of the strategic parameters will be available from centres nearer the starting point of a pandemic (ECDC 2008a). With 21<sup>st</sup> century travel patterns, a pandemic may spread more rapidly than those previously. Even if such data are available there will be a need to repeat many of the measurements within Europe, as pandemic strains evolve over time.

A feature of the early assessment process (component 2) is that all can benefit from it being undertaken wherever the pandemic virus first takes hold in Europe. It does not need to be done in every country, even if it could be. As a consequence, as protocols are developed, so called 'mock-up protocols'<sup>5</sup>, they need to be 'owned' by all countries and tested for seasonal influenza, so that all European countries would be willing to enact them in the event of being affected early and share the results quickly with the rest of Europe and the world. It may be impossible for any one country to determine all the strategic parameters, and there is an ample scope for local developments, as well as having European protocols, as long as those local developments are shared at a European level and beyond.

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<sup>3</sup> The proportion of all infections (symptomatic and asymptomatic) that die from the consequent illness.

<sup>4</sup> Evidence for this comes from reviewing contemporary accounts in *The Times*, London, UK.

<sup>5</sup> These are the equivalent of the mock-up protocols prepared for licensing a pandemic vaccine.

## Component 3 – Monitoring

The objective 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 radically from 'early assessment' as it will be needed in every European country and most localities within them (Table 1). Monitoring 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 (WHO 2009a).

Most monitoring will be internal 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. Closely allied to monitoring is communicating the results — upwards briefings. The list of what can be monitored or used for briefings is legion and there are often initially excessive central expectations of what can and should be delivered from local staff. A useful principle is that the data needed and demanded nationally and internationally should not exceed the information needed for management decisions.

It is important that monitoring systems be tested in seasonal epidemics and through exercises. What is difficult to anticipate in these is the impact of the pandemic (e.g. absenteeism) and the countermeasures (e.g. school closures), both of which will need to be monitored.

At least one European country (the UK) has 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 (ECDC 2008).

For monitoring systems, such as combined clinical and microbiology monitoring in primary care, consideration needs to be given to how the extra stresses in a pandemic will affect them and how healthcare systems may undergo planned reconfiguration. These systems may need to be made as resilient as possible. Some systems will undergo planned reconfiguration, for example, some countries report that they are planning to divert people with suspected uncomplicated influenza away from primary care doctors, which will distort monitoring through primary care.

In addition there will be international monitoring and communication. For Europe there are both the International Health Regulations and the pre-existing [Early Warning and Response System \(EWRS\)](#) mechanism under European Union Decision 2119 (WHO 2005b, European Parliament & Council 1998). However, neither are intended for use once Europe is within a health crisis, when such formal systems rapidly overload. WHO has suggested some formal weekly data returns and suggested a draft list (Table 4). The number of items are considerable and they are not necessarily compatible with the internal monitoring that countries are already planning. Numeric comparisons (numbers of cases, deaths) are likely to be difficult or misleading as they will probably reflect differences in surveillance systems. When analysed by a working group of ECDC's Advisory Forum in early 2009, Table 4 was considered too complex by a number of European countries who could not collect such data routinely. Simplicity will be key, and perhaps the most important international monitoring is showing where community transmission has started by country and, if available, by region in the country, whether transmission is rising, unchanging or falling, and if possible also what is the impact on the health services and other essential services. Within Europe, countries will especially want 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. Some countries have communicated these ahead of time, what one country calls its 'Planning Presumptions' (Department of Health and Cabinet Office UK, 2009).

## Component 4 – Investigations of the impact of countermeasures

The objective is to determine the impact of the various proposed countermeasures and treatments intended to mitigate the pandemic (Ferguson 2006, Germann 2006). For the pharmaceutical measures (those involving antimicrobials and vaccines), it is also to measure effectiveness and to detect and assess any adverse effects as rapidly as possible. There are similarities with the process of early assessment in that systems need to be pre-planned. Some of the same assessment field studies may be extended to then determine the impact or effectiveness of early public health interventions such as school closures/class dismissals, antivirals and human avian influenza vaccines if the latter are used (Cauchemez 2009, Hayden 2006, Jennings 2008). Effectiveness of public health measures are especially difficult to determine even outside of a pandemic. They are unlikely to be determined until after the pandemic first wave, at least.

Detecting and evaluating potential adverse effects of the pharmaceuticals are 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 will probably generate reports of adverse events by the chance coincidence of their use with severe illness (Kramarz 2008, US FDA 2006). Similarly, the rapid deployment of stockpiled human avian influenza vaccines and later specific pandemic vaccines will also make for likely coincidental occurrences inevitable (Jennings 2008, WHO 2004). Because of its previous reported association with one now historic vaccine (the 1976 'Swine Flu incident' in the USA) particular attention will undoubtedly be paid to looking for Guillain-Barré Syndrome, which is anyway likely to occur more in a pandemic through its association with influenza infection (Sencer 2006, Stowe 2009).

Producers of vaccines and medicines bear a legal responsibility for monitoring and evaluating safety, but leaving this to the companies alone will lack 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 (Verstraeten 2003, Taylor 2002, Stowe 2009). This is 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 hypothesised relationship being tested in others.

### Laboratory-based studies

All studies need to be grounded in reliable laboratory studies. As numbers build up, laboratory testing will decline, but it is important that a sample of currently transmitting viruses are examined in detail so as to detect expected virological change in the characteristics of the epidemic strain, such as the emergence of transmitting resistant viruses and pathogenicity markers. Laboratory testing needs to be protected and managed.

A particular role will be played by serology, for example, in the field studies, and it will be essential to develop simple and efficient methods for detecting evidence of infection whilst at the same time avoiding cross-reactions. In addition, there will be 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).

### Surveillance for seasonal influenza

It is more than likely that there will be co-circulating seasonal strains of influenza. These will need to be carefully monitored to ensure that they are not changing with or because of the new influenza.

### Operational consequences and planning

Performing comprehensive early assessment, monitoring and investigations of the effectiveness and safety of countermeasures in Europe is a major task. At the national level, the difficulty is that often the same central staff may be expected to perform or at least coordinate all three, which is hard in normal times and probably impossible in a pandemic without pre-planning and reinforcement. The experience of SARS in 2003 is informative. In Toronto and Hong Kong, so much time was spent by the authorities on monitoring, communication, and patient care that there was no time for public health staff to undertake early assessment or investigating the effect of countermeasures (Health Canada 2003, Hong Kong SARS Expert Committee 2003). Some strategic parameters were determined, but after the event, with academic staff playing a vital, if unplanned, role (Riley 2003).

## Next steps

For ECDC and WHO Regional Office for Europe the first main focus of the work in Europe in 2008/9 has been on component 2, the early assessment process, as that needs tackling at the European level. This is being undertaken with WHO Headquarters, who are taking global leadership (WHO 2009b), and experience from North America is being drawn upon by exchange of ECDC and United States CDC staff. This process started in 2007 by placement of CDC staff in ECDC and has been accelerated since the start of the pandemic by short-term placements in CDC. Working with EU Member States/EEA 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 (Meijer 2009). Lessons learnt from this experience have been incorporated into the plans on comprehensive early assessment.

Some of the countries involved in oseltamivir resistance investigations already possess template protocols and plans for studies to be performed early in the pandemic, which provide information on key parameters. Country protocols differ, and ECDC and WHO are collecting those existing country protocols and data forms on early assessment. Following a wider consultation 'mock-up protocols' will be developed with interested Member States to determine a number of the epidemiological strategic parameters, considering both the centralised and field investigation approaches. Minimum core common parameters from existing protocols and data collection forms will be extracted and included in mock-up protocols. The primary goals would be 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 comorbid conditions, pregnancy status, etc;
- severity of disease (severity of symptoms, complication rates, etc);
- case fatality ratios; and
- key data which would be used for modelling (Fraser 2009, Lipsitch 2009).

Those field studies may be designed as field outbreak investigations alone or analysis of cases identified through surveillance system coupled with outbreak investigations. Epidemiologic analysis of cases identified via routine surveillance posed serious problems in oseltamivir resistance investigation and also routine surveillance systems may not work during pandemic. Optimally, web-based data collection platforms would be planned to speed up and facilitate work. If follow-up is needed, it should be done via telephone contacts. In addition to study design issues, there is a need to proactively address data sharing, confidentiality and informed consent issues (ECDC/WHO 2008).

An issue of central regional data analysis versus local country data analysis with aggregation of results is important. While some information on strategic parameters may and should be collected and analysed in individual country investigations, the added value of regional, standardised data collection lies in analysing parameters where pooling data would be useful due to, for example, rare occurrence of events like incidence and especially mortality rates among some risk groups (such as pregnant women and those with underlying conditions). It is known from the oseltamivir resistance investigation that, without proactive preparation of common protocols, data collection forms and procedures for data sharing and analysis, country analyses tend to be performed in a divergent way, making data pooling at the European and global levels challenging (ECDC/WHO 2008).

Coordinated analysis of data across countries will nevertheless pose problems due to individual differences between the countries, e.g. the data being collected differently depending on the country's healthcare system. The proposed solution is to draw on the work done already by countries and design template 'mock-up protocols' that all countries with similar systems will work with.

Preliminary work on methods for component 4, investigating the effectiveness and safety of countermeasures, is underway with the main developments concerning the effectiveness and safety of vaccines (Table 5). A mechanism for estimating vaccine effectiveness has been being piloted in the 2008–2009 influenza season by Member States, coordinated by [Epicconcept](#) and ECDC. Following a successful ECDC call for tender, a contract has been awarded and discussions have also begun with the European Medicines Agency (EMA) under a concerted approach on pandemic vaccine roll-out (European Commission 2009).

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## Tables and figures

**Table 1. Characteristics of the four components for Europe**

| Component                            | Function  | Where  | Details   |
|--------------------------------------|---|--|---|
| 1. Early detection and investigation | Confirmation that a pandemic strain has emerged and attempting  | Wherever the first virus appears in the world and only there. Probably outside Europe                            | Routine outbreak detection, then special response   |
| 2. Early assessment                  | Determining the strategic parameters (Table 4)  | Whichever countries transmission first takes hold in Europe  | Special systems of field investigations and central referral  |
| 3. Monitoring                        | Providing information for communication and managing countries' essential systems   | All European countries   | Routine, but some will reconfigure in a pandemic and others are likely to   |
| 4. Assessing interventions           | Determining the effectiveness of pharmaceutical countermeasures and the impact of public health measures. Detecting and evaluating impact and adverse effects, especially reactions to drugs and vaccines | Some countries — early effectiveness studies may be based on the same localities as studies for early assessment | Specialist studies preferably based on systems developed for seasonal influenza. Adverse event detecting and evaluation |

**Table 2. What can and cannot be assumed for future pandemics**

| What probably can be assumed: The Known Knowns   | What cannot be assumed: The Known Unknowns  |
|--|---|
| <ul style="list-style-type: none"> <li>• Modes of transmission (droplet, direct and indirect contact)</li> <li>• Broad incubation period and serial interval</li> <li>• At what stage a person is infectious</li> <li>• Broad clinical presentation and case definition (what influenza looks like)</li> <li>• The general effectiveness of hygienic measures</li> <li>• That in temperate zones transmission will decline in the spring and summer</li> </ul> | <ul style="list-style-type: none"> <li>• Antigenic type and phenotype</li> <li>• Susceptibility/resistance to antivirals</li> <li>• Age groups most affected</li> <li>• Clinical attack rates</li> <li>• Pathogenicity (case fatality rates)</li> <li>• Severity of the pandemic</li> <li>• Precise parameters needed for modelling and forecasting (serial interval, <math>R_0</math>)</li> <li>• Precise clinical case definition</li> <li>• The duration, shape and tempo of the waves of infection</li> <li>• Complicating conditions (super-infections)</li> <li>• The effectiveness of interventions and countermeasures</li> </ul> |

**Table 3. Early detection and investigation — the rationale**

- Attempting the WHO early containment strategy, if it is not too late.
- WHO Director-General declaring that a pandemic has started — this will trigger multiple international and national actions.
- Early characterisation of the strain and passing isolates to start development of specific vaccines.
- Vaccine manufacturers switching from production of seasonal to pandemic vaccine.

## WHO component 2 suggested 'strategic parameters' and rationale

**Table 4. Early comprehensive assessment**

| Strategic parameter  | Rationale for determining — the actions that follow  |
|--|--|
| 1. Identify and monitor changing phenotypic/genotypic characteristics of the pandemic strain in Europe, including antiviral resistance and pathogenicity markers | <ul style="list-style-type: none"> <li>• Provide timely and representative virological input data to WHO</li> <li>• Develop specific pandemic vaccines</li> <li>• Deployment of human avian influenza vaccine (if A/H5 type)</li> <li>• Determine if any current vaccines would be useful</li> <li>• Determine antiviral resistance pattern to direct initial recommendations on use of antivirals</li> <li>• Determine if likely to be higher level virulence to prepare clinicians and consider more disruptive countermeasures</li> </ul> |
| 2. Broad estimate of severity of the pandemic including age-related mortality  | <ul style="list-style-type: none"> <li>• Determine the limits of public health actions that are justified and preventing excessive actions and reactions</li> </ul>  |
| 3. Confirm/determine case definition and its predictive value  | <ul style="list-style-type: none"> <li>• Confirm or refine default case definition for offering testing/treatment (antivirals)</li> <li>• Determine when laboratories can reduce the amount of confirmatory testing of cases</li> </ul>  |
| 4. Give estimates of incidence by age group or other risk parameters   | <ul style="list-style-type: none"> <li>• Target interventions and refine countermeasures, e.g. towards children</li> </ul>   |
| 5. Give estimates of disease, and especially severe disease, by age group or other risk parameters (e.g. those with chronic conditions, pregnant women)          | <ul style="list-style-type: none"> <li>• Target interventions and refine countermeasures, e.g. who to give antivirals and human avian influenza and specific pandemic vaccines</li> </ul>  |
| 6. Define pattern of disease for the pandemic strain   | <ul style="list-style-type: none"> <li>• Allow clinicians to confirm or refine their clinical diagnostic approach and determine any unusual presentations for case finding and improved patient management</li> </ul>  |
| 7. Determine if the modes of transmission conform to usual   | <ul style="list-style-type: none"> <li>• Confirm or refine default control measures</li> </ul>   |
| 8. Determine key parameters for modelling — reproductive number, serial interval, etc  | <ul style="list-style-type: none"> <li>• Modelling of current and near future case numbers for resource management (now-casting and forecasting)</li> </ul>  |
| 9. Monitoring of bacterial superinfection — bacterial type and resistance  | <ul style="list-style-type: none"> <li>• Refine antibiotic recommendations</li> <li>• Maybe limit the emergence of antimicrobial resistance</li> </ul>   |



**Table 5. Component 4 — Later studies and surveillance**

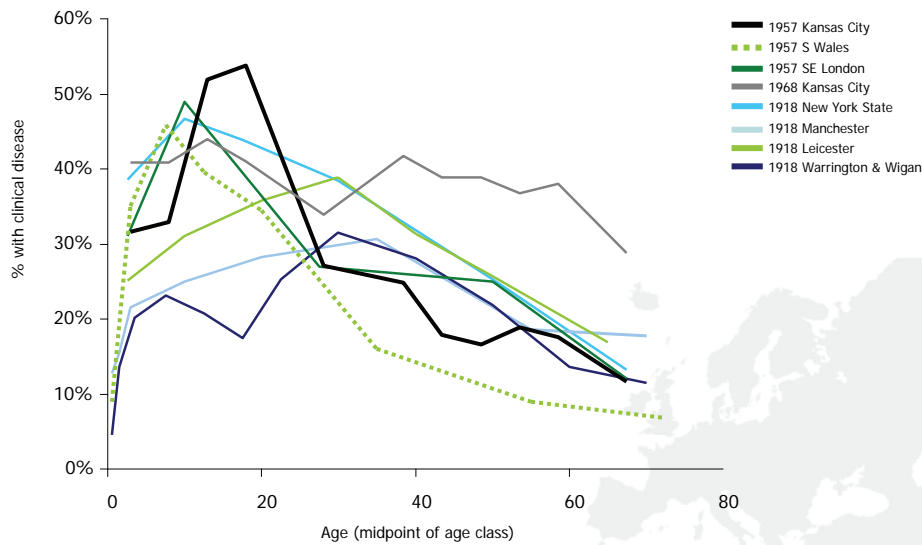
| Strategic parameter  | Rationale for determining — the actions that follow  |
|--|--|
| 10. Serological determination of who was infected in the first wave            | <ul style="list-style-type: none"> <li>• Inform preparedness for second and subsequent waves and targeting vaccines</li> </ul>   |
| 11. Determining the impact of non-pharmaceutical countermeasures               | <ul style="list-style-type: none"> <li>• Amending and adjusting interventions</li> </ul>   |
| 12. Estimate antiviral effectiveness   | <ul style="list-style-type: none"> <li>• Decide on or refine recommended use of antivirals for treatment</li> <li>• Estimate the impact at population level (effect on transmissibility) and refine use for prophylaxis and early treatment</li> </ul>                                   |
| 13. Estimate vaccine effectiveness   | <ul style="list-style-type: none"> <li>• Decide on or refine recommendations for use of vaccine</li> <li>• To trigger further investigations on pandemic vaccine (improve composition, adjuvants, boosters)</li> </ul>   |
| 14. Monitor/study antiviral safety investigate and evaluate initial concerns   | <ul style="list-style-type: none"> <li>• Proper investigation of credible adverse effects</li> <li>• Decide on recommendations for antivirals</li> <li>• To respond to possible safety concerns and minimise their impact on treatment programmes</li> </ul>                             |
| 15. Monitor/study vaccine safety and investigate and evaluate initial concerns | <ul style="list-style-type: none"> <li>• Deal properly with possible safety concerns and avoid these adversely affecting immunisation campaigns</li> <li>• Proper investigation of credible adverse effects</li> <li>• Decide on or refine recommendations for use of vaccine</li> </ul> |

**Table 6.** Suggested data requirements for international monitoring (WHO 2009b)

|  |  |
|--|--|
| <b>Data to be reported by all countries on a weekly basis</b>                | <b>Activity:</b> can be indicated by any of the following: laboratory-confirmed case(s) of influenza, or evidence <sup>6</sup> of increased or unusual respiratory disease activity. <ul style="list-style-type: none"> <li>• Yes</li> <li>• No</li> <li>• No information available for this week</li> </ul>   |
|  | <b>Geographic spread:</b> indicates how the activity is spread on the territory covered by the reporting site. For large countries there could be a number of reporting sites. Geographic spread as categorized below: <ul style="list-style-type: none"> <li>• Localised: limited to one area of the country only</li> <li>• Regional: appearing in multiple areas representing less than half of the area of the country</li> <li>• Widespread: appearing in multiple areas representing more than half of the area of the country</li> <li>• No information available: no information available for the previous one week period</li> </ul> |
|  | <b>Trend:</b> changes in the level of respiratory disease activity compared to the previous week. <ul style="list-style-type: none"> <li>• Increasing: evidence that the level of respiratory disease activity in the country is increasing compared to the previous week</li> <li>• Unchanged: evidence that the level of respiratory disease activity in the country is unchanged compared to the previous week</li> <li>• Decreasing: evidence that the level of respiratory disease activity in the country is decreasing compared to the previous week</li> <li>• No information available</li> </ul>                                     |
|  | <b>Intensity:</b> an estimate of the overall level of respiratory disease activity in the population. <ul style="list-style-type: none"> <li>• Low or moderate: normal or slightly increased observation of population affected by respiratory illness</li> <li>• High: a large proportion of the population is currently affected by respiratory illness</li> <li>• No information available</li> </ul>   |
|  | <b>Impact:</b> the degree of disruption of the healthcare infrastructure in the reporting unit due to influenza. <ul style="list-style-type: none"> <li>• Low: demands on healthcare infrastructure are not above usual levels</li> <li>• Moderate: demands on healthcare infrastructure are causing some stress to system above; usual levels but still below maximum capacity</li> <li>• Severe: demands on healthcare infrastructure exceeding capacity to provide care</li> <li>• No information available</li> </ul>  |
| <b>Data to be reported by countries with formal surveillance systems</b>     | Data from Influenza Like Illness (ILI) sentinel sites or outpatients visits: <ul style="list-style-type: none"> <li>• Number of ILI cases reported in the last one week period by age group</li> <li>• Number of total outpatient visits for all causes</li> <li>• Number of reporting sites</li> </ul>  |
|  | Data on mortality: <ul style="list-style-type: none"> <li>• Number of deaths related to acute respiratory disease by age group</li> <li>• Population covered</li> </ul>  |
|  | Data from Severe Acute Respiratory Illness (SARI) sentinel surveillance sites or inpatient facilities: <ul style="list-style-type: none"> <li>• Number of new SARI cases admitted in the last one week period by age group</li> <li>• Number of total admissions (from same facilities as number of SARI cases reported)</li> <li>• Number of SARI-related deaths by age</li> <li>• Number of SARI sentinel sites reporting</li> </ul>   |
| <b>Data from National Influenza Centres (NICs) or reporting laboratories</b> |  |

<sup>6</sup> Evidence can be based on any or all of the following: data from sentinel sites, data on school or work absenteeism related to respiratory disease, data regarding use of pharmaceuticals for symptomatic relief of respiratory disease, data from out patient department or emergency room visits for respiratory complaints, data from registrations on death due to respiratory disease, informal reports from district health authorities or healthcare providers, or other similar information sources (WHO 2009b).

**Figure 1. Age-specific clinical attack rate in previous pandemics**



Source: Peter Grove, Department of Health UK

**Figure 2. Severity of pandemics**

**There is an expectation that pandemics should be graded by severity**



But there are difficulties:

- Severity varies from country to country
- It can change over time
- Some relevant information is not available initially
- Key health information includes medical and scientific information:
  - epidemiological, clinical and virological characteristics
- There are also social and societal aspects:
  - vulnerability of populations;
  - capacity for response;
  - available health care;
  - communication; and
  - the level of advance planning

**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).