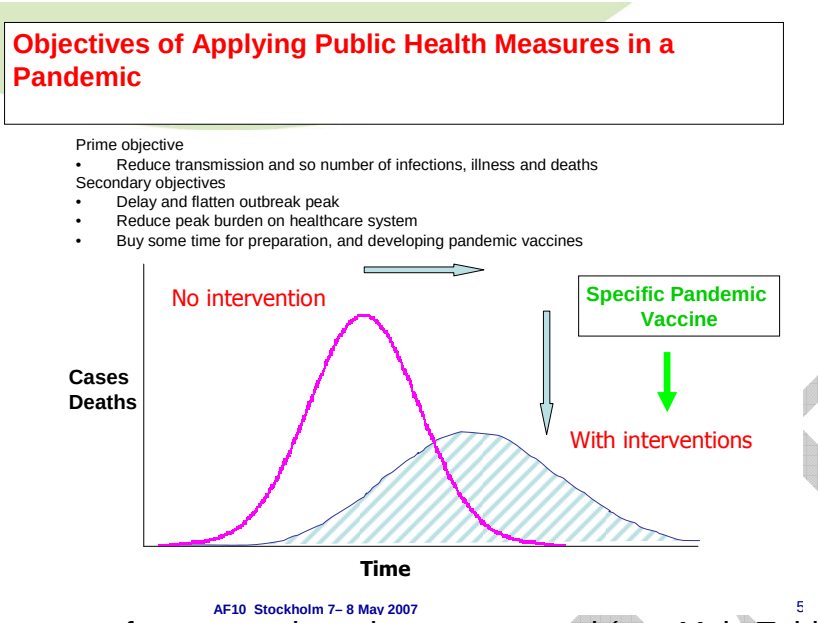
Influenza Pandemics and Severe Epidemics

Interim Guide to Public Health Measures to Reduce the Impact of Influenza Pandemics During Phase 6 - *'The ECDC Menu'*

EXECUTIVE SUMMARY

Application of public health measures (PHMs – see Main Table) to some extent will reduce the number of people who are infected, need medical care and die during the next influenza pandemic. They will also probably reduce the numbers affected by severe epidemics of seasonal influenza. By lowering and perhaps delaying the peak of a pandemic curve (Figure 1) the measures could also lessen the secondary consequences of pandemics that will result when many people fall sick at once, i.e. the impact of mass absenteeism on key functions (delivering health care, food supplies, fuel distribution, the utilities etc). They may even push back the epidemic curve of a pandemic towards when a pandemic vaccine starts to becomes available thus perhaps also reducing the total numbers affected, or to when influenza transmission declines naturally in the summer months.

Figure 1 Objectives of Applying Public Health Measures in a pandemic



A range of measures have been suggested (see Main Table) including personal actions (hand-washing and mask wearing) and pharmaceutical interventions (antivirals, human avian influenza vaccines and late in the pandemic specific vaccines) as well as community *social distancing* measures. It is thought by many that combinations of measures will be even more effective than single measures, so called '*defense in depth'* or '*layered interventions'.* Both modeling work and common sense suggests that early interventions will be more effective than waiting until a pandemic is well advanced.

Its hard to imagine that the measures like social distancing would not have some positive impact by reducing transmission of a human respiratory infection spreading from human to humans via droplets and indirect contact. **However the evidence base supporting each measure is often weak.** Its also unclear how a number of them will interact. For example will the social distancing measures be additive. Sometimes this is because of a lack of research (see Section U - *Research Implications*). More often it's because the measures are hard to evaluate with any experimental approach and when measures have been implemented in real situations they have been done so in combination. Hence the absolute positive effect and relative strengths of different measures are extremely hard to judge. Also the strength of effect could quite reasonably vary with the characteristics of the pandemic. For example interventions targeting children might have been quite effective with the 1957 pandemic where transmission in younger age-groups seems to have been especially important but they would have been less effective with the 1918-19 and 1968 pandemics. Hence it will not be possible to have fixed plans that fit every pandemic. Furthermore the effectiveness and costs of social distancing measures will presumably vary between European Countries or even within Countries (dense urban versus rural area).

Hence there will need to be default plans (exercised plans that will be implemented in the absence of other information) but with considerable flexibility and command and control structures that will allow changes to be made quickly in the light of new data and experience. There are more gaps than knowledge concerning the effectiveness and secondary effects of most measures and many will require careful consideration. The more drastic societal measures that have been suggested (e.g. proactive school closures and travel restrictions) have significant costs and consequences that will themselves vary by their setting. These are also difficult to sustain. Hence for ordinary seasonal influenza or a mild pandemic their application and especially their early application could be more damaging than just allowing the infection to run its course and treating those with more severe illness.

Some of the measures are relatively straightforward to implement and are already recommended for even mild seasonal influenza (e.g. regular hand-washing and early self-isolation when developing a febrile illness). These also have the advantage of empowering individuals and giving them useful advice at a difficult time. Others are going to be difficult to implement (timely mass use of antivirals by those becoming sick) and a third group others are costly, potentially highly disruptive to societal functions and difficult to sustain (border closures, internal transport restrictions). All the measures will require *Planning, Preparation* and *Practice*.

The point about costly and disruptive measures is crucial. In a mild pandemic, such as seen in 1957and 1968, some candidate community measures (proactive school closures, home working etc) which look as though they would reduce transmission would be more costly and disruptive than the effects of the pandemic itself. Hence such measures may only have a net benefit if implemented in a severe pandemic, for example one that was resulting in high hosptalisation rates or had a case fatality rate comparable to that of the 1918-19 *Spanish Flu.*

For these reasons early assessment of the clinical severity of a pandemic globally and in European settings will be crucial, for example by estimating the case fatality rate. Though early implementation of measures is logical too early application of the disruptive interventions will be costly and may make them hard to sustain.

A number of European countries are now thinking through their policy options for these measures. Because of Europe's diversity no single combination of measures will suit every European setting. *One size will <u>not</u> fit all*. However common discussions on the measures will be helpful and more efficient. Also some countries have already undertaken considerable relevant scientific work, some of which this document draws upon, but which all European countries could benefit from along with thinking from other countries.

Purpose In the light of the above considerations, and ECDC's mandate which is to give scientific advice rather than prescribe actions, the intention of this document is to present a *Menu* of the measures giving public health and scientific information on what is known or can be said about their likely effectiveness, costs (direct and indirect) their acceptability, public expectations and other more practical considerations. This is to help European States and EU institutions individually or collectively to decide on which measures they will apply. That said there are some measures which are either so self-evident or so ineffective that simply laying out the evidence should makes for easy policy decisions.

Audience The primary intended audience is those who develop policy and decision makers though secondary audiences are all those concerned with influenza the public and the media. The understanding by the latter of the measures and their limitations will be crucial to their successful application in a pandemic.

Scope – Phase 6 of a Pandemic The document only applies to measures that would be taken during Phase 6 of a pandemic or when there are epidemics of seasonal influenza. It does not address the somewhat different circumstances of phase 4 & 5, to the unique needs of the first emergence of a putative pandemic strain (the *WHO Rapid Containment* Strategy) or the complex planning and policy issues that arise over how to sustain key services in a pandemic, so called *Business Continuity Planning for a Pandemic.* The latter is anyway outside the remit of ECDC.

The document should be read along with previous guidance that ECDC has published on personal protective measures which is summarized in the text and tables. Relevant scientific guidance concerning antivirals has been published by ECDC [link to come] and advice on human H5N1 vaccines is being finalized. Both are either referred to or will be captured in a future version of this document.

1. **This is a consultation version of this document. Debate, comments and suggestions are all welcome to Influenza@ecdc.europa.eu preferably with the subject title *ECDC Pandemic Menu***
2. **The guidance is labeled interim as there will be further research findings and it is possible that new countermeasures will emerge. Therefore beyond the outcome of this consultation, the Guide will continue to be updated regularly.**

Main Table Characteristics of Potential Interventions To Reduce Transmission During Phase 6 of a Pandemic and Severe Epidemics of Seasonal Influenza (see main text pages 20 to 38 for detail and evidence)

International Travel (border closures, entry restrictions, travel advice)

Intervention	Quality of Evidence[1]	Effectiveness (benefits)	Direct costs	Indirect Costs and Risks[2]	Acceptability in Europe	Practicalities and other issues
1. Travel advice	B	Minimal	Small	Massive	Good	International travel will probably decline massively anyway
2. Entry screening	B, Bm	Minimal	Large	Large	May be expected by resident population	International travel will probably decline anyway
3.Border closures or severe travel restrictions	B, Bm	Minimal unless almost complete	Massive	Massive	Variable but may be expected by some in the resident populations	International travel will probably decline anyway

[1] Evidence of effectiveness: Grades A, B and C represented strongly, reasonably and poorly evidence-based recommendations, respectively.
Grade A Systematic reviews where are diverse primary studies to draw from (not primarily modeling), well designed epidemiologic studies or especially experimental studies (randomized controlled trials). **Grade B** represents evidence based on well-designed epidemiologic studies, substantial observational studies or experimental studies with 5 to 50 subjects or experimental studies with other limitations (like not having influenza as an end-point). The code Bm indicates modeling work, with emphasis placed on studies which have available good quality primary data. Hence quality can be both Bm & C . **Grade C** Represents evidence based on case reports, small poorly controlled observational studies, poorly substantiated larger studies, application of knowledge of mode of transmission, infectiousness period etc. Cm refers to modeling with few or poor quality primary data..

[2] Sometimes called second order and third order effects – e.g. closing borders resulting in disruption of trade and movement of essential supplies and workers

Personal Protective Measures (see main text pages 20 to 38 for detail and evidence)

Intervention	Quality of Evidence	Effectiveness (benefits)	Direct costs	Indirect Costs and Risks	Acceptability in Europe	Practicalities and other issues
4. Regular hand-washing	B	Probably reduces transmission	Small	Nil	Good, but compliance is unknown	Moderate[3]
5. Good respiratory hygiene (use & disposal of tissues)	B	Unknown but presumed	Small	Small	Good, but compliance is unknown	Small
6. General mask wearing outside the home	C, Cm	Unknown	Massive	Small	Unknown but little culture of mask wearing in most countries	Massive – difficulties of training, supply and types of masks, disposal and waste. May be perverse effects from misuse and re-use
7. Mask wearing in health care settings[4]	C	Unknown	Moderate	Small	Generally practiced extensively already	Moderate – difficulties of training, defining high risk situations, supply and types of mask especially respirators

[3] Need to make frequent hand washing far more available and possible in daily settings e.g. in public places, fast food outlets etc.
[4] Persons having face to face with many members of the public,

Intervention	Quality of Evidence	Effectiveness (benefits)	Direct costs	Indirect Costs and Risks	Acceptability in Europe	Practicalities and other issues
8. Mask wearing in other high risk situations[5]	C	Unknown	Moderate	Small	Unknown but makes sense	Moderate – difficulties of training, defining high risk situations, supply and types of mask
9. Mask-wearing by those with respiratory infections	C	Unknown but presumed	Moderate	May permit those ill and infectious to still circulate and infect others	Unknown but makes sense. Extends current hospital advice into home and public settings.	Difficulties of defining those who should comply, and supply and types of mask. Also compliance for those with restricted breathing due to respiratory infection
10. Early self-isolation of ill people [6]	C	Unknown but presumed	Moderate	Moderate[7] will increase risk to carers and they will be off work	Already standard advice in many countries	Need to train and equip home carers who will be at risk. Issue of compensation for lost wages and agreement of employers
11. Quarantine[8]	C	Unknown	Massive	Massive due to lost productivity	Unclear	Very hard to make work equitably and issue of compensation for lost wages

[5] Persons having face to face with many members of the public, in crowded travel settings
[6] Usually at home of a person who is starting to feel unwell and feverish.
[7] Person requires care at home and they and their carers are lost from work
[8] Isolation at home for some days of well people considered to have been exposed to infection

Social Distancing Measures (see main text pages 20 to 38 for detail and evidence)

Intervention	Quality of Evidence	Effectiveness (benefits)	Direct - costs	Indirect Costs and Risks	Acceptability in Europe	Practicalities
12. Internal travel restrictions	Cm, C	Minor delaying effect suggested	Major	Massive including social disruption[9]	Unknown	Key functions threatened. Issue of liability and legal basis[10]
13. Reactive school closures	Bm, C	May have greater effect than other social distancing	Moderate	Massive because of children needing to be cared for at home[11]	Unknown does not happen often in Europe	Children out of school need to be kept away from other children. Issue of liability and legal basis [10, 12] Difficulties of timing, sustainability and re-opening.
14. Proactive school closures	Bm, C	May have greater effect than other social distancing and be better than reactive	Moderate	As above[11]	As above	As above but even more difficulties of timing (may close to early), sustainability and re-opening. [10,12]
15. Reactive workplace closures	Cm	Unknown[8]	Major	Major	Unknown compensation issue crucial	Issue of liability, compensation and legal basis, also sustainability & re-opening. Not possible for key functions[13]
16. Home working and reducing meetings	Cm,C	Unknown	Moderate	Moderate	Likely to be acceptable	Less possible for key functions[13]
17. Cancelling public gatherings, international events etc.	C	Unknown	Massive[8,9]	Massive[8,9]	Probably depends on compensation issue and if insurance applies.[9] May be expected by the public	Issue of liability and legal backing. Difficulty of definitions about what is a public gathering, international meeting and when to lift bans.

[9] An advantage of this and some other interventions is that they will bring forward in a planned way what will probably happen anyway with time.
[10] Issue of who provides compensation if there is economic loss because of public (government) action
[11] Child requires care at home and their carers are lost from work
[12] Interventions targeted at children often assume they play an especially significant role in transmission which may not be the case in every pandemic /
[13] There is a complex process of distinguishing what are and are not *key functions* which is important but beyond the scope of this document

Use of Antivirals - Early Treatment (see main text pages 20 to 38 for detail and evidence)

Intervention	Quality of Evidence	Effectiveness (benefits)	Direct - costs	Indirect Costs and Risks	Acceptability in Europe	Practicalities
18 All those with symptoms	A (transmission and duration of illness only), Bm	Expected to be moderate but evidence on this weak[14]	Massive	Moderate	Expected by the public in most of the countries	Considerable logistical costs and difficulties in deciding who has influenza, delivering to all those who might benefit in a timely manner (under 24 or 48 hours) and managing stocks equitably.[15,]
19 Health and social care or exposed key workers	A	Small[15]	Major	Small	Considered part of staff protection and important for staff staying at work	Difficulties in defining who are health workers or exposed key workers.[15]

Use of Antivirals - Prophylaxis following a case

20 Family	B, Bm	Moderate	Massive	Moderate	Probably acceptable	Difficulties about case finding, defining families, speed of delivery, security and handling of stockpiles[16]
21 Family and social contacts	B, Bm	Moderate	Massive+	Moderate	Unknown but problem of people seemingly denied treatment	As above with problems of defining group boundaries
22 Family and geographical contacts	B, Bm	Moderate	Massive+	Moderate	Unknown but problem of people seemingly denied treatment	As above with even more problems of defining group boundaries

Use of Antivirals – Continuous Prophylaxis

23 Health or social care or key workers	C	Moderate	Massive	Moderate	Unclear – health workers may not use them at all, or not stay on them	Difficulties in defining who are health workers or key workers. Issue of how long can keep offering antivirals.

[14] The evidence from trials is that with seasonal influenza early treatment reduces duration of illness and transmission. **Estimates of the effect on hospitalization and mortality is observational, limited and far weaker**

[15] There are a series of major practical problems, deciding who has influenza, how to deliver the antivirals.

[16] There is a need to consider how early reports of plausible side effects will be quickly and effectively investigated.

Vaccines - Human Avian Influenza Vaccine[16] (see main text pages 20 to 38 for detail and evidence)

Intervention	Quality of Evidence	Effectiveness (benefits)	Direct - costs	Indirect Costs and Risks	Acceptability in Europe	Practicalities
24. Whole population	B, Bm	Unclear depends on antigenic type of pandemic[17]	Massive	Major[18]	Unknown[19]	Issues over whether
25. Health or social care workers or key workers	B, Bm	As above	Massive	As above	As above plus unclear that these groups will accept	Difficulties in defining who are health workers or key workers
26. Children vaccinated first	B, Bm	As above	Massive	As above	Especially unclear whether parents will accept especially if disease is milder in children and benefit is for others and safety profile not well established.[20]	Needs pre-planning

Vaccines – Specific Pandemic Vaccine

27. Pandemic vaccine	B, Bm	Minimal in first wave	Massive and requires prior investment	Small	Probably highly acceptable[20]	Difficulty of deciding on initial priority groups

[17] Assumes that the next pandemic is based on an H5 antigen. Benefit can be inferred from experimental serological responses however observational data and trials against the pandemic strain cannot be done before transmission starts and Phase 3. Trials may then be considered unethical.
[18] Financial risk that the next pandemic involves an antigenic strain not the current highly pathogenic avian influenza (A/H5).
[19] No country has ever tried to offer vaccination with such a low expected efficacy vaccine to its population, hence major communication challenges.
[20] There is a need to consider how early reports of plausible side effects will be quickly and effectively investigated

Main Text

Purpose and Scope The purpose of this document is to present to European Member States, the EU institutions and others a detailed guide or '*Menu'* of the many public health measures that have been proposed for reducing the transmission of human pandemic influenza **in WHO Phase 6 when the virus is spreading through Europe**. The guide provides qualitative public health and scientific information on what is known or can be said about their likely effectiveness, the direct costs, the risks and secondary consequences associated with their use, their likely acceptability, the probable public expectations and practical considerations. The findings are summarized in a **Main Table** (pages 5-10) but the reader is encouraged to consult the relevant parts of the text. The Guide does not provide information on important measures that will reduce illness and death but do not affect transmission (e.g. antibiotics and secondary care). That is more concerning clinical care and so is both outside the scope of the document and is less within ECDC's mandate.

Unlike some national guides or WHO's Annex One in its 2005 Pandemic Plan (which is included in this document- Annex I) **no explicit judgements or recommendations are made.** That is beyond ECDC's mandate which is to advise but not prescribe, though for a number of the measures the facts almost speak for themselves.

The content is intended to help European states individually or preferably collectively decide on which measures they may plan to apply and in what circumstances. **The document specifically addresses the situation of a pandemic of human influenza. However many of the same considerations will apply to severe epidemics of seasonal influenza which occur some winters and so the information is also pertinent to that situation.**

The guidance which has been subject to review by ECDC's Advisory Forum is labeled interim as there will be further research findings and it is possible that new countermeasures will emerge. Therefore beyond the outcome of this consultation the Guide will continue to be updated regularly.

Audience The primary audience for this document is those who develop health, health care and social policy and decision makers. Pandemic preparedness does not just include Ministries of Health and so this concerns other parts of governments, commercial sector and civil societies. Secondary audiences are all those concerned with influenza, the public and the media. The understanding by the latter of the measures and their limitations will be crucial to their successful application in a pandemic.

How to Use This Document This document can be used variously. Most simply by using the WHO 2005 Pandemic Plan Guidance Annex One on public health measures (Annex I) countries can apply those for a number of the Measures.

Alternatively it can be used as a resource for informing scientific development of international, national or local policy on the Measures. If so those are encourage to read first the General Considerations (pp 13-19). The Menu is designed to be self-standing but it is supported by other ECDC documentation such as that on the personal protective measures, antivirals and human H5N1 vaccines (links to come).

Consultation **This version of the document is for public consultation and comment, following an earlier limited consultation with EU member states. Following the consultation, which will end on 30th November 2007, the document will be modified to form an Interim version.** Comments and additional information should be sent to ECDC's Influenza Team at influenza@ecdc.europa.eu preferably with the subject title *ECDC Pandemic Menu*. Substantive comments with ECDC responses may be published on the ECDC web-site.

Definitions A glossary of the major terms used is available at page 51

Rationale Human influenza is a viral respiratory infection spreading from person to person by direct and indirect contact. Direct contact spread is primarily through large respiratory droplets produced when infected people cough and sneeze without covering their mouth and noses near other people. Indirect spread is when respiratory secretions settle on objects which are then touched by uninfected people who then touch their own faces. It is therefore self-evident that reductions in the transmission spread of pandemics and severe influenza epidemics (*mitigation* or *damage limitation*) may be accomplished using a variety of pharmaceutical and non-pharmaceutical countermeasures (Main Table).

Objectives The **primary objective** of this definition of the measures is ***to reduce early transmission and so reduce the overall number of cases, severe illness and especially deaths while a specific pandemic vaccine is being developed and becomes available, or virus virulence declines naturally.***

Secondary objectives are:

- *to flatten the epidemic peak and so reduce the peak burden on healthcare and other key systems (utilities, transport, food and fuel supply etc) through absenteeism,*
- *to push the epidemic curve back into the warmer months when influenza transmission normally declines and so*
- *buy some time for finalizing preparations and developing and starting production of pandemic vaccines.*

These desired impacts are shown graphically in Figure 1.

A specific pandemic vaccine The most effective countermeasure against a pandemic strain will be a specific pandemic vaccine available for the whole population. However vaccines that match the pandemic strain of influenza virus are not likely to be developed, produced and available in any quantity until some months after the pandemic begins. Also even in the EU demand will exceed global supply. These specific vaccines are unlikely to be available for the first wave of a pandemic strain in Europe.

The Measures Many Public Health Measures (PHMs) have been proposed (see Main Table). For this guide these measures are categorized into

- Travel measures
- Personal protective measures
- Social distancing measures
- Antivirals
- Vaccines

Other classifications and definitions are possible for example some guides mostly focus on social distancing (United States 2006) and the WHO Guide (Annex I) does not include the personal measures or anti-virals.

This wide definition means that the measures range from actions taken by individuals (e.g. regular hand-washing and early self-isolation) to others that require preparation by communities (e.g. closing schools). A number are controversial as their implementation could have major societal costs and consequences (Inglesby 2006, Institute of Medicine 2006) Many of the personal protective measures are simply those of good personal hygiene. These and the social distancing measures were for many years the only mass public health measures that could be used. Their use varied from one country to another during the three pandemics of the 20th Century with their greatest use in North America and other areas that were affected after Europe in the *Spanish Influenza* pandemic of 1918/19.(Potter 1998, Kilbourne 2006, Markel 2006, 2007) There is already a range of measures recommended by the World Health Organization for phases 4 to 6 of a pandemic.(WHO 2005a, WHO 2005b, Annex)

More recently pharmaceutical *i*nterventions have become available. These include early use of **antivirals** by people developing symptoms and their contacts, and human avian influenza vaccines.(Moscona 2005a, Hayden 2004, Halloran 2006, ECDC 2006b, WHO 2006c). These are the subject of separate ECDC background documents and the conclusions of these are drawn on through this document. Antivirals can be used for both clinical and public health purposes. They are intended to both protect and treat the individual and to reduce transmission onto others. However as will be explained antivirals alone cannot protect Europe's populations. They are most effective when started within 24 or 48 hours after onset of illness for treatment of ill persons, or post-exposure prophylaxis of exposed persons.(Halloran 2006, Moscona 2005, Monto 2006a) Once a person is a few days into their illness they may have little clinical effect and no effect on transmission. They will also be in limited supply and their

effective use poses challenges for timely diagnosis and dispensing. Also, the effectiveness of these drugs on a pandemic virus is unknown since this could be resistant to the drugs, or resistance could develop.(Moscona 2005b)

Human avian influenza vaccines try to anticipate the type of influenza virus most likely to cause the next pandemic (currently they are all built around influenza A/H5N1- the *bird flu* virus) with the hope that they will at least partially match the pandemic virus and offer some protective effect. (WHO 2006c) Two Scientific Groups convened by ECDC during 2007 to answer questions on these vaccines will shortly publish their guidance. The arguments and conclusions of these groups will be drawn on for this document after their reports have been finalised.

Limitations This document deals schematically with some issues that are the responsibility of bodies outside the health sector: schools, transport, mass gatherings etc only to the extent where these are required for public health purposes. However it does not address the many issues that will need to be considered in preparing non-health sector institutions for a pandemic. **This document also does not deal with the unique circumstances of the first emergence of a pandemic strain[21] or suggested scenarios before Phase 6 with less efficiently transmitting viruses when case finding, contact tracing and containment may be possible.**

Acknowledgements The information and arguments in this document represents the distilled information arising from ECDC program of joint self assessments of European Union and EEA countries which is mirrored by a similar program of WHO's European Region. The basis of all the work is the European Commission Communications of 2005 and WHO's 2005 Pandemic Planning Guidance (European Commission 2005a, European Commission 2005b, WHO 2005). ECDC is also grateful for detailed comments that arose from an earlier round of consultation with EU Member States and others through its Advisory Forum in mid 2007 and the comments of experts in a number of organizations. However the content is eventually the responsibility of ECDC.

[21] There is a WHO protocol for this to which ECDC has contributed http://www.who.int/csr/disease/avian_influenza/guidelines/draftprotocol/en/index.html

General Considerations

A. **What Will Happen Naturally** Based on what happened in the 1957 and 1968 pandemics and modeling it is possible to suggest what is likely to happen in the next pandemic should it start in East Asia.[22] Some epidemiological *assumptions* for this are listed in Table 2. However there are many caveats mentioned in the *Important Variations* and described in sections C and D below. However it can be presupposed that following emergence of a pandemic strain in East Asia there will be spread to Europe after an interval of 1-3 months (in the absence of seasonality, in high summer spread may be slower). One third of Europe's population would become ill (how ill would depend on the severity of the strain), there would be about 15% absenteeism of the working population at peak and in any one country the first wave would be over approximately 3 months after the first case in that country.

B. **Scientific Evidence and Experience** The scientific evidence on the effectiveness of the public health measures (PHMs) contains more gaps than certainties.(WHO 2004b, WHO 2006a, WHO 2006b, Inglesby 2006, Institute of Medicine 2006) There are also significant holes in our knowledge about the basic characteristics of influenza transmission (Table 2). Until recently neither have been the subject of much research attention nor funding. Attempts to further examine existing data (*data-mining*) or examining historical information (what interventions seemed to work somewhat in the three pandemics of the 20th Century) have revealed important and interesting observations. But they can only generate hypotheses and suggestions. The evidence base for the use of the measures against influenza is limited and primarily comprises anecdotal observations and systematic analyses of observations from previous influenza pandemics and seasonal outbreaks plus inferences from other scenarios and other respiratory infections, especially the SARS outbreaks in 2003.(Lo 2005, WHO 2003, WHO 2006a, WHO 2006b) There have been virtually no field studies or trials of PHMs during a pandemic or even during seasonal epidemics to evaluate their likely effectiveness and possible adverse secondary effects.(WHO 2006a, WHO 2006b) Some purists insist that only randomized control trials (RCTs) or randomized placebo controlled trials (for pharmaceutical measures) provide proof of effectiveness and therefore that if there are not definitive trials that the measures should not even be applied.(Institute of Medicine 2006) Certainly good RCTs provide the best evidence for any measure and there should be more trials carried out on seasonal influenza, for example of the personal protective measures and antivirals. However it is possible to become paralysed by the lack of trials and some interventions simply cannot be trialed. (Smith 2003) Consider the use of multiple partially-effective interventions (*defense in depth* or *layering of measures*) intended to limit transmission or spread of a pandemic strain. Studies would be impossible to perform prospectively in the absence of a pandemic and such trials would be very difficult

[22] East Asia is chosen as an illustration and because it is where the last two pandemics originated.

to enact during a pandemic. Certainly there could be no use of placebos. In the light of this, mathematical models have been used to investigate what happened retrospectively in the United States where social distancing interventions were applied extensively during Spanish influenza (Bootsma 2007, Hatchett 2007, Markel 2006 & 2007). These historical analyses are reaching some kind of consensus namely that the social distancing interventions had some impact, that they worked better if they were effected early in the pandemic but that they were often abandoned too early and pandemic infection returned. Another approach has been to apply reasonable assumptions and project the possible impact of the interventions. (Ferguson 2006, Germann 2006, Glass 2006, Wu 2006, Glass 2007). Again these studies have some form of consensus but the most impressive studies find the effects, especially of individual interventions (such as school closures) are more modest than hoped for. Ferguson 2006, Germann 2006, Glass 2007).

Modeling studies are essential to investigate possible mechanisms and suggest what is more or less likely to happen. Their major role is thus to map out the range of possible risks and to suggest which responses to pandemic influenza are robust and most likely to work given the underlying uncertainties. The most complex models cannot start to approach the complexity and diversity of even quite simple human societies. Hence phrases like "*modeling has clearly shown that …"* need to be viewed with caution Modeling work is particularly constrained by uncertainty and variation in the assumptions for values that have to be fed into models (Table 2). For example assumptions like that influenza transmission is equally divided between the home, workplaces & schools and public places are often just that - assumptions. Hence in the Main Table this document makes a distinction between Modeling Studies that have available stronger primary data for their assumptions (Type *Bm*) studies and those that have to rely on less strong data (Type *Cm*)

C. **Diversity in the Characteristics and Severity Between Pandemics**

Pandemics are not standard. In particular those of 1918-19, 1957, 1968 differed in:

- The type of influenza viruses causing them
- Their severity – the proportion of infections that result in severe disease or death (the Case Fatality Rate or CFR)
- The infectivity and reproductive number R_o
- The prior immunity and hence the groups experiencing the most transmission and most affected
- Whether there was a single or multiple waves

These are crucial variables. The severity of a pandemic, whether it is mild, moderate or severe will determine how drastic the public health measures that can be justified. Measures like proactive closures of schools (PHM 14) and cancellation of public events (PHM 17) might be considered for a severe pandemic like that of 1918-19 but would probably be excessive for the milder

pandemics of 1957 and 1968. (United States 2006, SGDN France 2007, DH UK 2007)

Similarly if transmission is focused in one age-band (as it was in 1957 in younger people) it may be worthwhile focusing on measures in those age-groups. However this would not have been so useful in 1968 when transmission was spread across all age-groups and in 1918-19 transmission seems to have been most intense in young adult age groups. (Figure 2).

This fact emphasises the need for:

- **early evaluation of the characteristics of pandemics**
- **flexibility in the actions planned**
- **national command and control structures that will allow rapid tailoring or even changing of strategies**
- **early evaluation of the effectiveness of the countermeasures**

A further complication is that the characteristics of pandemic are not static. Pandemics change with time and as they spread, generally becoming less severe over time. This is because these RNA viruses constantly evolve and immunity rises in the population. Hence even severity is measured elsewhere and is found to be high it will be important to repeat the measurements when the pandemic reaches Europe. Early measuring of the characteristics is the subject of an ECDC project *Surveillance in a Pandemic.*

D. **Diversity within the Pandemic** Influenza never affects all localities in the same way at the same time. This is seen each year through the European Influenza Surveillance Scheme with seasonal influenza and will be equally true with a pandemic. Even if most places are eventually badly affected this will not happen at the same time and really a pandemic is best seen as a series of over-lapping local epidemics. This will have advantages and disadvantages. Given the patterns of spread seen with seasonal influenza in Europe (most commonly from West to East and South to North) it may be possible to give more warning to places in the North and East. Equally within countries with command and control structures it may be possible to move some health care resources (key staff, antibiotics and antivirals) around to relieve the most badly pressed areas. However there are dangers and issues arising from the diversity of the pandemics and Europe (see next item). Firstly proactive measures may be started too early. Secondly it will be a challenge for communicators to explain why certain measures are being enacted in one place but not another. Then with measures involving limited resources (antivirals, masks etc) care will be needed to ensure that supplies are not expended in the areas first affected leaving other populations with none when they are affected later.

E. **The Diversity of Europe** It is self-evident that Europe is a highly diverse region with varying population densities, social and legal frameworks both between and within countries. Hence the "*one size will fit all"* rule will not apply to

some public health measures. Consider proactive early school closures (PHM 13 and 14). These may make particular sense in some dispersed rural areas and secondary schools where the schools are important foci for the mixing of young people from scattered communities. However they may make less sense and actually be counterproductive in dense urban areas where many parents may have to take time off work to care for children and where it will be difficult to stop children mixing anyway.(Inglesby 2006, Glass 2007)

F. **Isolated Communities** Some places in Europe are sufficiently isolated that they miss the pandemic. This was seen for a few places in the 1918-19 pandemic. (Markel 2006a, Markel 2006b) The places that achieved this were exceptional and relatively self-sufficient. Europe has become far more inter-connected of late and it is unlikely that more than few per cent of its citizens live in communities that could self-isolate in this way. However there are some such communities and they might reasonably make different arrangements.

G. **Secondary, Social and Perverse Effects** This concept, essentially looking at what are the costs, risks and consequences of applying the Measures themselves, is crucial. Measures, especially those in the *Social Distancing* group (PHMs 11 to 16) almost certainly would have major secondary and unintended effects. Though they might reduce influenza transmission they might, on balance, be judged negative or unacceptable, certainly if it there has not been planning to overcome the secondary effects. For example consider *Internal Travel Restrictions.* This might slow or reduce transmission but if they meant that in highly inter-dependent European societies food or fuel supplies broke down they would not be regarded a success. Equally if schools are closed (PHMs 12 & 13) it has to determined who will look after the out of school children? Will perhaps important staff (notably health care workers) be lost operationally because they have to take time off to look after their children. It is especially difficult to predict how populations will respond socially to a pandemic though there are reportedly attempts to do so in a few countries, though few published reports.(Keystone 2007) Finally there are areas where the evidence is lacking to know what will happen and whether there would be *perverse effects* that is when a measure expected to do one thing results in something else. For example specialists differ in their view over whether general use of simple masks by the general public will increase or reduce transmission.[23](Institute of Medicine 2006)

H. **Timing of Use, Triggering and Sustainability** It is a general principle that early prevention is best with infectious diseases. This is sometimes called the *getting ahead of the curve* principle (Figure 3). It means that public health measures, if they are effective, will need to be introduced early. For example if it is decided to close schools it will be more effective in reducing transmission to do so as the pandemic is approaching (*Proactive Closure)* not to wait until cases are

[23] It is suggested that people may reuse contaminated masks and that constantly adjusting masks may result in more contamination of hands with virus.

confirmed in the School (*Reactive Closure*).(Glass 2006, Germann 2006, United States 2006). There will need to be clear t

However things may not be that simple because of the uncertainty of movement of influenza, *Secondary Effects* and *Sustainability*. Some of the measures will be difficult to sustain because of their secondary effects. If they are introduced too early the measures may break down as people get tired and enthusiasm wanes. Then transmission will still take off. There is historical evidence of this happening in the United States in the 1918-19 where a number of big cities attempted social distancing measures. (Inglesby 2006, Bootsma 2007, Markel 2006 & 2007)

I. **Dealing with the First Outbreaks in a European Country** A difficult issue is what to do when the first outbreak occur in a country during global Phase 6. Based on what is recommended to be done on the first emergence of a pandemic strain in the world (Longini 2005, Ferguson 2005, WHO 2007a) some European countries have plans for trying to stifle first infections using large amounts of antivirals. In exercises a number of authorities have tried to contain the first outbreaks using conventional measures (contact tracing) and distributing large amounts of antivirals. The scenarios that have been played though are generally that the measures have failed and the virus has escaped. This is what modeling exercises would predicted, though in reality it is not at all clear what would happen and its possible that an exceptional pandemic virus with low infectivity might be containable. Equally there are some isolated places in Europe where there are few visitors and even a normal pandemic strain might be containable. However in the exercises, more normal viruses and usual European settings attempts at containment has resulted in significant human and antiviral resources being expended and public health staff being exhausted before the pandemic has properly started. There have also been difficulties in explaining the switch of antiviral strategy to professionals and the public.

J. **Complete or Partial Protection?** Many of the measures are not expected or even intended to give complete protection. They will reduce but not eliminate risk. This is taking a public health approach reducing the impact on the population overall. This is especially important with the measures that have significant secondary effects where complete implementation may on balance be unacceptable. That is why some authorities intend to apply not one but a number of measures (see the next item *Multiple Layered Measures – Defense in Depth*). (United States 2006, SGDN France 2007, Department of Health & Cabinet Office UK 2007).

K. **Multiple Layered Measures – '*Defense in Depth*'** Current thinking is that the impact of any single public health measure will be limited. This is both because they do not work perfectly and because they are hard to enact. The thinking is that by applying a number of measures simultaneously there will be a cumulative effect on transmission. Some have argued that given the relatively low infectivity of pandemic influenza it may be possible to prevent transmission

chains building up or to interrupt transmission (Figure 4). (United States 2006, German 2006, SGDN France 2007, Department of Health & Cabinet Office UK 2007) However that is assuming a cumulative effect of the measures which is a reasonable but still theoretical concept. There is some encouragement for this view from the experience when SARS took place in Hong Kong. Multiple measures were enacted by the authorities (closing schools, forbidding public events) or just happened because they made sense to the citizens (staying home and wearing masks when people went out). (Wu). Though this was not thought to be what controlled SARS, there was a coincidental significant impact on influenza incidence as reflected in laboratory reports.(Donnelly 2003, WHO 2003) However there are also important considerations of cumulative costs and secondary effects with multiple measures.(Inglesby 2006)

L. **The Necessity of Intersectoral Planning and Preparation** Intersectoral planning and preparation is crucial for many of the Public Health Measures. For example if regular hand-washing (PHM 4) is considered important there needs to be facilities in schools, public places, food outlets etc. to allow this (Figure 5). If it is thought that masks will be needed for some workers (PHM 8) these will need to be ordered by employers. Actions involving schools (PHMs 13 & 14) will need preparation not just by Educational Authorities, private and public schools but also other sectors and industry and civil society. Parents will have to seek alternative care for their children if schools are closed, otherwise the effects of the closures will be undermined. (Glass 2007) If they have to take time off work is it agreed that they will be paid?

M. **Legal Issues, Liability and Ethics** Enacting some of the public health measures require legal powers and obviously this has to be planned for. There is also the complex area of who is liable for any financial loss which can be said to be due to the measure rather than the pandemic. This is very difficult area where there are varied systems and traditions in different European countries. For example if its thought that an international or national meeting should be cancelled should this be a decision by the authorities who may then be financially liable or is it better to wait until its clear that many people are cancelling coming in which case the organizers will have to cancel themselves? These considerations can prevent early action even when that is desirable. Ethical issues arise whenever it will be necessary to ration measures or with issues like giving treatments or vaccines to children for the benefit of other age groups (PHM 24). WHO has produced a document on this, as have some individual European countries.(WHO 2007b) It is advisable for every country to have a mechanism whereby ethical issues arising from pandemic planning can be considered by a independent but pragmatic group. Some countries have simply used existing national ethics committees. Others have established a special group. Both mechanisms can be made to work but it's essential to have them ready to deal with unanticipated issues in the heat of a pandemic.(Gostin 2006)

N. **General vs. Selective Measures** General measures (everyone wearing masks, everyone taking antivirals) has simplicity and equity. However they may not make sense to people who perceive obvious variation in risk and therefore they can be less acceptable than selective measures for those at higher risk. (e.g. people exposed to the general public wearing masks). Selective measures allow more possibilities for ensuring quality in the application of the measure and can allow more efficient use of supplies. However the recurrent issues with selective measures are so-called *boundaries issues* and *policing*. Deciding, and subsequently communicating who should practice measures and who should not is challenging. and it will be very difficult to prevent people feeling left out of benefiting from measures, or getting anxious and annoyed that some people are perceived to be breaking the rules.

O. **Early Recognition and Diagnosis** A number of the measures (e.g. early use of antivirals) will require early recognition and diagnosis of influenza as infectivity is considered greatest within a day after onset of symptoms and children and people with disabilities will need special consideration. It must be appreciated that this will not be by laboratory test. There will not be the time, laboratories will be too busy and the point of use (bed-side) tests may not work with the new pandemic strain of virus. Hence much of the diagnosis will be presumptive by signs and symptoms alone.

P. **Planning, Preparation and Practice** General emergency planning in both general and pandemic planning in particular consists of the '*Three Ps'*

- Planning
- Preparedness
- Practice (exercises)

Some of the more difficult public health measures are especially challenging to plan for and plans that look reasonable on paper break down when attempts are made to enact them. For example early treatment and / prophylaxis with anti-virals (PHM 18 to 23). One of ECDC's most difficult local *Acid Tests* is *Can local services robustly and effectively deliver anti-virals to most of those that need them inside the time limit of 48 hours since start of symptoms?* (ECDC 2006d) Some European countries have devised plans for the distribution of antivirals, tried it out in desk-top or field exercises and then found they have had to think again. Hence there is no substitute for a programme of small and larger scale exercises to try out the plans, to get familiar with them and see if they are really likely to work. This is an essential step for moving from plans to actual preparedness and there is no room for assuming "*it will be alright on the night*". Some exercises will need to involve decision-makers including politicians so that they can understand the issues, make decisions which require resources, get used to the uncertainties and especially appreciate that there are no easy answers.

Q. **Communications** The importance of this for the public health measures cannot be over-emphasised. All the measures require close cooperation by the

public, professionals, decision makers et al. Communication materials explaining them will need to be prepared ahead of time, pre-tested and probably re-written. Equally there will need to be surge capacity in communication specialists for the pandemic as there is for other key staff. Finally documents like this need to be disseminated amongst the media and communication specialists.

R. **Special Groups – Special Considerations** There will be a number of groups who will find it especially difficult to comply with measures. In some cases numbers will be substantial. Planning will need to take this into account. Some candidate groups are listed in Table 3.

S. ***Protective sequestration* - children and adolescents** It was suggested by some authorities that early in a pandemic children and adolescents should be prevented from congregating in groups through closing child care facilities and schools and requiring them to stay at home for the local duration of a pandemic (three months).(Glass 2006) This might be possible in some settings but not in most and after some thought no countries seem to have considered this as a serious option for a mass scale.(Institute of Medicine 2006)

T. **European Interoperability** This multifaceted term has a number of meanings, both negative and positive (Table 4). It can mean European states or regions considering the impact of their enacting public health measures on their neighbours. E.g. Closing borders (PHM 3) could stop movements of essential workers. Because of modern communications there can also be indirect effects through the media if one state is seen in others unexpectedly enacting certain measures such as screening entrants (PHM 2) or mask wearing (PHMs 6 -9). Even if European Countries undertake the same measures problems will arise as they do this at different times if there is not preparation. Hence there are many advantages to European States agreeing beforehand on the same or similar actions and enacting these with similar timing, especially as there are a number of potential measures where the pros and cons do not point to clear-cut decisions (e.g. school closures and mask wearing (but also see D, E & Q. Diversity of Pandemics, Diversity of Europe and Communications).

There are other potentially very positive aspects of European Interoperability. For example if a few work for all. There is a strong tradition of this in the influenza field with four WHO Collaborating Centres serving to do specialist virology for the world. Work such as measuring the likely anti-viral resistance, determining case fatality rates, the effectiveness of antivirals etc could be efficiently spread around Europe rather than duplicated in all 27 states. Also there has been careful thinking about the Public Health Measures in a number of states. If more of this can be done collectively on particular policy areas that knowledge and work can be shared and conclusions emerge from a common understanding of what is known and not known. Even if States eventually come to different decisions e.g. whether to purchase human H5N1 vaccines (PHM 24-25) and whether and when to close schools proactively (PHM 14) at least it will be done on a common basis.

U. Research Implications There is considerable research being funded on influenza by DG Research at the European level.(DG Research 2007) Much of this is '*bottom-up'* research that is suggested from the research communities. However there is also need for more directed research and specific questions such as is being supported in the United States (ECDC Influenza Team 2007).

THE MENU OF MEASURES

The measures considered are:

Travel Measures - Restrictions on international travel

1. Travel advice
2. Entry screening
3. Border closures

Personal protective measures

4. Regular hand-washing
5. Respiratory hygiene
6. General mask wearing outside the home
7. Mask-wearing in health-care settings
8. Mask wearing in high-risk situations
9. Mask-wearing by people with respiratory infections
10. Early self-isolation of ill people
11. Quarantine measures

Social distancing measures

12. Internal travel restrictions
13. Reactive school closures
14. Proactive school closures
15. Reactive workplace closures
16. Home working and reducing meetings
17. Cancelling public gathering, international events etc

A*ntivirals – Early Treatment*

18. All those with symptoms
19. Health care or exposed key workers

Antivirals - Prophylaxis following a case

20. Family
21. Family and other social contacts
22. Family and geographical contacts

Antivirals – Continuous prophylaxis

23. Health care and key workers

Vaccines - Human H5 vaccines

24. for the whole population
25. for children
26. for health care workers

Vaccines – Specific pandemic vaccine

27. Specific pandemic vaccines

For each measure the entry considers:

- The objective and rationale
- The evidence of effectiveness or what is considered to be the likely effectiveness and benefits
- The direct costs of the measure
- The secondary effects: indirect costs, risks, and potential adverse effects
- Likely acceptability and expectations in Europe
- Practicalities, experience and other issues
- Standing WHO Policy from Annex One of the 2005 Global Influenza Preparedness Plan (Recommendations for non-pharmaceutical public health measures, pages 42-46)
  http://www.who.int/csr/resources/publications/influenza/WHO_CDS_CSR_GIP_2005_5.pdf

To reduce repetition at points a number of the entries refer back to the General Considerations. The information is also summarized in the **Main Table** (pages 5-10)**.**

Travel Measures - Restrictions on international travel

1. Travel advice

Objective and Rationale: To reduce the number of people who are infected during a trip abroad perhaps to countries where transmission is higher through advising against international travel during the pandemic unless travel is essential. A second objective is to reduce transmission among people who are traveling (in airports queues, on planes etc) by insisting that people with febrile illnesses should not travel until they have recovered.
Evidence of effectiveness: While there is no objective evidence, it is considered that when people travel they meet more people than usual and are less able to protect themselves from infectious diseases. The role of formal (official) versus informal travel advice (from the media) is not entirely clear-cut. During the SARS crisis of 2003 international travel to affected areas declined steeply well before formal travel advice was issued. However the net number of influenza infections that are likely to be prevented is small compared to the total of all infections. Modeling studies suggest that the effect on stopping international spread is small unless there is near 100% adherence through there may be a small delaying effect.(Cooper) *Minimal*
Direct costs: The costs of issuing the advice: *Small*
Secondary effects: There will be considerable impact on the travel industry though the experience of SARS suggests it will be impossible to determine what was due to the advice versus people applying common sense (WHO 2003). Given this complex issues of liability may well arise and be costly to resolve irrespective if costs are borne by individuals, companies, insurance or the public purse. *Large*
Likely acceptability and expectations: This is unknown. There are considerable concerns that some European residents aboard will attempt to get home despite the advice and perhaps put themselves at greater risk than if they

stayed where they were. Some citizens may also expect to be evacuated home. Additionally people may try to leave Member States for other EU countries or non-European countries.

Practicalities and experience: It will be important to prepare and test messages ahead of time and to ensure that citizens living abroad make plans for what they would do in a pandemic. Evacuation of well or sick citizens in any numbers is unlikely as this will usually be impractical given the numbers of people with influenza. A difficulty is the diversity of situations that EU residents will face abroad so advice will not be able to cover all eventualities. Another difficulty that occurred during SARS is to persuade multiple airlines to accept that people who are sick with febrile illness should not lose their tickets if they follow advice not to travel. An additional confusion may be of member states issuing conflicting advice so a citizen will not know whether to follow the advice issued by their own country or the by the country where they are located.
WHO Policy (2005) Global Influenza Preparedness Plan Annex

2. Entry screening

Objective and Rationale: This objective of this intuitive measure is rather unclear. Presumably it is to reduce the number of people entering a country with infection focusing on those coming from the countries that are first experiencing Phase 6.
Evidence of effectiveness: The evidence from SARS is that both entry and exit screening was quite ineffective in preventing spread.(WHO 2003) Application of what we know about the natural history of influenza suggests that attempts to screen out infected persons will be equally unsuccessful because many infectious people may be presymptomatic or asymptomatic (see Glossary). That is also the conclusion of modeling exercises.(Cooper) *Minimal*
Direct costs: The experience of SARS is that the staff costs are considerable as are the opportunity costs in that this ties up health care staff who would probably be better employed elsewhere.(Health Canada 2003) *Large*
Secondary effects: These are considerable especially the issues over what to do with people who are detected as being febrile on entry, their investigation, diagnosis and care (Health Canada 2003). *Moderate*
Likely acceptability and expectations: A difficulty is that following from the experience of SARS there is likely to be an expectation among the public, the media and decision makers that there will be some kind of entry screening. This requires some preparation perhaps by exercises to explain to decision makers as to why this is not desirable and anticipated to be ineffective.
Practicalities and experience: It will be important to prepare the ground among the public and decisions makers to explain why this measure will not be desirable. An important point to make is the opportunity costs. Not only will this measure be ineffective it will also probably tie-up public health or clinical staff better employed on other tasks. A difficulty during SARS was that a few European countries with small amounts of direct international travel seemingly

can enact the measures visibly, forgetting that many more people will enter those countries via large European hubs and then travel on to the country through internal European flights.
WHO Policy (2005) Global Influenza Preparedness Plan

3. Border closures

Objective and Rationale: To prevent influenza coming into the country
Evidence of effectiveness: The experience is that unless there is little international travel to a country and almost complete cessation of travel, the attempts at border closure will be unsuccessful in preventing entry. That is also the strong suggestion of modeling exercises.(Cooper) *Minimal unless almost complete and rapidly implemented*
Direct costs: For most settings in Europe the direct costs of trying to close borders would be huge. *Massive*
Secondary effects: In Europe there is so much essential day to day travel across borders that the idea of closing most borders is inconceivable. *Massive*
Likely acceptability and expectations: Despite the above considerations there is still likely that the public and some decision makers may wish to close borders during a pandemic. This requires some preparation perhaps by exercises to explain to decision makers as to why this is not desirable.
Practicalities and experience: Usually border closures would be both undesirable and / or impossible. However there are some circumstances where it would be conceivable, though the first is for public order rather than public health purposes. Two example of this are 1. if there is pressure on a country with antivirals or other services from people coming in from a neighboring with few antivirals. For these countries temporary border closures may be considered for public order purposes. This could be especially the case for EU countries with borders on the edges of the EU thought there may also be some internal EU borders where this applies. Also there are a few settings in Europe which are so isolated that they could cut themselves off. **See General Considerations, F. Isolated Communities**.
WHO Policy (2005) Global Influenza Preparedness Plan

Personal protective measures

4. Regular hand-washing

Objective and Rationale: To reduce transmission from person to person by indirect contact.
Evidence of effectiveness: Though there has been some trials of hand-washing on respiratory infections in general (which have mostly shown a positive impact) and other related research there has never been a published trial of the effects of hand-washing on influenza.(Schumann 1983, Roberts 2000, Ryan 2001, WHO 2006a, WHO 2006b, ECDC 2006c)) It is also unclear how much transmission of influenza takes place through indirect transmission by hands.(Brankston 2007,

ECDC 2007b) That said it is self-evident that there will be benefits that will extend to other infections spread through indirect contact.(Ryan 2001, White 2003)
Direct costs: In many settings it is quite difficult to wash hands regularly and to increase the amount of hand-washing would require considerable investment in schools, fast-food settings and public places (Figure 5). *Moderate*
Secondary effects: *Nil*
Likely acceptability and expectations: The major limiting factor to acceptability is the facilities for hand-washing. If it is easy for people to wash their hands they will do so.
Practicalities and experience: The international experience is that the level of hand-washing can be increased if the ease of hand-washing is increased. There is no consensus on the duration, frequency or type of hand-washing (soap and water vs. alcohol gels) though street dispensers of alcohol gels are effective in inactivating influenza and other respiratory viruses.
WHO Policy (2005) Global Influenza Preparedness Plan

5. Respiratory hygiene (proper use and disposal of tissues)

Objective : To reduce transmission from person to person by droplet transmission.
Evidence of effectiveness: There have never been trials of respiratory hygiene on either respiratory infections generally or specifically influenza (WHO 2006a, WHO 2006b).
Direct costs: These are modest. *Small*
Secondary effects: The only major costs are the purchase or tissues and the disposal of massive amounts of contaminated paper. *Small*
Likely acceptability and expectations: Respiratory hygiene would be expected in a pandemic and probably well accepted. They also empower people and give them a practical measure to enact.
Practicalities and experience: Supplies of materials (disposable tissues) are available. May need educational programmers thought these can be enacted in ordinary seasonal influenza seasons.
WHO Policy (2005) Global Influenza Preparedness Plan

Masks

There are many issues around masks including the following.

Types which range from the simplest or even home made masks through surgical masks to complex respirators (essentially masks with filters) which need 'fit testing' and are produced in many different sizes to fit all the population. This gives major problems over storage and supplies. There are considerable discussions over the types of masks that are recommended with a few authorities recommending the more demanding and expensive respirators in all circumstances and most others suggesting that simpler masks are sufficient.(Tellier 2006, Brankston 2007)

Training People cannot simply be supplied with masks. Some training in use and disposal is considered essential and the evidence is that though people can be supplied with masks and respirators they will not often use them correctly, especially the more demanding respirators (Cummings 2007).

The Evidence There is hardly any experimental or observational evidence for or against use of masks by the public in relation to influenza or other respiratory infections. There is limited but controversial evidence from their use during SARS which suggests some protection from another rather different virus.(Donnelly 2003, WHO 2004) However there are some anomalies in these data. For example seeming to show protection from mask wearing in public places when it was not at all sure there was transmission. The United States CDC is sponsoring some trials that may throw light on this important topic.

Secondary Effects Some specialists have suggested there could be perverse effects with mask wearing increasing indirect transmission as it would allow those with symptoms to feel they can appear in public places, go to work etc and that constant touching and adjusting of wet masks with the hands will actually increase direct transmission.

6. General mask wearing outside the home

See discussion above on Masks and *L. General vs. Selective Measures.*

Objective and Rationale: General reducing of transmission in public places, the workplace and schools.
Evidence of effectiveness: There have been no trials. Mask wearing in public is common in some societies in Asia. It has not been remarked that infection rates are any lower there. There are some authorities who argue that there could be perverse effects because people may reuse contaminated masks and that constantly adjusting masks may result in more contamination of hands with virus.
Direct costs: Even though the unit cost (the cost per mask) is low with two or more masks per citizen a day when they are outside over the 3 to 5 month period of a pandemic the supply costs are huge. There would also need to be considerable planning to ensure supplies. *Massive*
Secondary effects: These are few. *Small*.
Likely acceptability and expectations: This is unknown. There is little tradition of mask-wearing in the EU. However one or two European countries have announced they will purchase masks for their residents which is likely to be raising expectations.
Practicalities and experience: Proper use of masks is not that easy so there are massive implications for training and communication. It is unclear whether simple masks should be seen as something the authorities or health providers supply along with some instructions, or a commodity residents would purchase

commercially. Supply will be a major problem. Early attempts at marketing masks in influenza seasons are not proving easy in Europe.
WHO Policy (2005) Global Influenza Preparedness Plan. Permitted but not recommended.

7. Mask wearing in health-care settings

See discussion above on Masks and *L. General vs. Selective Measures.*

This refers to mask-wearing by people who are at higher risk through possible or probable exposure to persons who are infectious.

Objective and Rationale: The prime objective is to reduce transmission in higher risk settings but another is to allow persons in key activities to continue to work while giving them some protection. Respirators would be used in high risk settings when aerosols may be generated
Evidence of effectiveness: There are no trial and few other data. Hence the effectiveness in reducing transmission is unknown though often presumed in health care settings.(Brankston 2007, Canada 2006)
Direct costs: The costs of supply and training. *Moderate*
Secondary effects: *Small*
Likely acceptability and expectations: This is likely to be good as there is a tradition of mask-wearing in health care settings in the EU. It is quite likely that representatives (trade unions) could request or insist that their members have higher level protection in all circumstances.
Practicalities and experience:. In health care setting there are more high risk circumstances and this is where the greatest amount of use of respirators will take place though a balance will need to be established, as operational studies in the EU have shown that people wearing respirators find it considerably harder to carry our practical tasks.(HPA 2007) There will be boundary issues and issues around communication, training and disposal of used masks. There are some suggestions that masks could be cleaned or sterilized and re-used.
WHO Policy (2005) Global Influenza Preparedness Plan. No policy

8. Mask wearing in other high-risk situations

See discussion above on Masks and *L. General vs. Selective Measures.*

This refers to mask-wearing by people who are at higher risk through possible or probable exposure to persons who are infectious. It is helpful to consider three scenarios and groups:

- Providing Care for sick people with presumed in the home
- Crowded public places (internal travel)
- Occupations with face to face contact with the public

Objective and Rationale: The prime objective is to reduce transmission in higher risk settings but another is to allow persons in key activities to continue to work while giving them some protection.
Evidence of effectiveness: There are no trial and few other data. Hence the effectiveness in reducing transmission is unknown though often presumed in health care settings.(Brankston 2007, Canada 2006)
Direct costs: The costs of supply and training. *Moderate*
Secondary effects: *Small*
Likely acceptability and expectations: This is unknown. There is no tradition of mask-wearing in the EU. However one or two European countries have announced they will purchase masks for their residents. It is quite likely that representatives (trade unions) could request or insist that their members have protection in certain circumstances.
Practicalities and experience: Some authorities consider that certain workers, such as *First Responders* and people working at counters, check-outs will expect to be supplied with masks if they are to continue working. There will be issues around communication, training and disposal of used masks. There are some suggestions that masks could be cleaned or sterilized and re-used.
WHO Policy (2005) Global Influenza Preparedness Plan. No policy but UN staff guidance is that they should to be equipped with a limited supply of simple masks.

9. Mask wearing by people with respiratory symptoms

See discussion above on Masks and *L. General vs. Selective Measures.* This is an extension of what is now practice in some health care setting of insisting that all those people with symptoms wear masks. This may be the best use of limited amounts of masks.
Objective and Rationale: To reduce transmission from those people known or presumed to be infected and infectious with respiratory infections.
Evidence of effectiveness: There are no trial and few other data. Hence the effectiveness in reducing transmission is unknown though often presumed in health care settings.
Direct costs: The supplies required per person would be considerably more than for other mask wearing as the masks would presumably be contaminated very quickly and require changing. *Moderate*
Secondary effects: Some authorities have suggested perverse effects could result if mask-wearing was seen as an alternative to *Early Self Isolation of Ill People (PHM 10)*
Likely acceptability and expectations: This may be better accepted than some mask-wearing as it makes sense and is an extension of practice in some health care settings. It may also make Early Self Isolation in home settings more acceptable.
Practicalities and experience: There is little experience outside of health care settings. People who are very ill find it hard to wear masks though this is less of a

problem for people with mild illness which is accepted practice in Asia. See discussion above on Masks and *L. General vs. Selective Measures*
WHO Policy (2005) Global Influenza Preparedness Plan

10. Voluntary isolation of cases not requiring hospitalization

Ill persons likely to have influenza and not needing hospital care would be requested to remain voluntarily in a single, dedicated room through the duration of symptoms. This would usually be in their own homes, but could be elsewhere.
Objective and Rationale: reducing transmission by reducing contact between cases in their most infectious phase and uninfected persons.
Evidence of effectiveness: No published evidence from trials (trials have not been attempted) but this measure makes good sense. Modeling studies have suggested that cumulative attack rates would be reduced somewhat by this measure.(Germann 2006, Ferguson 2006) .
Direct costs: There can be financial and practical disincentives if the person will lose wages or they are needed to care for others e.g. children and spouses. There will also need to be many other preparations (see Practicalities and experience) *Moderate*
Secondary Effects: People in the home of the person may be put at risk of infection and there are other possible adverse clinical outcomes may result for persons who do not receive adequate care and support while isolated, especially the elderly or persons who live alone. There would be issues of people not being available for work including caregivers – although many ill persons and caregivers would be absent from work anyway even without a specific isolation policy. If case isolation and infection control within households is not effectively applied, household care may increase transmission in households and those in homes with sick people will feel put at risk. *Moderate*
Likely acceptability and expectations: Acceptability is considered high as this is an extension of advice during seasonal influenza. However acceptability will vary by circumstance (see Practicalities).
Practicalities and experience: This is one of the measures where prompt recognition of illness will be important. (*See General Consideration O*) There will need to be planning concerning support of financial, social, physical, and other needs of the patient and caregivers e.g. allowing paid time off work for ill persons and care-givers. Training and supplies will be essential for infection control for household members providing care for the ill person. There will be some people for whom this is an impossibility including persons in crowded households (who cannot have their own room); people who become ill while traveling, people in institutions, migrants and the homeless. During the SARS outbreaks of 2003, there was a generally good degree of voluntary compliance with this measure in a number of affected centres, though people seemingly not complying did cause problems in one or two countries.(Health Canada 2003)
WHO Policy (2005) Global Influenza Preparedness Plan: Recommended at all pandemic phases and for seasonal influenza

11. Voluntary quarantine of household contacts (including *protective sequestration*)

People who were household contacts of a person with proven or suspected influenza before the ill person was isolated might be asked to remain at home for a defined period (e.g. one incubation period 3 days) after the last exposure. If symptoms of illness occur they would then self-isolate themselves and seek medical advice. This follows from the observation that the group at highest risk of acquiring influenza is those who are a household contacts of a case. Also since infectivity is high early in illness then quarantine of household contacts before they became ill may help prevent their infecting others before they can isolate themselves. This measure might be combined with home treatment with antivirals (PHM 20). An extreme variant of this is *protective sequestration* (see Glossary). Modeling studies have suggested that cumulative attack rates would be reduced somewhat by this measure though less than might be thought intuitively.(Germann 2006, Ferguson 2006) Another more feasible variant is *work quarantine* (see Glossary for different definitions) where quarantine is only observed in those working in settings where there is high risk of chains of transmission or there are people at high risk of disease. E.g. for nursing staff.

Objective and Rationale: Reducing transmission attempting to prevent escape of influenza from family settings
Evidence of effectiveness No published evidence from trials (trials have not been attempted). However this measure makes sense from application of infectious disease control.
Direct costs: This will result in significant numbers of people being off work *Massive*
Secondary effects: With many larger numbers of people staying home the costs and adverse effects will be like those of early self-isolation only considerably greater. There is likely to be particular legal problems of paying wages or compensation to well people.
Likely acceptability in Europe This is unknown but probably low and compliance might be especially difficult with a measure for which no personal benefit is perceived and the community benefit is unclear.
Practicalities and experience This needs rapid and effective identification of cases in the household and then voluntary compliance by household contacts and an ability to provide support to households that are under quarantine plus information on infection control in the home. Otherwise similar to isolation of ill persons (see PHM 10). Sequential illnesses among people in same household would result in contacts remaining in quarantine for considerable time. Experience from previous pandemics and the SARS episodes is variable but often negative in communities with cultural similarities to Europe (Canada and in the 1918-19 pandemic).(WHO 2006a, WHO 2006b. Digiovanni 2004) Lack of compliance or abuse (real or perceived) by some people undermined confidence in the measure and there would be particular problems with special groups (Table 3).

WHO policy: Not recommended in Phase 6.[24]

Social Distancing Measures

This term should be used cautiously. It is a collective term covering a number of quite distinct and different measures which are best considered individually on their merits. Vague policy recommendations such as *increase social distancing* are not recommended.

12. Internal Travel Restrictions

Objective and Rationale: To prevent or slow extension
Evidence of effectiveness: This makes theoretical sense and there are some observations that this measure was successful in a few setting in previous pandemics. However these were unusual and rather isolated setting where there was very limited travel anyway.(Markel 2006a, Markel 2006b) *Minor delaying effect*
Direct costs: The costs to the transport system through loss of revenue are considerable though internal travel is likely to decline anyway. Other direct costs are on travel dependent industry and trade. *Major*
Secondary effects: In most European setting this measure would result in huge social costs as many functions like food distribution and fuel supply break down. *Massive*
Likely acceptability and expectations: Acceptability is unknown in Europe though reduction in non-essential travel is likely to be good.
Practicalities and experience: The most common experience reported during the 1918-19 pandemic was that where travel was frequent these measures when tried was both ineffective and quickly broke down.(2006a, 2006b)
WHO Policy (2005) Global Influenza Preparedness Plan: Not recommended in Phase 6.[25]

Educational Setting and Day-care Based Interventions

These are felt by some authorities to be especially important for two reasons. Firstly respiratory infections are always observed to spread easily in day-care and school settings and secondly one of the three pandemics of the 20th century (that of 1957) showed a particular focus of transmission in children. See General Considerations B and Fig 3. Also in some pandemics schools have closed 'naturally' and its felt it may be better to do so in a controlled way and planned way. **Certainly all schools and day care institutions should have a plan for**

[24] Note is recommended in Phases 4 and 5 where dealing with a small and manageable number of localized cases
[25] Note this is recommended to an extent in the very different circumstance of the very first emergence of a pandemic strain anywhere in the world – the Rapid Containment Strategy (WHO 2007).

how they could close in a crisis and parents and carers would need to be involved in this planning so they can make their own arrangements. Schools and educational authorities would also need to agree plans for re-opening.

At least three major difficulties arise. The need to define and measure in a crisis what is the level of severity and the focus of transmission in children to justify closures. The secondary effects will probably be massive as the children have to be cared for, especially if they are not to simply mix and transmit virus outside of school. In many settings schools perform special social functions providing social care, meals and pastoral care as well as education.

13. Reactive School and Day Care Closures

This is the planned closure of schools when it is seen that there is transmission taking place in the school.

Objective and Rationale: To reduce the anticipated amplification of influenza transmission in schools

Evidence of effectiveness: There are some observational analyses that suggest some positive effect when seasonal influenza outbreaks or pandemics have coincided with school holidays or school closures for other reasons.(WHO 2006a, WHO 2006b) However the effects are smaller than might be predicted by modeling studies, perhaps because children mix outside of schools.(Inglesby 2006) Another model is what happens when school-age children are immunized (Jordan 2006) A major concern is that if there is any delay in appreciating that transmission has started in the children then there may be little effect as the damage will already have been done. Hence the preference stated by some for *Proactive Closures.*

Direct costs: The costs of the planning and logistics of school closures (Table 5) are considerable. *Moderate*

Secondary effects: The costs and disruption of school closures are immense especially for European societies that have no tradition of school closures outside the holiday seasons. In some European countries a significant proportion of health care workers have school age children and so would need to have time off work to supervise or care for their children. This raises issues similar to those that arise under voluntary quarantine (PHM 10). *Massive*

Likely acceptability and expectations: This is not well known since there is little tradition of school closures in Europe. However some EU countries are planning such closures.

Practicalities and experience: There are huge practicalities but ones that would need to be faced up to with the likelihood that in a severe pandemic schools would close anyway (Table 5). Major difficulties can be experienced in that some countries will be seen to be closing schools while others will not or will close schools at a later stage. This will require preparation of communication strategies.

WHO Policy (2005) Global Influenza Preparedness Plan: Consider school closures in Phase 6

14. Proactive School and Day Care Closures

This is the planned closure of schools when it is judged that influenza transmission is approaching the school but before it starts in the school itself
Objective and Rationale: To prevent the amplification of influenza transmission in schools.
Evidence of effectiveness: See last item 13 Reactive School Closures. The advantage of Proactive Closures is that they can be done before any transmission has taken place in the schools. The disadvantage is the difficulty of timing in that the intervention may be implemented too early and then be exceptionally costly and difficult to sustain.
Direct costs: The costs of the planning and logistics of school closures (Table 5) are considerable. *Moderate*
Secondary effects: The costs and disruption of school closures are immense especially for European societies that have no tradition of school closures outside the holiday seasons. See 13 above. *Massive*
Likely acceptability and expectations: See 13 above.
Practicalities and experience: See 13 above and Table 5.
WHO Policy (2005) Global Influenza Preparedness Plan: Consider school closures in Phase 6

Measures in the Workplace and Public Places

These are measures that are attempting to reduce transmission. Decisions are made difficult because of the lack of objective information on the amount of influenza transmission that takes place in the workplace, on transport going to and from work and in other public places. Modeling studies often make assumptions on the proportion of transmission in workplace and public settings however there are few if any empirical data underpinning these assumptions and the published figures should be approached with caution.(German 2006, Ferguson 2006) Generally there have been no plans for proactive workplace closures because of the lack of certainty that there are large amounts of transmission in workplaces therefore that is not considered as a measure.

15. Reactive workplace closures

Objective and Rationale: To reduce workplace transmission.
Evidence of effectiveness: There is hardly any information on this and no studies. It may be significant that there are few reports of influenza transmission and outbreaks in workplace settings.

Direct costs: These depend on the workplace however since most work is productive there will be some significant costs of closure for any period of time, especially if it was thought necessary to close for much of the three months that a pandemic would affect a local area. *Major*
Secondary effects: As for the direct costs there would be major economic costs. In addition in the highly interdependent societies of Europe there would be very significant effects in organisations dependent on the organisation that was closing. For example a factory closing would affect both its suppliers and those that received its output. *Massive*
Likely acceptability and expectations: Some organisations are used to closing or at least scaling activities down during holiday periods but not for this extended periods. There will be major anxieties by staff about security of wages and employment.
Practicalities and experience: Though some organisations close or scale down in holiday periods they do not close for this period of time. The practicalities would be major and it is doubtful that planning for this eventually would have any priority compared to PHM15 changing patterns of work and Business Continuity Planning (coping with 30% of staff being off for extended periods). Some businesses will need to increase operations in a pandemic (e.g. healthcare supplies).
WHO Policy (2005) Global Influenza Preparedness Plan: Not mentioned

16. Home working, Reducing Meetings, Safety in the Workplace

This could be part of a package of measures to reduce risk in the workplace, on the way to and from work and public places. There would be many advantages to all organisations and businesses having a programme of education and some potential components are shown in Table 6.

Objective and Rationale: To reduce transmission outside home and educational settings.
Evidence of effectiveness: There is hardly any information on this and no studies. It may be significant that there are few reports of influenza transmission or outbreaks in workplace settings.
Direct costs: These depend on the extent of the measures (see Table 6). *Variable to moderate*
Secondary effects: These depend on the extent of the measures. *Variable to Moderate*
Likely acceptability and expectations: Some companies have already started on this planning with Business Continuity Planning.
Practicalities and experience: A candidate package of measures is suggested in Table 6. The selection from this will depend on the company and the type of work.
WHO Policy (2005) Global Influenza Preparedness Plan: No mention

17. Cancelling public gathering, international events etc

Decisions are made difficult because of the lack of objective information on the amount of influenza transmission that takes place in the workplace, on transport going to and from work and in other public places. Modeling studies make assumptions on the proportion of transmission in workplace and public settings however there are few if any empirical data underpinning these assumptions and they should be recognized as such.(WHO 2006a, WHO 2006b)

Objectives: To reduce transmission and dissemination of influenza through large gathering. To reduce the risk to people traveling to events and becoming sick away from home
Evidence of effectiveness: Common sense would suggest that large meetings, conferences, international events would be important in spreading infectious diseases though there are actually few reports of this. This is in contrast to other infections, for example gastrointestinal illnesses where explosive spread following small or large gatherings are reported quite commonly. SARS provides an interesting model with the international dissemination from one hotel in Hong Kong though dissemination was not related to any specific meeting.
Direct costs: Any decision to cancel all events over a period would be controversial and costly. The issue of liability and meetings insurance would be crucial. *Major*
Secondary effects: As for the direct costs there would be many secondary effects on those who service meeting and events. *Major*
Likely acceptability and expectations: The public may expect this to happen.
Practicalities and experience: Meetings and events are often cancelled and most larger organizers will have procedures for this. The issue of who is liable is crucial as although there is insurance for this it frequently states that it does not apply where the cancellation is due to another body's action. There will be *boundary issues* over what is a large enough public gathering to warrant cancelling.
WHO Policy (2005) Global Influenza Preparedness Plan: No mention

ANTIVIRALS AND OTHER MEDICATIONS

Much reliance is being put on the use of antivirals (mostly oseltamivir) in Europe for prophylaxis or early treatment for the pandemic influenza strain. The evidence base for use as **prophylaxis in reducing transmission** is limited but relatively good.(Hayden 1996, Hayden 2004, Halloran 2007) Essentially a seminal re-analysis of four randomized placebo-controlled trials of oseltamivir and zanamavir found that both were effective in preventing infection and disease in low-risk (well young adults) contacts of low-risk cases with laboratory confirmed infections with **human seasonal influenza**. Similarly for **early treatment** both drugs were effective in reducing but not eliminating the experience of symptoms.(Halloran 2007,Jefferson 2006) While there was significant reductions

in the proportion of subjects experiencing symptoms in absolute terms the symptoms experienced were mild and the reduction in duration of those treated only of a day or so.

Effect on Severe Disease and Death? There is as yet only limited information of the effect of early treatment with oseltamivir on reducing the risk of severe disease and death. Trial data will not be helpful as they are always too small. Also there is the problem that the observed effects to date can only be on seasonal influenza. The evidence is of some benefit from early treatment against H5N1 (WHO 2007). [Link to ECDC papers] What data there is suggests some benefit though its not clear if it is as great as some of the assumptions that have been made, for example that early treatment will reduce hosptialisations by 50%.(Gani 2005) The limited work to date is summarized in a separate paper by ECDC (Kaiser 2003, McGeer 2006, Nordstrom 2005). Antivirals are little used in Europe for influenza and the experience of Japan the one country that has used oseltamivir extensively against seasonal influenza requires further analysis.(Kawai 2005) Finally all that experience may or may not apply against the novel pandemic strain. Where there is more certainty and unanimity is that with any influenza early treatment is essential. There is no firm 'cut-off' (though its common to read a time of 48 hours since the start of symptoms). The trial data are consistent with 24 hours being better than 48 hours.(Moscona 2006a)

Adverse Effects It is known with the older antivirals that severe side effects are rare. However it is not clear if there are rare and severe side-effects with oseltamivir and zamanivir because of their not having been used much in Europe. Reports of an association with rare neuropsychiatric events in Japan may be the results of coincidence but are the subject of investigations at present.

Logistical Difficulties In applying the ECDC *Acid Tests* on early antiviral treatment there are substantial logistic difficulties in delivering large amounts of antivirals to many people when and where they need them within 24 or 48 hours.(ECDC 2006d) The experience of operational modeling and some exercises has also revealed considerable difficulties in handling the antivirals in a pandemic. Some countries that have devised systems for delivery have had to redesign their systems as a consequence. The simplest solution of allowing or encouraging home stocks is undesirable on a number of grounds (Table 6).(Brett 2005) The same is true for dispersal of stockpiles to local health care providers because of the probable uneven need in a pandemic. Antivirals will need to be distributed through conventional primary care or parallel systems. Therefore practicalities will revolve around the pre-existing systems or alternatives that are being devised. Storing stocks as powder is now appreciated to be inconvenient and many of those stocks are being converted to more manageable capsules.

Presumptive Treatment Most of the treatment will need to be without confirmation of a diagnosis. There will not be the human or laboratory resources and there will certainly not be time before treatment must start. Depending on the

level of other circulating viruses there may be a lot of antivirals that are used for other perhaps trivial infections, seasonal influenza, respiratory synctial virus etc. Hence there may be considerable 'wastage' in the use of antivirals.

Use of Antibiotics It is appreciated that treatment with antibiotics may improve the prognosis of infected persons whose condition is deteriorating, and may have significant impact on influenza-related mortality and morbidity due to secondary infections. While this will do nothing for reducing transmission it could reduce pressure on hospitals. However this means that there will also need to be stockpiles of antibiotics developed.

Early Treatment with Antivirals

18. Early Treatment of all those with symptoms

See General Antivirals Discussion above

Objective and Rationale: To reduce the risk that people infected will progress to severe disease or death
Evidence of effectiveness: No direct evidence. Small effect inferred from trials against seasonal influenza.
Direct costs: With countries acquiring large national stockpile investments are considerable. *Massive*
Secondary effects: Aside from the competing costs (monies spent on anti-virals cannot be used for other things) there is the unclear risk of possible rare but severe side-effects.
Likely acceptability and expectations: It is thought that acceptability by professionals and patients will be high and the expectations are almost excessive in that it is a common belief that having an antiviral stockpile is a solution in itself. It is an essential tool but not sufficient.
Practicalities and experience: Major logistical difficulties discussed above. Additionally the proportion of stockpiles as oseltamivir, M2 inhibitors, the amounts in capsules versus powder and paediatric suspensions.
WHO Policy No policy on antivirals

19. Health Care or Other Exposed Key Workers

See General Antivirals Discussion above. Some countries are seeing it important to protect health care workers and perhaps others who may be put *in harms way* through their work and ensure they have early treatment if they develop symptoms.

Objective and Rationale: To protect persons whose work makes especially expose them to influenza in a pandemic.
Evidence of effectiveness: No direct evidence. Small effect inferred from trials against seasonal influenza.

Direct costs: Because there are substantial numbers of health care workers the costs of having treatment for all of them through a pandemic is substantial. However will only need to treat those that become ill though there will be a case for testing to see if the person has influenza. The differs to concerns around long term prophylaxis (see 23 below). *Major*
Secondary effects: Unclear risk of possible rare but severe side-effects.
Likely acceptability and expectations: It is thought that acceptability by professionals will be high.
Practicalities and experience: Major logistical issues discussed above.
WHO Policy No policy on antivirals

Antiviral Prophylaxis Following a Single Case

20. Given to Family (Household) Members of Influenza Cases

See General Antivirals Discussion Above This is based on the observation of the high risk of transmission in households

Objective and Rationale: To prevent secondary and subsequent cases**.**
Evidence of effectiveness: No direct evidence. Moderate effect inferred from trials against seasonal influenza.
Direct costs: These could be massive. One calculation has suggested it would potentially require stockpiles for at least 100% of the population (one course per person) if it was not highly successful initially and there was repeated introductions of the pandemic strain.(Wu 2007) *Massive*
Secondary effects: Unclear risk of possible rare but severe side-effects. May speed up development of antiviral resistance. *Moderate*
Likely acceptability and expectations: It is thought there would be significant abuse if it was perceived as a way of obtaining family stocks of antivirals.
Practicalities and experience: Major logistical issues discussed above. Giving prophylaxis for the family when starting early treatment of a case would be logistically attractive if it was not for the very large stockpiles that might be needed. Another difficulty will be *boundary issues*, deciding who is in a household. Prophylactic antivirals are only effective as long as they are being taken; therefore, once the prophylaxis is completed, a second member of the household could become ill with influenza from a different external source, thus counteracting the rationale for the previous prophylaxis.
WHO Policy (2005) No policy on antivirals.

21. Family and Social Contacts

See General Antivirals Discussion above. This is an extension beyond PHM 20 to include other social contacts.

Objective and Rationale: To prevent secondary and subsequent cases**.**
Evidence of effectiveness: No direct evidence. Moderate effect inferred from trials against seasonal influenza.
Direct costs: These could be huge. *Massive*

Secondary effects: Unclear risk of possible rare but severe side-effects. May speed up development of antiviral resistance. *Moderate*
Likely acceptability and expectations: It is thought there would be significant abuse if it was perceived as a way of obtaining family stocks of antivirals.
Practicalities and experience: Major logistical issues discussed above. Giving prophylaxis for the family when starting early treatment of a case would be logistically attractive if it was not for the very large stockpiles that might be needed. Another difficulty will be *boundary issues*.
WHO Policy No antiviral policy

22. Family and Geographical Contacts

See General Antivirals Discussion Above. This means prophylactic use in the workplace or classroom once a case has been diagnosed.

Objective and Rationale: To prevent secondary and subsequent cases**.**
Evidence of effectiveness: No direct evidence. Moderate effect inferred from trials against seasonal influenza.
Direct costs: These could be huge. *Massive*
Secondary effects: Unclear risk of possible rare but severe side-effects. May speed up development of antiviral resistance. *Moderate*
Likely acceptability and expectations: It is thought there would be significant abuse if it was perceived as a way of obtaining family stocks of antivirals.
Practicalities and experience: Major logistical issues discussed above. Giving prophylaxis for the family when starting early treatment of a case would be logistically attractive if it was not for the very large stockpiles that might be needed. Another difficulty will be *boundary issues*,
WHO Policy No antiviral policy

Continuous Prophylaxis

See General Antivirals Discussion Above

23. Health Care or Other Key Workers

Objective and Rationale: There are two possible objectives. Firstly as a variant of PHM 19 protecting health care workers who are likely to be exposed. Secondly there are benefits to keeping some particular key workers healthy through the pandemic until a pandemic vaccine is produced and available.
Evidence of effectiveness: No direct evidence. Moderate effect inferred from trials against seasonal influenza.
Direct costs: This depends on the objective. The costs would be massive for all health care workers given the size of this workforce. For the key workers it depends on the size of the population. *Massive*
Secondary effects: Unclear risk of possible rare but severe side-effects. May speed up development of antiviral resistance. *Moderate*
Likely acceptability and expectations: It is not entirely clear that continuous medication will be well accepted in the face of real or suspected side effects. It

also depends on the perceived risk. Experience with other prophylactic treatments is that a significant proportion of those that start long courses come off them after a while.
Practicalities and experience: Presently use of antivirals is limited so that use would be beyond the indicated limit. There could be stockpile difficulties if there were delays in a pandemic vaccine becoming available and of course the protective effect will stop as soon as treatment ceases.
WHO Policy: No policy on antivirals

Vaccines – Human Avian Influenza Vaccines

This section will be added when the ECDC Guidance on these Vaccines has been published

24. Whole Population

Objective:
Evidence of effectiveness:
Direct costs:
Secondary effects:
Likely acceptability and expectations:
Practicalities and experience:
WHO Policy (2005) Global Influenza Preparedness Plan:

TABLES AND FIGURES

Table 2 Human influenza: characteristics for the transmission and control

The following parameters are known to apply to seasonal influenza. It is often assumed that they would apply to a new pandemic strain and they are reasonable default positions. However it needs to be appreciated that the parameters could be very different and need to be rapidly investigated early in a pandemic.

- Person-to person spread, primarily by the respiratory route through large droplets over short distances (beyond one metre risk falls considerably) with some transmission also by contact with respiratory secretions such as on hands and surfaces[26];(Brankston 2007)
- Aerosol transmission occurs but seems to be uncommon under usual circumstances; it may be made more likely by some medical procedures (e.g. intubation, bronchial lavage) (Tellier 2006, Brankston 2007)
- The incubation period (the period between infection and onset of symptoms) is a mean of 2-3 days (range 1-4 days);
- Peak infectivity is early in illness; with infectivity directly correlated with the severity of fever and symptoms[27];(Foy 2005)
- The period of communicability is typically up to 5 days after symptom onset in adults and 7 days in children[28]
- Each case will infect on average between 1.4 and 1.9 other people in the absence of interventions (i.e. R_0 =1.4 to 1.9);(Hall 2007)
- Influenza viruses are easily made inactive by washing with soap, alcohol based hand sanitizers, and cleaning with normal household detergents and cleaners.(Bean 1982, Shurman 1983)
- Barrier methods such as proper use of tissues and simple masks are thought to reduce transmission from infected persons though the evidence base for this is weak see http://www.eurosurveillance.org/ew/2007/070510.asp#1
- In seasonal influenza and some pandemics children seem to account for a disproportionately large number of transmissions

Important Variations There are some important parameters that are known to have varied significantly in the three pandemics that have been well studied. See http://www.ecdc.eu.int/Health_topics/Pandemic_Influenza/stats.html these are:

- Severity of disease – the case fatality rate

[26] Human influenza viruses can survive on environmental surfaces, especially so on hard non-porous materials (up to 48h)

[27] Virus may be detected in the secretions of infected but pre-symptomatic persons, but there is only limited evidence of transmission from presymptomatic individuals. I.e. some transmission takes place from persons without symptoms but it seems to be unusual;

[28] Virus excretion may be more prolonged in immunocompromised patients

- Age-groups most affected and where transmission has been concentrated

In addition the severity of disease will change over time so that case fatality rate needs to be monitored over time

Table 3 Some Groups Requiring Special Planning

Group	Special Difficulties
The elderly especially those living alone	Will be less able to care for themselves at home, but may not need hospitalisation when ill
Children	May not readily know what to do if they develop symptoms and may be less likely to comply with measures
Homeless people	Will be unable to care for themselves at home, but will not need hospitalisation when ill
People travelling but 'caught' in a European country	Will be unfamiliar with the country, systems and language
Physically handicapped people	May be less able to care for themselves at home, but may not need hospitalisation when ill
People with learning difficulties	May not readily know what to do if they develop symptoms and may be less likely to comply with measures
People with special communication needs[+]	Will not receive or
People in institutions	More likely to be in crowded circumstances where infection control will be difficult
People living in poverty	More likely to be in crowded circumstances and more limited access to health care.

[+] Those with hearing difficulties, visually impaired, not speaking the national languages

Table 4 European Interoperability and Pandemic Planning

Negative

1. I do something in my state that impacts negatively direct on your state E.g. Closing borders if that stops daily commuting for work

2. I do something in my state that causes questions in another state – especially if its done without warning. E.g. starting publicly screening people coming off flights

Positive

3. A few of us work for all. Actions that can be undertaken most efficiently in a few MS rather than all Member States but all MS benefiting e.g. Monitoring for the development of antiviral resistance

4. All of us share thinking and analyses on particular policy areas so that conclusions emerge from a common understanding of what is known and not known e.g. whether and when to close Schools proactively

5. (A variant of 4) some of us move from 4 to agreeing on certain joint measures

6. We share our experience and development while recognizing the diversity across Europe one size will not fit all) – the Member State to Member State approach Measures enacted in one state that will potentially cause some confusion in other states E.g. mask-wearing

7. I talk specifically with my neighbours in relation to all the above.

8. I warn all others as to what we plan to do in our MS in a pandemic (*Pandemic Presumptions)*

9. ECDC and WHO develop common mechanisms and tools for preparing and dealing with pandemics e.g. the Assessment Tool

Table 5 Some Practicalities arising from School Closures

1. Educating, supervising and entertaining the children out of day care and school.
2. Negotiating leave (preferably paid) for parents/carers to enable them to be off work to care for children who are not sick.
3. Additional stress on those having to cover the work of those who are staying home with children.
4. Continuity of pastoral care and social programmes administered through schools.
5. The complexity of schools and school systems (public and private; state and religious based.
6. Defining the triggers points and timing for closure and re-opening of schools and geographic areas that would be involved given that a national system may not be desirable (see *C Diversity in the Pandemic*).
7. Defining practices for tertiary (University sector) education institutions with halls of residence, students whose homes are elsewhere in the country or even abroad and who may be 'trapped' at their college setting.
8. Communication with the staff, student body and families
9. Meeting the needs of special groups (See Table 3)

Table 6 A Candidate Package of Measures for Workplace and Public Settings

Staff Protection

Educating staff on personal protective measures
Ensuring early exclusion of ill workers especially those developing illness in working hours with masks for their safe travel home,
Promotion and support of hygiene measures in the workplace,
Planning no-cost or low-cost flu leave policies to allow employees to stay at home in isolation or caring for ill family members.
Shift working to reduce over-lap at work and reduce crowding on transport (see also
Where permitted Specific social distancing measures will differ by industry; for example, telecommuting may be more difficult for production than service sectors. Some measures may interact with community social distancing measures, such as staggering shifts to reduce social contact while commuting. Such interventions and the altered business operations to facilitate them would be one of many components in business continuity of operations planning.

Business continuity planning

Planning for loss of up to 30% of staff for an extended period.

Goals:

- Reduce workplace contacts by 50%
- Promote a safe environment and promote confidence in the workplace
- Maintain business continuity, especially for critical infrastructure

Table 7 **Some Operational Disadvantages Arising from Home Stockpiles of Antivirals** (Brett 2005)

1. National stockpiles automatically have to be more than 100% of populations on equity grounds

2. Stocks cannot be moved around the country to where they are most needed

3. There is likely to be early use and exhaustion of stocks

The likelihood of early development of antiviral resistance increases

Glossary

- *Asymptomatic Infections:* Infections that do not cause any symptoms
- *Boundary Issues:* Deciding how to divide populations into those receiving and not receiving a treatment. E.g. who is and who is not a social contact of a case.
- *Case Fatality Rate or CFR:* The proportion of people infected that die as a consequence of their infection.
- *Isolation and Quarantine:*
  - *Isolation:* Applies to people experiencing illness meaning separation or restriction of movement of ill persons with an infectious disease to prevent transmission to others.
  - *Quarantine:* Applies to people exposed who may or may not be infected but are not ill. It means separation or restriction of movement of exposed persons who may become infectious to others.
- *Infection control* : A collection of measures intended to reduce the risk of transmission from an infected person to un-infected persons (e.g. hand and respiratory hygiene, masks and respirators, disinfection)
- *Interoperability:* An imprecise term applied to a bundle of ideas as to how countries might plan to act before and during a pandemic (Table X). It is recommended to consider each of these ideas separately.
- *Non-pharmaceutical interventions*: Measures that do not include pharmaceutical products such as vaccines and drugs
- *Presymptomatic Infections:* Infections early in the incubation period that have not yet caused clinical symptoms.
- *Protective sequestration*: A term used to describe when healthy people attempt to isolate themselves to reduce the risk of exposure to an infection
- *Personal Protective Measures:* Infection control measures that individual people can undertake e.g. hand-washing
- *Reproductive Number* or R_0 :The average number of people that will one person with influenza infects (usually meaning in the absence of applying countermeasures)
- *Respiratory Hygiene:* Use and disposal of tissues to cover mouth and nostrils when coughing and sneezing and their proper disposal
- *Respirators:* Specialist masks that can prevent the transmission of very small particles e.g. infectious organisms transmitted in aerosols
- *Secondary effects:* The costs, risks and consequences of applying the Public Health Measures themselves,
- *Social distancing*: An imprecise term often applied to the collection of measures intended to decrease the frequency of contact among people and so possibly reduce influenza transmission. It is considered by most authorities better to describe the specific measures
- *Surgical masks:* Masks worn when undertaking surgical procedures, mostly intended to prevent droplet transmission of respiratory infections from the wearer (not able to protect against infections in aerosols)

- *Work Quarantine*: This has two different meanings.
  - One is when quarantine is observed or special measures taken by health or social care workers people who have been exposed and who work in a setting where influenza is especially liable to transmit (or where there are people at higher risk from infection). Examples would be people working in old peoples homes and nurses in high risk settings (e.g. neonatal care nurseries, intensive care units).
  - Another meaning is from the time of SARS when some health care workers chose to stay away from their families when off-duty so as not to carry the infection home, a practice seen earlier among nurses at the time of Spanish Influenza.

Figures

Figure 1 Objectives of Applying Public Health Measures in a pandemic

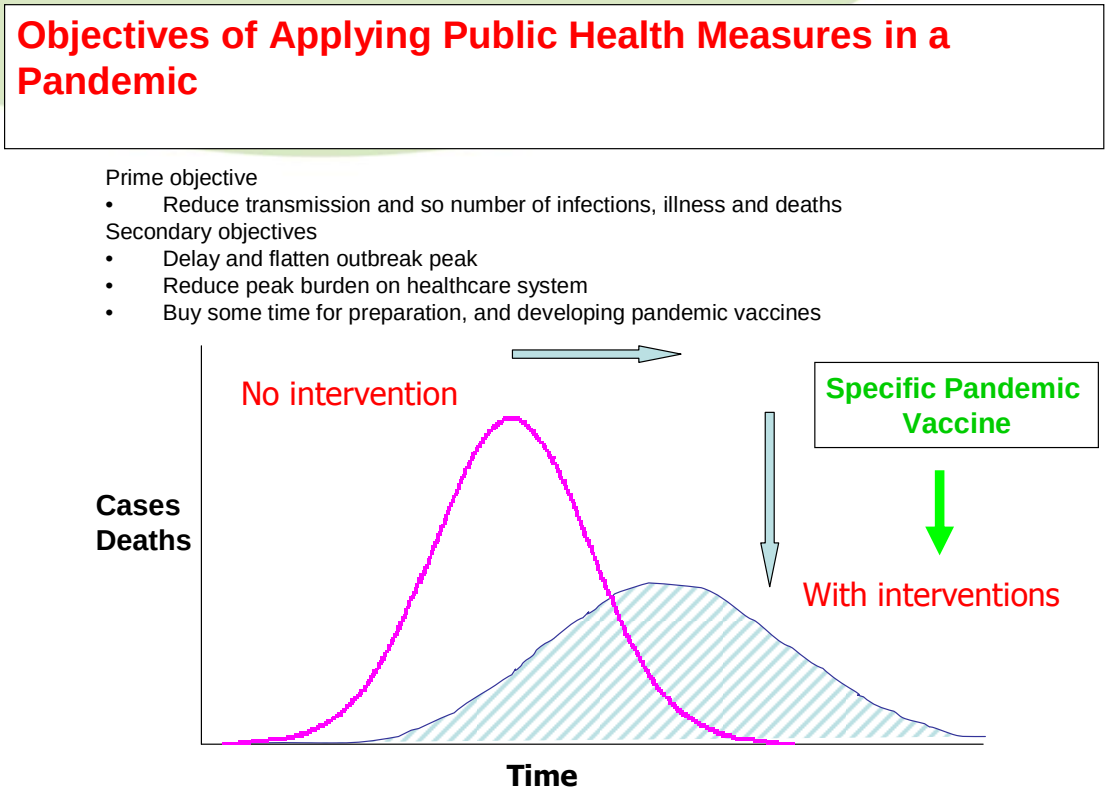


Figure 2 – Estimated age specific transmissions profiles of the three pandemics of the 20th Century (reproduced from Glass 2006)

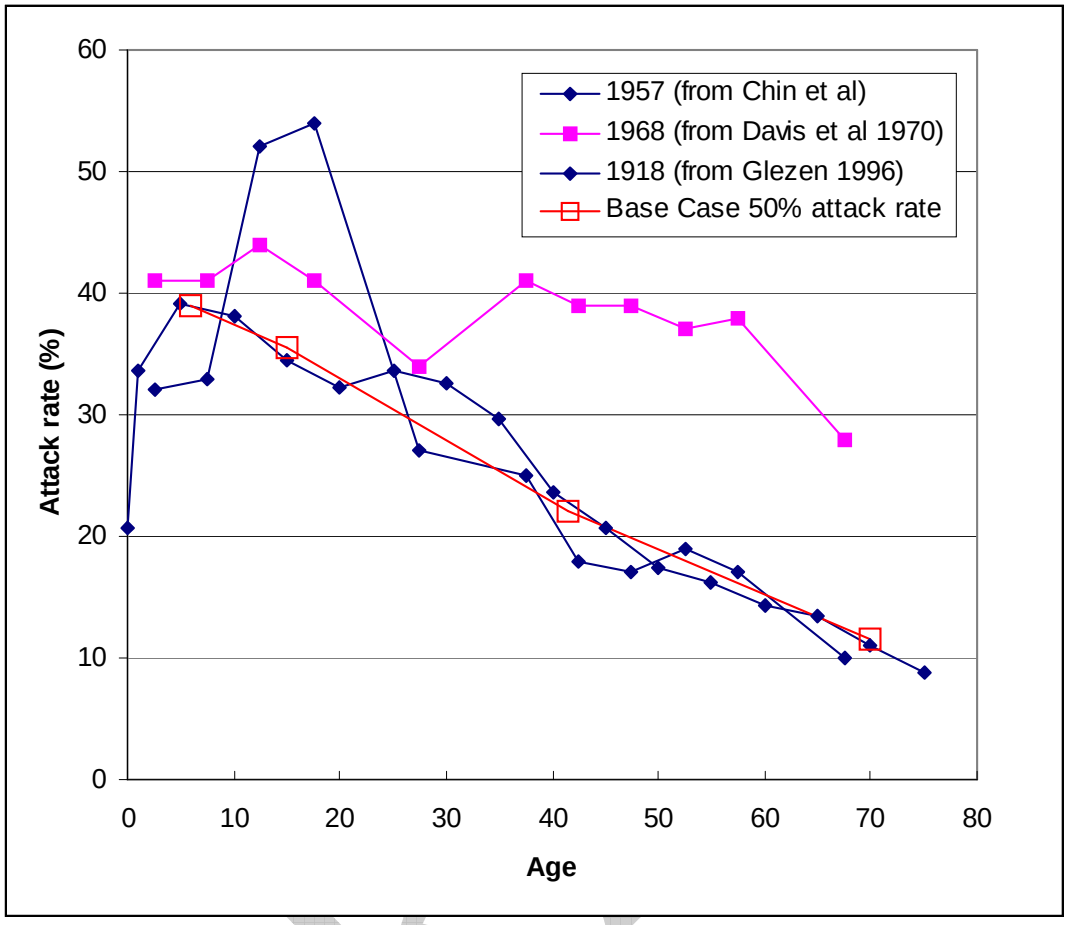
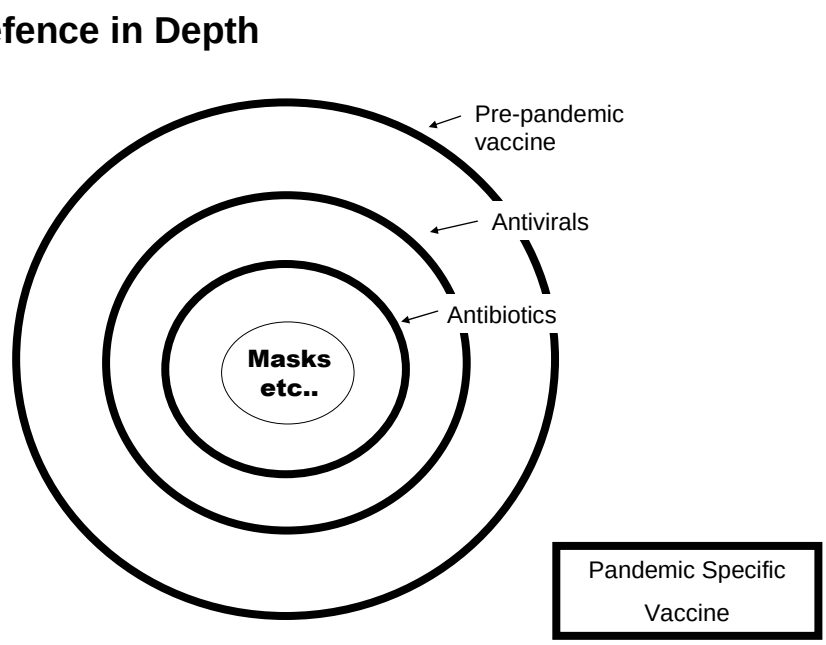


Figure 3 Getting Ahead of the Curve (to come)

Figure 4 Multiple Measures Diagram



Source Grove P: Antivirals – the impact of combined strategies
http://www.dh.gov.uk/en/PandemicFlu/DH_076566

Figure 5 Public Hand-washing Facility in a Shopping Area (Hong Kong)

References

1. Bean B, Moore BM. Sterner B, Peterson LR, Gerding DN, Balfour HH.. Survival of influenza viruses on environmental surfaces. J. Infect Dis 1982; 146: 47-51
2. Bootsma MC and Ferguson NM The effect of public health measures on the 1918 influenza pandemic in US cities Proc Natl Acad Sci USA published on line Apr 6 2007
3. Brankston G, Gitterman G, Hirji J, Lemieux C, Gardam M Transmission of influenza A in human beings. Lancet Infectious Diseases 2007; 7 (4):257 -265.
4. Brett AS, Zuger A. The run on Tamiflu – should physicians prescribe on demand? NEJM 2005: 353: 2636-7.
5. Canadian Pandemic Plan 2006 Guidance Infection Control and Occupational Health Guidelines During Pandemic Influenza in Traditional and Non-traditional Health Care http://www.phac-aspc.gc.ca/cpip-pclcpi/pdf-e/15-CPIP-Appendix-F-Infection-Control_e.pdf
6. Cooper BS, Pitman RJ, Edmunds WJ, Gay NJ. Delaying the international spread of pandemic influenza. PLoS Med 3(6): 212.DOI: 10.1371/journal.pmed.0030212
7. Cummings KJ, Cox-Ganser J, Riggs MA, Edwards N, Kreiss K. Respirator donning in post-hurricane New Orleans. Emerg Infect Dis [serial on the Internet]. 2007 May [*date cited*]. Available from http://www.cdc.gov/EID/content/13/5/700.htm
8. Department of Health and Cabinet Office, UK 2007 Pandemic flu draft framework and guidance http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_073185
9. DG Research 2007. Influenza Research EU Funded Projects 2001-2007 http://ec.europa.eu/research/health/poverty-diseases/doc/influenza-research_en.pdf
10. Digiovanni C, Conley J, Chiu D, Zaborski J. Factors influencing compliance with quarantine in Toronto during the 2003 SARS outbreak. Biosecur Bioterror 2004; 2: 265-272.
11. Donnelly CA, Ghani AC, Leung GM, Hedley AJ, Fraser C, Riley S et al. Epidemiological determinants of spread of causal agent of severe acute respiratory syndrome in Hong Kong. Lancet Published online 7 May 2003.
12. ECDC Influenza team, ECDC Influenza transmission: research needs for informing infection control policies and practice. Eurosurveillance 2007 http://www.eurosurveillance.org/ew/2007/070510.asp#1
13. ECDC (2006a) Oseltamivir prophylaxis following suspected exposure to H5N1 influenza. April 2006 http://www.ecdc.eu.int/avian_influenza/pdf/Post_exposure_oseltamivir.pdf Oseltamivir Advice.pdf
14. ECDC (2006b) Interim Recommendations Personal (non-Pharmaceutical) Protective Measures for Reducing Transmission of Human Influenza October 2006. http://ecdc.europa.eu/documents/pdf/PPHM_Recommendations.pdf
15. ECDC (2006d) The Acid Tests. http://www.ecdc.eu.int/pdf/Acid%20Tests.pdf
16. ECDC (2007a) Pandemic Influenza Preparedness in the European Union Status Report as of Autumn 2006 ECDC January 2007 http://www.ecdc.eu.int/pdf/Pandemic_preparedness.pdf
17. ECDC (2007b) Influenza transmission: research needs for informing infection control policies and practice. Eurosurveillance Weekly 2007; 12: 5. http://www.eurosurveillance.org/ew/2007/070510.asp#
18. (EISS) European Influenza Surveillance Scheme. http://www.eiss.org/index.cgi
19. European Commission (2005a). Communication from the Commission to the Council, the European Parliament, the European economic and social committee and the committee of the regions on pandemic influenza preparedness and response planning in the European Community, at http://europa.eu.int/eur-lex/lex/LexUriServ/site/en/com/2005/com2005_0607en01.pdf

20. European Commission (2005b) Communication on strengthening coordination on generic preparedness planning for public health emergencies at EU levelBrussels 28.11.2005 Com (2005) 605 http://eur-lex.europa.eu/LexUriServ/site/en/com/2005/com2005_0605en01.pdf
21. Ferguson NM (2003), Mallett S, Jackson H, Roberts N, Ward P. A population-dynamic model for evaluating the potential spread of drug-resistant influenza virus infections during community-based use of antivirals. *J Antimicrob Chemother.* 2003;51:977-990.
22. Ferguson DM (2005) Cummings DA, Cauchemez S, Fraser C, Riley S, Meeyai A, Iamsirithaworn S, Burke DS.Strategies for containing an emerging influenza pandemic in Southeast Asia, Nature, 2005 Sep 8;437(7056):209-14. Epub 2005 Aug 3.
23. Ferguson NM (2006), Cummings DA, Fraser C, Cajka JC, Cooley PC, Burke DS.Strategies for mitigating an influenza pandemic Nature 2006 Jul 27;442(7101):448-52. Epub 2006 Apr 26; doi:10.1038/nature04795
24. Ferguson NM (2006) Cummings DA, Fraser C, Cajka JC, Cooley PC, Burke DS Supplementary material and downloadable movie presentation: Nature 2006 Jul 27;442(7101):448-52
25. Foy HM, Cooney MK, Allan ID, Albrecht JK. Influenza B in households: virus shedding without symptoms or antibody response. Am J Epidemiol. 1987 Sep;126(3):506-15.
26. Gani R, Hughes H, Fleming D, Griffin T, Medlock J, Leach S. Potential impact of antiviral drug use during influenza pandemic. Emerg Infect Dis [serial on the Internet]. 2005 Sept [*date cited*]. Available from http://www.cdc.gov/ncidod/EID/vol11no09/04-1344.htm
27. Germann TC, Kadau K, Longini IM, Macken CA. Mitigation strategies for pandemic influenza in the United States PNAS 2006; 103: 5935-40 www.pnas.org/cgi/doi/10.1073/pnas.0601266103
28. Germann TC Kadau K, Longini IM, Macken CA. Mitigation strategies for pandemic influenza in the United States PNAS 2006; 103: 5935-40 Supporting information
29. Glass K. and Barnes B. How much would closing schools reduce transmission during an influenza pandemic Epidemiology 2007 18 (5), 623-628
30. Glass RJ, Glass LM, Beyeler WE, Min HJ. Targeted social distancing design for pandemic influenza. Emerg Infect Dis [serial on the Internet]. 2006 Nov [cited October 10th 2006]. Available from http://www.cdc.gov/ncidod/EID/vol12no11/06-0255.htm
31. Glezen WP. Merging infections: pandemic influenza. Epidemiologic Reviews 1996; 18: 64-76
32. Gostin L. Public health strategies for pandemic influenza. Ethics and the law. JAMA 2006; 295:1700-1704.
33. Hall IM, Gani R, Hughes HE, Leach S. Real-time epidemic forecasting for pandemic influenza. Epidemiol Inf 2007 Apr;135(3):372-85. Epub 2006 Aug 24
34. Halloran ME, Haydn FG, Yang Y, Longini IM, Monto AS. Antiviral effects on influenza transmission and pathogenicity: observations from household based trials. Am J Epidemiol 2007 Jan 15;165(2):212-21. Epub 2006 Nov 6 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=search&DB=pubmed
35. Hatchett RJ, Mecher CE, Lipsitch M Public health interventions and epidemic intensity during the 1918 influenza pandemic Proc Natl Acad Sci U S A. published online Apr 6, 2007
36. Hayden FG (1996), Osterhaus, A.D.M.E., Treanor, J.J., Fleming, D.M, Aoki, F.Y., Nicholson, K.G., et al. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenza virus infections. N Engl J Med 1996;332;874-80.
37. Hayden FG (2004). Pandemic influenza: is an antiviral response realistic? Paed Inf Dis J 2004; 23: (Suppl 11) S262-269.
38. Health Canada. Learning from SARS. Renewal of public health in Canada. A report of the National Advisory Committee on SARS and Public Health, October 2003. http://www.hc-sc.gc.ca/english/pdf/sars/sars-e.pdf.
39. Health Protection Agency 2007 The use of facemasks during an influenza pandemic http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGidance/DH_077276

40. Inglesby TV, Nuzzo JB, O'Toole T, Henderson DA. Disease mitigation measures in the control of pandemic influenza. Biosecurity and Bioterrorism: Biodefense Strategy, Practice and Science. 2006; 4 (4): 1-10.
41. Institute of Medicine 2006 Modeling Community Containment Washington DC 2006 http://www.iom.edu/CMS/3793/37624/37630/38059.aspx
42. Jefferson T, Demicheli V, Rivetti D, Jones M, Di Pietrantonj C, Rivetti A. Antivirals for influenza in healthy adults: systematic review. Lancet 2006 Jan 28;367(9507):303-13
43. The Keystone Centre Public Engagement Project on Community Control Measures for Pandemic Influenza October 2006-December 2006. USA May 2007 http://www.keystone.org/spp/health-pandemic.html#community
44. Kilbourne ED. Influenza pandemics of the 20th century. Emerg Infect Dis [serial on the Internet]. 2006 Jan [*date cited*]. Available from http://www.cdc.gov/ncidod/EID/vol12no01/05-1254.htm
45. Jordan R, Connock M, Albon E, Fry-Smith A, Olowokure B, Hawker J, Burls A. Universal vaccination of children against influenza: Are there indirect benefits to the community? A systematic review of the evidence. Vaccine; 2006: 24: 1047-1062
46. Kaiser L et al. Impact of oseltamivir on influenza-related lower respiratory tract complications and hospitalizations. Arch Int Med 2003; 167: 1667-72
47. Kawai N, Ikematsu H, Iwaki N, et al. Factors influencing the effectiveness of oseltamivir and amantadine for the treatment of influenza: a multicenter study from Japan of the 2002-2003 influenza season. *Clin Infect Dis.* 2005;40:1309-1316.
48. Kilbourne ED. Influenza pandemics of the 20th century. Emerg Infect Dis [serial on the Internet]. 2006 Jan [*date cited*]. Available from http://www.cdc.gov/ncidod/EID/vol12no01/05-1254.htm
49. Lim WS. Thorax 2007;62;1-46 (Reference Lim WS first author http://thorax.bmj.com/cgi/content/full/62/suppl_1/1#BIBL
50. Lipsitch M, Cohen T, Murray M, Levin BR. Antiviral resistance and the control of pandemic influenza. *PLoS Med.* 2007;4:e15.
51. Lo JYC, Tsang THF, Leung Y-H, Yeung EYH, Wu T, Lim WWL. Respiratory infections during SARS outbreak, Hong Kong, 2003. Emerg Infect Dis [serial on the Internet]. 2005 Nov [cited Oct 10th 2006] Available from http://www.cdc.gov/ncidod/EID/vol11no11/05-0729.htm
52. Longini IM Jr, Koopman JS, Monto AS, Fox JP.Estimating household and community transmission parameters for influenza. Am J Epidemiol. 1982 May;115(5):736-51.
53. Longini IM Nizam A, Xu S, Ungchusak K, Hanshaoworakul W, Cummings DA, Halloran ME. Containing pandemic influenza at the source. Science 2005 Aug 12;309(5737):1083-7. Epub 2005 Aug 3.
54. Markel H (2006a), Stern A, Navarro JA, Michalsen JR. A historical assessment of non-pharmaceutical disease mitigation measures employed by selected communities during the second wave of the 1918-1920 Influenza Pandemic. Fort Belvoir, Va: Defense Threat Reduction Agency; 2006. [Accessed October 10 2006]. Available at: http://www.med.umich.edu/medschool/chm/influenza/assets/dtra_final_influenza_report.pdf
55. Markel H (2006b), Stern AM, Navarro JA, Michalsen JR, Monto AS, DiGiovanni Jr C. Nonpharmaceutical influenza mitigation strategies, US communities, 1918–1920 pandemic. Emerg Infect Dis [serial on the Internet]. 2006 Dec [*date cited*]. Available from http://www.cdc.gov/ncidod/EID/vol12no12/06-0506.htm
56. Markel H, Lipman B B, Alexander Navarro J, et al Non-pharmaceutical interventions implemented by US cities during the 1918-19 influenza pandemic JAMA 2007 298(6):644-54
57. Monto AS (2006a). Vaccines and antiviral drugs in pandemic preparedness. Emerg Infect Dis [serial on the Internet]. 2006 Jan [date cited]. Available from http://www.cdc.gov/ncidod/EID/vol12no01/05-1068.htm
58. Monto AS (2006b), McKimm-Breschkin JL, Macken C, et al. Detection of influenza viruses resistant to neuraminidase inhibitors in global surveillance during the first 3 years of their use. *Antimicrob Agents Chemother.* 2006;50:2395-2402.

59. Moscona (2005a) Neuraminidase Inhibitors for Influenza N Engl J Med 2005; 353:1363-1373 http://content.nejm.org/cgi/reprint/353/13/1363.pdf
60. Moscona (2005b) A. Oseltamivir resistance—disabling our influenza defenses. *N Engl J Med.* 2005;353:2633-2636.
61. Nordstrom BL et al. Risk of influenza and other complications of influenza-like illness in patients treated with oseltamivir. Curr Med Res and Opinion 2005; 21: 761-68
62. Potter CW. Chronicle of Influenza pandemics. In Nicholson KG, Webster RG, Hay AJ , eds. Textbook of influenza. London: Blackwell scientific publications: 1998, p3-18
63. Roberts L, Smith W, Jorm L, Patel M, Douglas RM, McGilchrist C. Effect of infection control measures on the frequency of upper respiratory infection in child care: a randomized, controlled trial. Pediatrics. 2000 Apr;105(4 Pt 1):738-42
64. Ryan MAK, Christian RS, Wohlrabe BS. (2001). Handwashing and respiratory illness among young adults in military training. Am J Preventative Medicine; 21 (2): 79-83.
65. SGDN, France Plan Pandemie Grippale January 2007 http://www.grippeaviaire.gouv.fr/IMG/pdf/plan_pandemie_grippale_2007.pdf
66. Shurmann W, Eggers HJ. (1983). Antiviral activity of an alcoholic hand disinfectant. Comparison of the in vitro suspension test with in vivo experiments on hands, and on individual fingertips. Antiviral research; (3): 25-41.
67. Smith GCS, Pell JP. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials. BMJ 2003; 327: 1459-61
68. Sullivan KM, Monto A, Longini I, Estimates of the US health impact of influenza. *Am J Pub Health*. 1993; 83:1712-16.
69. Tellier R. Review of aerosol transmission of influenza A virus. Tellier R. Emerg Infectious Diseases 2006; 12: 1657-62
70. United States (2006) Department of Health and Human Services and Centers for Disease Prevention and Control. Interim pre-pandemic planning guidance: Community strategy for pandemic influenza Mitigation in the United States. Dec 2006 http://www.pandemicflu.gov/plan/community/community_mitigation.pdf
71. US Interim Public Health Guidance for the Use of Facemasks and Respirators in Non-Occupational Community Settings during an Influenza Pandemic. HHS USA May 2007a http://www.pandemicflu.gov/vaccine/maskguidance.html
72. US Interim Guidance on Planning for the Use of Surgical Masks and Respirators in Health Care Settings during an Influenza Pandemic. Oct 2006. Available from: http://www.pandemicflu.gov/plan/healthcare/maskguidancehc.html
73. White C, Kolble R, Carlson R et al. (2003). The effect of hand hygiene on illness rate among students in university residence halls. Am J Infection Control; 31: 364-70.
74. WHO (2003) Working Group on Prevention of International and Community Transmission of SARS. Public health interventions and SARS spread, 2003. Emerg Infect Dis 2004; 10: 1900-1906. [accessed October 10] Available at: http://www.cdc.gov/nciod/EID/vol10no11/04-0729.htm
75. WHO (2004b).*Consultation on priority public health interventions before and during an influenza pandemic.* Geneva. World Health Organization, 2004, (WHO/CDS/CSR/RMD/2004.9). http:www.who.int/csr/disease/avian_influenza/consultation/en/
76. WHO (2005a). WHO Global Influenza Preparedness Plan. 2005 http://www.who.int/csr/resources/publications/influenza/WHO_CDS_CSR_GIP_2005_5.pdf
77. WHO (2005b). WHO Global Influenza Preparedness Plan. 2005 Annex One Recommendations for non-pharmaceutical public health measures (pages 42-46) http://www.who.int/csr/resources/publications/influenza/WHO_CDS_CSR_GIP_2005_5.pdf
78. WHO (2006a). Nonpharmaceutical interventions for pandemic influenza, international measures. Emerg Infect Dis [serial on the Internet]. 2006 Jan [cited Oct 10 2006]. Available from http://www.cdc.gov/ncidod/EID/vol12no01/05-1370.htm

79. WHO (2006b). Nonpharmaceutical interventions for pandemic influenza, national and community measures. Emerg Infect Dis [serial on the Internet]. 2006 Jan [cited Oct 10 2006]. Available from http://www.cdc.gov/ncidod/EID/vol12no01/05-1371.htm
80. WHO (2006c). Antigenic and genetic characteristics of H5N1 viruses and candidate vaccine viruses developed for potential use as pre-pandemic vaccines. WHO 18 August 2006 http://www.who.int/csr/disease/avian_influenza/guidelines/h5n1virus2006_08_18/en/index.html
81. WHO (2007a) Interim Protocol: Rapid operations to contain the initial emergence of pandemic influenza. WHO Updated May 2007 http://www.who.int/csr/disease/avian_influenza/guidelines/draftprotocol/en/index.html
82. WHO (2007b). Addressing Ethical Issues in Pandemic Influenza Planning Examining the wide range of issues raised by a potential influenza pandemic. Report of a Technical Meeting (October 2006). WHO Geneva May 2007 http://www.who.int/ethics/influenza_project/en/index.html
83. Wu JT, Riley S, Fraser C, Leung GM. Reducing the impact of the next influenza pandemic using household-based public health interventions, PLoS Med 3(9): e361. DOI: 10.1371/journal.pmed.0030361.

Annex I – Extract from WHO global preparedness plan; Recommendations for non-pharmaceutical Public Health interventions (Annex1 of original document)[29]

WHO/CDS/CSR/GIP/2005.5

WHO global influenza preparedness plan

The role of WHO and recommendations for national measures before and during pandemics

Department of Communicable Disease
Surveillance and Response
Global Influenza Programme

ANNEX 1

Recommendations For Non-pharmaceutical Public Health Interventions

MEASURES AT THE NATIONAL LEVEL[30[1]]
(for persons living or traveling within an affected country)

Measures	Pandemic alert period[a] Phase 3	Pandemic alert period[a] Phases 4 and 5	Pandemic period[a] Phase 6	Comments
Public health information, communication				
Information for public on risks and risk avoidance (tailored to target population)	Y	Y	Y	
Information for professionals.	Y	Y	Y	
Advice on universal hygiene behaviour.	Y	Y	Y	.
Preparatory information on next phase.	Y	Y	Y	
Measures to reduce risk that cases transmit infection				
Confinement:				
• Confine cases (mild and severe) as appropriate to local situation; provide	Y	Y	Y	Need to plan for large numbers of

[29] The Annex from the WHO global influenza preparedness plan is reproduced here with kind permission from WHO. For more information, see: http://www.who.int/csr/resources/publications/influenza/WHO_CDS_CSR_GIP_2005_5.pdf

[30[1]] Source : WHO consultation on priority public health intervention before and during an influenza pandemic. Geneva, World Health Organization. (Document WHO/CDS/CSR/RMD/2004.9.)

medical and social care				severe cases
Face masks:[b]				
• Symptomatic persons	Y	Y	Y	Logistics need to be considered.
• Exposed persons: undertake risk assessment considering: evidence of human-to-human transmission; closeness of contact;frequency of exposure	C	C	C	Consider recommending masks based on risk assessment.
• Persons seeking care (respiratory illness) in risk area (waiting room),	Y	Y	Y	Need more data, especially on use by well persons.
Measures to reduce risk that contacts transmit infection				
Tracing and follow-up of contacts.	Y	Y	N	Not feasible once pandemic starts.
Voluntary quarantine (such as home confinement) of healthy contacts with health monitoring; provide medical and social care,	N	Y	N	Voluntary quarantine should also apply to contacts of known cases undergoing antiviral prophylaxis, as efficacy not known.
Self-health monitoring and reporting if ill but no restrictions on movement.	Y	C	Y	Not relevant for contacts in quarantine.

	Pandemic alert period[a]		Pandemic period[a]	
Measures	Phase 3	Phases *4* and 5	Phase 6	**Comments**
Advise contacts to reduce social interaction	N	NR	N	Not relevant for contacts in quarantine, see also measures to increase social distance.
Advise contacts to defer travel to unaffected areas.	N	NR	Y	Not relevant for contacts in quarantine. Precautionary principle when unclear whether human-to-human transmission is occurring; see also travel measures.
Provide contacts with antiviral proplylaxis.[c]	Y	Y	N	Principle of early aggressive measure to avert pandemic
Measures to increase social distance				
Voluntary home confinement of symptomatic persons	Y	Y	Y	Measures needed to reduce risk of transmission to other household members.
Closure of schools (including preschool, higher education) in conjunction with other measures (limiting after-school activities) to reduce mixing of children	N	C	C	Depends on epidemiological context – extent to which these settings contribute to transmissions.
Population-wide measures to reduce mixing of adults (furlough non-essential workers, close workplaces, discourage mass gatherings).[d]	N	C	C	Consider in certain circumstances – extent to which unlinked community transmission and transmission in workplaces occurs.
Masks in public places.	N	N	N	Not known to be effective; permitted but not encouraged.

Measures to decrease interval between symptom onset and patient isolation				
Public campaign to encourage prompt self-diagnosis.	Y	Y	Y	
Urge entire population (affected area) to check for fever at least once daily	N	N	N	
Set up fever telephone hotlines with ambulance response.	N	C	N	
Set up fever clinics with appropriate infection control.	N	C	N	
Introduce thermal scanning in public places.	N	N	N	Not effective based on experience, also requires individual and public health action for identified febrile persons.
Disinfection measures				
Hand-washing	Y	Y	Y	
Household disinfection of potentially contaminated surfaces	Y	Y	Y	

	Pandemic alert period[a]		Pandemic period[a]	
Measures	Phase 3	Phases *4* and 5	Phase 6	**Comments**
Widespread environmental disinfection.	N	N	N	
Air disinfection.	N	N	N	
Measures for persons entering or exiting an infected area within the country				
Advise to avoid contact with high-risk environments (such as infected poultry farms, live-poultry markets).	Y	Y	Y	
Recommended deferral of non-essential travel to affected areas.	N	Y	Y	If significant areas of country remain unaffected.
Restrict travel to and from affected areas.	N	N[e]	N	Enforcement of travel restrictions considered impractical in most countries but likely to occur voluntarily when risk appreciated by the public.
Cordon sanitaire.	N	N	N	Enforcement considered impractical.
Disinfection of clothing, shoes or other objects of persons exiting affected areas.	N	N	N	Not recommended for public health purposes, but may be required by veterinary authorities to prevent spread of infection to animals.

MEASURES AT THE INTERNATIONAL LEVEL

Measures at borders for persons entering or exiting a country				
Information to travellers				
• Outbreak notice.	Y	Y	Y	Message must be tailored to phase. While travel would remain a matter of personal choice, transparency must be ensured in order to allow for informed decision-making. Consequences for the traveler may include personal risk to health and economic harm.
• Recommend that travelers to areas experiencing outbreaks of highly pathogenic avian influenza avoid contact with poultry farms and live animal markets	Y	Y	C	
• Recommend deferral of non-essential international travel to affected areas.	N	Y	Y	
• Recommend deferral of non-essential international travel from affected areas.	N	Y	Y	
	See Screening Tables			
Measures at borders for international travelers coming from or going to affected areas.				
Health alert notices to travelers to and from affected areas.	N	Y	Y	WHO negotiates with appropriate organizations (e.g. International Air Transport Association) to ensure that health alert notices are distributed; WHO facilitates shared notice formats among countries.
Medical surveillance				
• Daily self-checking for fever; travelers from affected area;	N	Y	Y	
travelers to affected area.	N	N	Y	

	Pandemic alert period[a]		Pandemic period[a]	
Measures	Phase 3	Phases 4 and 5	Phase 6	**Comments**
• Self-reporting if symptoms appear in travelers from affected areas.	Y	Y	Y	Contacts of confirmed cases should be encouraged to monitor health. Quarantine may be indicated. Persons on affected conveyance should be traced and similarly advised.
• Advice on how to behave if ill after travel in affected areas (seek health care, give travel history, receive influenza laboratory test); if pandemic virus detected, patient should be isolated and public health officials, including WHO, notified.	Y	Y	Y	
Entry screening for travelers coming from affected areas.				Due to lack of proven health benefit, practice should be permitted (for political reasons, to promote public confidence) but not encouraged. Travelers should receive health alert notices instead.
• Screening for symptoms (visual detection of symptoms).	N	N	N	Entry screening may be considered where host country suspects that exit screening (see below) at traveller´s viewpoint of embarkation is suboptimal.
• Screening for at-risk travelers (health declaration, questionnaire).	N	N	N	

• Thermal screening.	N	N	N	
• Medical examination	N	N	N	
Entry screening for geographically isolated infection-free areas (islands), using the options above.	N	Y	Y	Feasible, may prevent entrance of pandemic virus. May also be relevant where country´s internal surveillance capacity is limited.
Exit Screening for all travelers from areas with human infections				More feasible than entry screening for detecting early cases.
• Screening for symptoms (visual detection of symptoms).	N	N	N	Not feasible due to passenger volume.
• Screening for at-risk travelers (health declaration, questionnaire).	N	Y	Y	
• Thermal scanning or ear-temperature measurement.	N	Y	Y	Thermal scanning less sensitive and specific but may be more practical than ear-temperature scanning.
• Stop-list of isolated or quarantined persons	N	N	N	May be feasible in certain countries, but generally not encouraged.
• Recommend that ill persons postpone travel	Y	Y	Y	
• Medical examination for travelers at risk or with fever	N	N	N	Not feasible to implement at borders.
Measures for countries with porous borders (including informal or illegal crossing points) adjoining affected areas				
Raise awareness among health-care providers and general public to facilitate surveillance and response measures, such as social distancing, quarantine or isolation.	N	Y	Y	WHO to post relevant guidelines on web for use by countries in developing posters, mass-media messages and similar measures. Possible benefits include rumour control.

Measures	Pandemic alert period[a] Phase 3	Pandemic alert period[a] Phases *4* and 5	Pandemic period[a] Phase 6	**Comments**
Measures for travelers on board international conveyances from affected areas.				
Recommend self-reporting if influenza-like symptoms appear.	N	Y	Y	
Separate sick travelers (if possible) on board.	N	Y	Y	On flights from affected areas, masks should be offered to all passengers upon boarding.
Advise health authority at countries of traveller´s embarkation, destination and transit that a person on board is ill (airline is responsible to notify destination only).	Y	Y	Y	Established requirement for destination, but not uniformly observed in practice.
Share epidemiological information for contact tracing with national public health authorities	N	Y	Y	Countries to share this information directly with others, as appropriate.

[a] Y = yes, should be done at this phase; N = no, not necessary at this phase; C = should be considered; NR = not relevant.

[b] Quality and type of mask depend on risk group. Cases: surgical mask; health-care workers; N95 or equivalent; others: depends on risk.

[c] Implementation depends on adequate supplies and may require a global stockpile with a prenegotiated targeting and delivery strategy to ensure availability in the area where a potential pandemic virus emerges. Prophylactic use will depend on evidence of effectiveness. Targeted use is required because of potential for drug resistance, side-effects and limited supplies. Targeted use might consider: public prevention; protection of health-care workers; protection of other essential service providers; individual treatment.

[d] Given a pandemic strain causing significant morbidity and mortality in all age groups and the absence of a vaccine, authorities should seriously consider introducing population-wide measures to reduce the number of cases and deaths. Decisions can be guided by mathematical and economic modeling. If modeling indicates a reduction in the absolute numbers of cases and deaths, decisions to introduce measures involving multiple government sectors will then need to balance the protection of priority functions against the risk of social and economic disruption.

[e] Could be considered as an emergency measure to avert or delay a pandemic.