Joining forces in influenza pandemic preparedness

INFLUENZA PREPAREDNESS STAKEHOLDER CONFERENCE
ON THE CENTENARY OF THE 1918 INFLUENZA PANDEMIC
22 JANUARY 2019, CHATHAM HOUSE, LONDON, UK

MEETING REPORT
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About Chatham House

The Chatham House Centre on Global Health Security was established through seed funding from the UK Department of Health, as part of a government-wide initiative called Health is Global. This initiative recognized that each country’s capacity to protect its own citizens’ health would in turn protect UK citizens. The Centre conducts its work in recognition that there are two interrelated aspects to health security: personal health security is pursued at the individual level through access to healthcare and medicines, and at the collective level through protecting societies from the transnational spread of disease.

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About ESWI

The European Scientific Working Group on Influenza (ESWI) is an independent organization of socially-concerned members and partners. ESWI’s partners share the objective to improve public health protection against influenza, turning the ESWI network into a unique and effective organization to address influenza issues in Europe.

Partnership organizations like ESWI are established to meet specific objectives and to undertake projects to address problems that neither partner tackles adequately on his own. A successful long-term partnership is built on common grounds. In the case of ESWI, this common ground is a social concern to improve public health in Europe.

For further information on ESWI, please refer to the ESWI website at www.eswi.org or contact the ESWI manager, Mrs Christel Smeys, christel.smeys@eswi.org or at +32 498 45 02 29.

ESWI’S PARTNER ORGANIZATIONS

The following partners have provided grants to support the Conference. Grants imply that the partners financially supported the Conference but have not been involved in the preparation of the Conference in any way.
A hundred years ago, an influenza pandemic stunned the world, killing more than 50 million people worldwide. The world remains vulnerable to such outbreaks, and due to the fast evolution of the influenza virus, globalization and intercontinental travel, outbreaks on the scale and severity of the 1918 pandemic would have a devastating effect today. But lessons learned from the past century of research and international cooperation should help prepare the world for future pandemics.

The Influenza Preparedness Stakeholder Conference on the Centenary of the 1918 Pandemic provided an opportunity to review the advances made over the past 100 years, evaluate current preparedness levels and discuss the pathways required to improve policy engagement. The meeting fostered debate among key players in (pre-) pandemic preparedness and response and the meeting culminated in an extensive stakeholders debate.

Chairs:

Dr. David L. Heymann, Chatham House
Dr. Ab Osterhaus, RIZ Hannover, Germany and ESWI chair
Faculty:
- Mrs Laura Spinney, writer and science journalist, Paris, France
- Dr Gülşah Gabriel, Heinrich Pette Institute, Hamburg, Germany and ESWI vice-president
- Dr Terry Jones, University of Cambridge, UK
- Dr Susanne Herold, University of Giessen, Germany and ESWI member
- Dr Florian Krammer, Icahn School of Medicine at Mount Sinai, USA
- Dr Danuta Skowronska, BC Centre for Disease Control, University of British Colombia, Canada
- Dr Jonathan Van Tam, Deputy Chief Medical Officer, England
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- Dr Marc van Ranst, Flu Commissioner, Belgium
- Mrs Ann Moen, Chief Influenza Preparedness and Response, World Health Organization
- Mr John Ryan, Commission Public Health Directorate, European Commission
- Dr Marco Cavaleri, Head of Anti-infectives and Vaccines, European Medicines Agency
- Dr Beverly Taylor, International Federation of Pharmaceutical Manufacturers & Associations
- Dr Tanya Scanlon, Head of High Consequence Infectious Diseases and Pandemic Flu Policy, Department of Health and Social Care, UK

Stakeholder panel on pandemic influenza planning and coordination

FACILITATORS:
- Dr David L. Heymann, Chatham House
- Dr Ab Osterhaus, ESWI

PARTICIPANTS:
- Mrs Ann Moen, WHO
- Dr Pasi Penttinen, ECDC
- Mr. John Ryan, European Commission
- Dr Tanya Scanlon, national government representative
- Dr Gülşah Gabriel, ESWI
- Dr Marco Cavaleri, EMA
- Dr Beverly Taylor, IFPMA
- Dr Marie Mazur, Vice President, Pandemic Response Solutions Seqirus
- Dr Thomas Breuer, Senior Vice President, Chief Medical Officer GSK
- Dr Olivier Espeisse, Public Affairs Director Ceva
How devastating was the 1918 pandemic and why?

Mrs Laura Spinney, Writer and science journalist, France


The H1N1 “Spanish” influenza pandemic occurred in three waves between 1918 and 1921, with the second wave of late 1918 proving the most lethal. The total death toll has been estimated at 50-100 million people, meaning that the 1918 flu pandemic was probably more lethal than either world war, and possibly more than both put together.

However, mortality rates varied considerably across space – from 0.5 per cent in New York City, US, to 6.1 per cent in Gujarat, India, 9.9 per cent in Ciskei, South Africa, and 40 per cent in Bristol Bay in Alaska, US. Socioeconomic status was probably the most important factor shaping that geographical variation – with the poorest, least well-housed and -nourished, and those with underlying diseases and limited access to healthcare resources tending to experience the highest mortality rates.

Spinney closed by paraphrasing French flu historian Patrick Zylberman: the 1918 flu may have been democratic, but the society it struck was not.

Post-presentation discussion centred on the role that opportunistic, pneumonia-causing bacteria and the absence of antibiotics may have had in determining the pandemic’s impact. While this should be considered, however – especially in light of its implications for future flu pandemics, when issues of antibiotic supply and distribution will become important – it was emphasised that the high virulence of the 1918 flu virus itself should not be underestimated.

If that estimate range is correct, then the global mortality rate of the 1918 flu pandemic was at least 2.5 per cent, compared to 0.1 per cent, on average, for other flu pandemics. Viral, environmental and social factors are thought to have contributed to its exceptional lethality. One theory, for example, holds that this was partly due to the exceptional conditions created by the First World War, and in particular to the high density of young men in the trenches of the Western Front.
The threat of a new influenza pandemic: its certainty, its unpredictability (or not?), its potential magnitude and speed

Dr Gülsah Gabriel, Heinrich Pette Institute, Germany

Influenza is an infectious viral disease, frequently observed in aquatic birds. The influenza subtype H7N9 has been known to cross the species barrier and to mutate, which poses a threat to humans. ‘Vaccination is the best way to increase immunity and protect patients against influenza and its subtypes’, said Dr Gülsah Gabriel of the Heinrich Pette Institute in Germany.

Influenza is a classic zoonotic disease found, typically apathogenically, in aquatic birds, some of which are migratory. Qinghai Lake in Qinghai province, China, is considered one of the key melting pots for migratory birds and the mixing, and reassortment, of the influenza virus subtypes they carry.

It is believed that influenza subtypes of avian origin harbour the highest potential to cause large outbreaks and pandemics, as humans are typically immunologically naïve to them. Again in China, wet markets are a prime location for the spread of novel influenza subtypes to jump from bird to human, as the on-site slaughter of potentially infected poultry exposes people to a high virus load.

H7N9 is one subtype that has repeatedly crossed the species barrier, with a mortality rate of almost 40 per cent. As yet, no sustained human-to-human transmission has occurred. However, China has, at great economic cost, developed strict rules around the closing of affected poultry markets, which has led to a reduction in human infections. In September 2017, China introduced a poultry vaccination campaign and thus far no additional human infections have been reported. However, scientists have subsequently identified mutations in the H7N9 virus found in reservoir ducks that have made the virus more virulent. The only thing predictable about influenza is its unpredictability.

Currently, vaccine fatigue, leading to low influenza vaccination uptake, has been seen to varying degrees throughout Europe and compliance is equally low among pregnant women despite their increased risk. Administration of the vaccine during pregnancy has been shown to protect not only mother and foetus from influenza, but also to provide broad-spectrum immunity to non-related infections during the first six months of life. Studies from the US suggest that doctors who both recommend and offer same-visit vaccination can increase compliance from 20 per cent to up to 67 per cent, highlighting the importance of practitioners in improving compliance rates.

Post-presentation discussion highlighted the equal importance of well-resourced healthcare systems that can provide practitioners with on-site vaccinations, and the key role that government policy and communications can play in overcoming vaccination fatigue.
China’s vaccination campaign reduced human H7N9 cases, but increased host range and virulence in ducks calls for high vigilance.

"The only thing predictable about influenza is its unpredictability"
Virus evolution studies using ancient sequences

Dr Terry Jones, University of Cambridge, UK

By using samples of hepatitis B virus uncovered by archaeologists, new methods in viral analysis have been developed. These new methods are important, said Dr Terry Jones of the University of Cambridge UK, as it allows virologists to investigate whether current vaccines can provide sufficient protection against historical viruses, should these viruses return.

There is potential to understand the historical evolution of the influenza virus using recent bioinformatics work completed on ancient hepatitis B virus genomes. Key questions around when the disease first infected humans, how it first spread, how new genotypes arise and where they come from, are common among influenza and hepatitis B virologists. However, until recently, virologists have been trying to understand the evolution of viruses with a limited dataset: virus genomes from, at most, the past few decades.

A new method of analysis has been developed using samples of hepatitis B virus uncovered by archaeologists in ancient mass burial sites across Western Europe and Eurasia, some more than 8,000 years old. Phylogenetic analysis of these samples led to the discovery of a clade of hepatitis B virus that has since become extinct. This is particularly relevant in the study of virology because unlike animals, which cannot be restored following extinction, it is possible that viruses can mutate into subtypes that have previously circulated among humans or other animals. By understanding historical variations and acknowledging their potential to return, it is possible to investigate whether current vaccines, antivirals and diagnostic tests would be fit for purpose and to prepare accordingly.

Extracting ancient viral DNA is most likely in the case of blood-borne viruses, as virus may be found in the blood supply to teeth and bones. RNA viruses, such as the influenza virus, pose additional challenges, as they tend not to be as stable as DNA viruses, and are more dependent on the environment: the 1918 recovery of the influenza virus was taken from a dead body found in the permafrost, which had likely remained frozen for approximately 80 years. The prospect of finding ancient influenza viruses remains to be seen but may be more likely given climate change and the increasing melting of permafrost.

“It is possible that viruses can mutate into subtypes that have previously circulated among humans or other animals.”
Coping with the 2009 pandemic – what did we learn?

Dr Susanne Herold, *University of Giessen, Germany*

SOME OF THE MAIN CHALLENGES THAT EMERGED DURING THE 2009 H1N1 PANDEMIC WAS A LACK OF AFFORDABLE DIAGNOSTICS, AND PROVIDING SPECIALISED TREATMENT TO A LARGE NUMBER OF PATIENTS. DR SUSANNE HEROLD OF THE UNIVERSITY OF GIESSEN IN GERMANY CALLED FOR ‘A BETTER UNDERSTANDING OF THE CLINICAL ASPECTS INVOLVED IN INFLUENZA DIAGNOSTICS AND TREATMENT, SO THAT PREPAREDNESS PLANS FOR THE NEXT PANDEMIC CAN BE DEVELOPED’.

Understanding the clinical aspects of the 2009 H1N1 pandemic and seasonal influenza can help the development of preparedness plans for the next pandemic. The 2009 H1N1 pandemic showed that influenza can cause life-threatening disease, particularly in at-risk groups, which make up a considerable and increasing number of patients in Europe. At-risk groups include the very young, the very old, pregnant women and, particularly, those patients with chronic heart and lung diseases such as asthma, chronic kidney and liver disease, neurologic disorders, immunosuppression, and people with obesity and diabetes.

Influenza is associated with severe complications that require invasive treatments administered by highly skilled practitioners with expensive machinery and yet hospitals often reach capacity during seasonal influenza epidemics and would not be able to cope with a large pandemic. Furthermore, the survival rate of patients with influenza-associated acute respiratory distress syndrome ranges at only 50 per cent, despite the invasive treatments provided.

There is a lack of affordable, highly sensitive point-of-care diagnostics that are able to differentiate between pandemic and seasonal influenza, and other respiratory viruses. Standard diagnosis via clinical symptoms is imprecise, while cheap and routinely available rapid point-of-care tests have a sensitivity range of 20-70 per cent, with many false negatives. Polymerase chain reaction (PCR) tests are rare and expensive, but some affordable options are reaching the market – these should be made readily available in preparation for a pandemic.

Mandatory vaccination of healthcare workers, and/or prophylactic treatment should be discussed, given the high frequency of in-hospital transmission and resulting deaths.

“Influenza is associated with severe complications that require invasive treatments administered by highly skilled practitioners”
**Pre-pandemic and pandemic vaccines**

*Dr Florian Krammer, Icahn School of Medicine at Mount Sinai, US*

**Since influenza viruses can re-assort at an incredibly fast rate, it is difficult to develop the correct vaccines in advance. This was a particular challenge during the 2009 pandemic. Dr Florian Krammer said that one way to address this problem is to stockpile pandemic vaccines, although there are associated risks. Providing boosters is also an option. ‘Unknown viruses that are circulating remain a key challenge in vaccine preparation, and vaccine hesitancy remains a problem,’ observed Dr Florian Krammer from the Icahn School of Medicine at Mount Sinai, in the US.**

Influenza subtypes are dictated by their haemagglutinin and neuraminidase subtypes, of which there is great diversity among animal reservoirs. These animal reservoirs are largely avian and there is a great deal of circulation within birds, but also across to other species such as pigs, horses and marine mammals. This cross-species jumping provides viruses with the opportunities to re-assort and adapt to mammalian cells and can thus pose a threat to humans.

Re-assortment events are incredibly difficult to predict, and it is unknown which virus will cause the next pandemic. There is typically a six-month vaccine development period from the isolation of the pandemic virus to the shipping of the vaccine. Meanwhile, the virus itself may take only a few weeks to travel the world and infect hundreds of millions of people. In 2009, the second wave of the H1N1 pandemic was already over by the time the vaccine was shipped — the response was too late and there was too little vaccine.

There are a number of ways to avoid these problems. The first is to stockpile, which has been done for vaccines against viruses of pandemic potential. Additional live-attenuated vaccines have also been developed and stockpiled, though with the added risk of accidental release of a replicating virus, and without the opportunity to test because of the risk of re-assortment with a seasonal virus. Another issue is that, even with pre-pandemic testing, by the time a potential pandemic virus becomes a concern it can split into antigenic lineages and thus be mismatched with the pre-emptive vaccine that was created for it, as happened in 2017 with H7N9. The unpredictability of re-assortment, and the likelihood of viruses circulating that are currently unknown remains a key challenge.
As vaccines against pandemic-potential viruses typically have poor immunogenicity, an additional option of prime-boost regimens may be possible. This involves priming those directly involved in a pandemic response – such as healthcare workers, police officers and the military – with a low immunogenicity non-adjuvanted inactivated vaccine, followed by administration of a live-attenuated vaccine at the time of a pandemic. Additional solutions include improved vaccine platforms – e.g., the use of viral vectors and recombinant-protein based vaccines, which have much higher immunogenicity. There is great interest in developing universal influenza virus vaccines, although this will take considerable time.

Finally, vaccine hesitancy is an issue, global distribution to low- and middle-income countries is difficult, and even high-income countries are lacking the production capacity that would be required to produce the quantity of vaccine needed during a pandemic.
Epidemiology of influenza vaccination in interpandemic years

Dr Danuta Skowronski,  
BC Centre for Disease Control, University of British Columbia, Canada

LEARNING FROM THE DEVELOPMENT AND USE OF SEASONAL INFLUENZA VACCINE IS USEFUL FOR FURTHERING UNDERSTANDING OF INFLUENZA IMMUNO-EPIDEMIIOLOGY, AND ASSISTS IN THE DEVELOPMENT OF VACCINATION CANDIDATES, INCLUDING, POTENTIALLY, A UNIVERSAL INFLUENZA VACCINE. THERE ARE, HOWEVER, A FEW QUESTIONS TO BE ANSWERED REGARDING CURRENT SEASONAL VACCINATION PRACTICE, SAID DR DANUTA SKOWRONSKI OF THE BC CENTRE FOR DISEASE CONTROL, UNIVERSITY OF BRITISH COLUMBIA IN CANADA.

The short-term safety and benefits of annual influenza vaccination for reducing disease burden are well established, although cost-effectiveness assessments vary with the outcome being considered (e.g. outpatient, inpatient or death); the incidence/risk of those outcomes by target group; and the perspective (societal or healthcare) adopted in the economic analysis. Less certain are the long-term implications of annually re-administered influenza vaccine, particularly for universal influenza immunization programs (UIIP) such as in Canada and the United States that begin in infancy and span annual re-vaccination across the lifespan. The general assumption underpinning such programs is that individuals can be considered neutrally immunologically recalibrated before each annual dose of influenza vaccine. Although investigators began to question this assumption decades ago, observations during the 2009 pandemic reinforced a potential role for prior influenza exposures on current influenza risk. In particular the lasting imprints made by original childhood priming exposures on subsequent seasonal and pandemic influenza risk at the individual and population level (e.g. cohort effects) and on vaccine effectiveness have become of renewed interest.

There are practical implications of seasonal influenza vaccine programs for pandemic preparedness. One important goal is to establish and rehearse large-scale production capacity by creating an annually renewed market for sustained influenza vaccine manufacturing that can be more readily ramped up in the event of a pandemic. However, there continue to be considerable delays between the identification of both seasonal and pandemic strains and vaccine availability. For instance, the 2009 pandemic vaccine was first rolled out in many areas at, or even well passed, the peak of the autumn pandemic wave, diminishing its overall population benefit. This underscores the need for dose-sparing and time-saving innovations. Delays in pandemic vaccine availability might be offset, and pandemic vaccine production capacity enhanced, if seasonal multi-valent influenza vaccine production lines could be re-directed toward full-scale mono-valent pandemic vaccine production once a pandemic has been declared. This is particularly relevant since during pandemics, the novel subtype generally displaces circulation of non-pandemic influenza viruses.
Seasonal influenza vaccine effectiveness is recurrently suboptimal against influenza A(H3N2) subtype viruses which are also associated with the greatest disease burden especially in elderly adults (a negative corollary of their greater protection against A(H1N1) viruses). Addressing these seasonal vaccine shortcomings may be viewed as opportunities for improved immuno-epidemiological understanding and development of enhanced vaccine options. On the other hand, could short-term enhancements that offer only marginal improvement over standard influenza vaccines (but at disproportionately increased cost) diminish market motivation and overall investment in the pursuit of more radically innovative universal vaccines with broader and longer lasting protection (that obviate the need for annual re-administration)?

Ultimately, seasonal influenza vaccine programs offer unique opportunities for knowledge generation, capacity building and infrastructure rehearsal that public health may strategically leverage for pandemic preparedness; however, this will require optimal balance between competing synergistic and antagonistic considerations on the short and long term.

<table>
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<tr>
<th>Potential synergies between seasonal influenza vaccine programs and pandemic goals</th>
<th>Potential antagonistic effects between seasonal influenza vaccine programs and pandemic goals</th>
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<tr>
<td>Establishing large-scale production capacity by creating an annually renewed market for sustained manufacturing</td>
<td>Competition between seasonal/pandemic vaccine production when a pandemic is declared?</td>
</tr>
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| Every influenza season is an opportunity to rehearse all aspects of epidemic and pandemic response:  
  - Mass vaccine production and delivery on a shortened time scale  
  - Recommendations for adjunct protective measures while awaiting vaccine availability (e.g. social distancing, antiviral medication)  
  - Rapid response research and evaluation (e.g. effectiveness, safety)  
  - Crisis communications to build credibility, trust, acceptance and compliance | Impact on public trust: more generally when issues arise around seasonal influenza (e.g. vaccine availability, effectiveness, safety) |
| Stimulate research infrastructure and develop innovations to improve annual influenza vaccine performance (e.g. dose-sparing, time saving, immunogenicity enhancing) | Effects on market motivation for radical innovation and lasting improvements in vaccine protection (e.g. universal vaccine pursuit) |
| Incremental understanding of influenza immuno-epidemiology to inform vaccine development options in the short and long term | Unknown long term effects of annual seasonal vaccination on immuno-epidemiology (e.g. recalibration of immunologic landscapes, imprinting and back-boosting, contribution to cohort effects; potential negative effects on pandemic risk) |
Antivirals –
scientific point of view

Dr Jonathan Van Tam, Deputy Chief Medical Officer, England

DO ANTIVIRALS REDUCE COMPLICATED ILLNESS, HOSPITALIZATION AND DEATH? BASED ON ANALYSES, TREATING PATIENTS WHO ARE SEVERELY UNWELL WITH NEURAMINIDASE INHIBITORS SUCH AS OSELTAMIVIR SHOULD BE SUPPORTED FOR PANDEMIC INFLUENZA INFECTIONS, SAID DR JONATHAN VAN TAM, THE DEPUTY CHIEF MEDICAL OFFICER OF ENGLAND.

There are several antivirals on the market. Neuraminidase inhibitors are one type that have a particularly good evidence base, are available globally and are affordable for many nations. Although randomized controlled trials (RCTs) and the subsequent licensing of oseltamivir and zanamivir were focused on the reduction of symptoms in uncomplicated community illness, our interest is typically in the broader public health benefits: do these antivirals reduce complicated illness, hospitalizations and deaths? These are relatively rare outcomes and are incredibly complex, and difficult and expensive to study.

RCTs, and meta-analyses of these, have shown that oseltamivir reduces illness duration in both adults and children, reduces hospitalizations and potentially reduces mortality among hospitalized patients. However, observational studies have identified a number of behaviours that seem to confound these results, requiring careful analysis.

A further study using individual patient data from around the world found that oseltamivir treatment led to a modest reduction in mortality rates across adults, pregnant women and intensive care unit (ICU) patients, but not children. This reduction was still visible in ICU adults treated beyond the recommended 48 hours post-onset of illness up to potentially five and a half days, but the evidence suggests that the earlier the treatment, the greater the likelihood of reducing mortality. Additional studies using the same data indicate a reduction in hospitalization and length of stay of approximately 1.15 days.

The conclusions of these analyses indicate that it is important to treat patients who are severely unwell, including those who are deteriorating in the community, with neuraminidase inhibitors, and that early treatment upon arrival at the hospital should be supported for pandemic influenza infections.

“Evidence suggests that the earlier the treatment, the greater the likelihood of reducing mortality”
Non-medical interventions

Dr Pasi Penttinen,
Head of Disease Programme Influenza and other Respiratory Viruses, ECDC

WHEN PREPARING FOR A PANDEMIC, IT IS ALSO IMPORTANT TO HAVE NON-PHARMACEUTICAL INTERVENTIONS (NPI’S) AVAILABLE. A REVIEW OF EUROPEAN PANDEMIC INFLUENZA PLANS SHOWS THAT THERE ARE STRATEGIES IN PLACE TO COMMUNICATE THE NPI’S, BUT EXECUTION OF THESE INTERVENTIONS REMAINS CHALLENGING. BY IMPROVING SURVEILLANCE AND MONITORING AND ADDRESSING KNOWLEDGE GAPS, IMPLEMENTATION OF THESE NPI’S COULD IMPROVE, SAID DR PASI PENTTINEN, HEAD OF DISEASE PROGRAMME INFLUENZA AND OTHER RESPIRATORY VIRUSES OF THE ECDC.

Non-pharmaceutical interventions (NPIs) are necessary in the case of pandemics because of the time period required for novel vaccine development. NPIs include personal protective measures such as hand hygiene and facemasks, social distancing, environmental controls and travel measures. Most of these measures are aimed at decreasing population-level transmission. Most were employed during the 1918 pandemic – in 100 years we are yet to come up with anything new.

A review of 28 European pandemic influenza preparedness plans found that 21 countries (75 per cent) have a policy on NPIs, and 19 (68 per cent) have a strategy in place to communicate that policy. However, only 11 plans (39 per cent) discuss vulnerable populations such as migrants, the homeless and mobile populations, and only 10 (36 per cent) describe third-sector engagement with non-governmental and voluntary organizations that can play a big role in implementing the NPI.

The evidence base for NPIs is difficult to interpret in terms of developing guidelines, leading to a lot of variation from country to country. Much of the uncertainty is linked to gaps in knowledge on influenza transmission and a limited understanding of the socioeconomic costs of different measures. An argument has been made for a Swiss-cheese (layering to cover holes) approach to layering of NPIs in the hope of slowing transmission and delaying the pandemic peak, however there is as yet no evidence for this.

The implementation of these measures requires many elements: operationalization, including stockpiling, funding, local plans and a means of addressing challenges to compliance; communication; interoperability across borders; simulation exercises; intervention impact monitoring; and agreed-upon triggers for activation and deactivation. An additional question is whether these plans can and should be rolled out during particularly severe seasons, rather than just during pandemics.

Future activities include improving surveillance and monitoring during regular seasons to enhance mechanisms for non-pharmaceutical intervention implementation during pandemics, addressing the knowledge gaps with applied implementation research and the publication of WHO guidance this year.
Communication and public engagement

Dr Marc van Ranst, Flu Commissioner, Belgium

‘HAVING A SINGLE VOICE FOR INFORMATION IN ORDER TO PREVENT CONFUSION IS CRUCIAL’, STATED DR MARC VAN RANST. THE BEST WAY TO PREVENT WIDESPREAD PANIC ABOUT A PANDEMIC IS COMMUNICATING WITH THE MEDIA AND REASSURING THE PUBLIC THROUGH ACCURATE INFORMATION, THE BELGIAN FLU COMMISIONER STATED.

Experience as the flu commissioner in Belgium during the 2009 H1N1 pandemic showed that it was crucial to be omnipresent and communicative with the media from day one, to ensure that there is a single voice for information in order to prevent confusion. Communications teams must be properly funded and good relationships with media must be maintained. Social media are also a good option for communication, but they also allow for the spread of false information.

Particularly helpful was the establishment of a call centre for the public. This enabled public reassurance and also allowed the flu commissioner to understand the sorts of questions that were being discussed in the community, so that the answers could be worked into interviews with the media.

Another useful strategy was to pre-empt future possibilities, such as high case numbers and deaths. This appeared to sensitize the media and the public and prevent widespread panic.

It is, however, important to be aware of other media influences. It is rare to be the only source of information and this was seen in the disparate vaccination rates between Flanders and Wallonia: the latter is French-speaking and was also hearing messaging from France.

Appointing a non-political spokesperson to the role of influenza commissioner was also vital in preventing political attacks that sought to discredit the commissioner’s information.

“Communications teams must be properly funded and good relationships with media must be maintained”
The new WHO global influenza strategy/ pandemic preparedness priorities

Mrs Ann Moen, Chief,
Influenza Preparedness and Response, World Health Organization

‘DEVELOPING CAPACITY STARTS WITH BUILDING ON EXISTING SUCCESSES, BUT THERE ARE KEY CHALLENGES’, OBSERVED ANN MOEN, CHIEF OF INFLUENZA PREPAREDNESS AND RESPONSE OF THE WORLD HEALTH ORGANIZATION. THESE INCLUDE IMPERFECT MEDICAL INTERVENTIONS AND UNPREPAREDNESS FOR PANDEMICS. WHO IS WORKING ON GUIDELINES AND STRATEGIES TO ADDRESS THESE CHALLENGES, SO IT WON’T BE NECESSARY TO WAIT UNTIL A PANDEMIC TO IMPLEMENT PREVENTATIVE MEASURES.

WHO will soon publish its Global Influenza Strategy for 2030. It is a global strategy in which all stakeholders have a role to play. Its key components are building capacity for influenza response through improved lab and animal-human interface surveillance, vaccination development and clinical care. Influenza response capacity is considered core to the International Health Regulations (IHR) and the major principle behind the new guidance document is that programmes for seasonal influenza surveillance and vaccination are essential for pandemic preparedness.

Building capacity starts with building from existing successes, such as the Global Influenza Surveillance and Response System (with 114 labs in 114 countries), the Pandemic Influenza Preparedness (PIP) Framework and the Global Action Plan for Vaccines, which has increased the number of vaccine manufacturers in low- and middle-income countries.

There are, however, two key challenges. The first is that existing medical interventions are imperfect: seasonal influenza control relies on annual vaccination with suboptimal immunogenicity, antivirals are costly and current vaccine production is tied to identification of the pandemic strain. The strategic objective outlined in the guide that seeks to overcome this problem is the development of better global tools through the promotion of research and innovation to address unmet needs.

The second challenge is that many countries remain unprepared to handle pandemic influenza and other emerging diseases. Therefore the new guide sets out the strategic objective of stronger country capacities within 10 years, including the integration of core-capacity building for influenza labs, surveillance and response into national action plans for protecting against and preparing for infectious diseases.

Additional needs include a timely way to estimate severity, for which an assessment guide was rolled out in 2017, and the integration of seasonal influenza prevention programmes into universal healthcare plans of all countries, so that it is not necessary to wait until a pandemic to practice the delivery of the vaccines, the antivirals and the NPIs mentioned earlier.

WHO is working on a number of guidelines and implementing strategies for pandemic preparedness planning and integration, all of which are aligned with the IHR and the Joint External Evaluation (JEE) core capacities.

Programmes for seasonal influenza surveillance and vaccination are essential for pandemic preparedness.”
EU challenges: joint procurement and equal access

Mr John Ryan,
Director public health and crisis management, European Commission

AS PART OF THE EU PUBLIC HEALTH STRATEGY, MEASURES WERE PUT IN PLACE TO OVERCOME THE DIFFICULTIES IN OBTAINING VACCINES AT A SUITABLE PRICE WHILE ALSO ENSURING SECURITY OF SUPPLY. THIS INCLUDED THE DEVELOPMENT OF A JOINT PROCUREMENT MECHANISM. THE AIM OF THIS MECHANISM IS TO ‘IMPROVE MEMBER STATES’ PREPAREDNESS TO MITIGATE CROSS-BORDER THREATS TO HEALTH AND TO ENABLE MORE ACCESS TO SPECIFIC MEDICAL COUNTERMEASURES’, STATED JOHN RYAN, DIRECTOR OF PUBLIC HEALTH AND CRISIS MANAGEMENT, EUROPEAN COMMISSION.

The 2009 pandemic forced the EU to scale up its capacity for risk assessment and response, specifically to improve the resilience of its health sector, strengthen preparedness and response across sectors, and improve cooperation and communication between the different stakeholders.

One key activity was developing a Joint Procurement Mechanism for purchasing of pharmaceutical countermeasures, including vaccines, antivirals, and others, to overcome the difficulties in obtaining vaccines at a suitable price and ensuring security of supply. The mechanism was established under Decision 1082/2013/EU on serious cross-border threats and covers infectious diseases, biotoxins, chemical and environmental threats; participation is voluntary, and 24 member states signed the agreement, which was approved by the European Commission (EC) in April 2014.

In 2016, the first procurement procedure for botulinum anti-toxin was successfully concluded, and the procurement of pandemic influenza vaccines, involving 18 member states, is currently underway. The call for tender documentation is publicly available. Contractors must meet specific criteria, which include holding a valid EU marketing authorization for a pandemic preparedness vaccine.

Member states have expressed interest in additional procedures covering personal protective equipment, anti-toxins, diagnostics and vaccines.

The aim of this mechanism is to improve member states’ preparedness to mitigate cross-border threats to health, to enable more equitable access to specific medical countermeasures and to improve the security of supply, together with more balanced conditions of access and price for the participating member states.

One further essential element of the EC’s public health strategy is to reinforce EU action on vaccination. This requires three key pillars of action: 1) tackling vaccine hesitancy and improving vaccination coverage across Europe; 2) developing sustainable vaccination policies in the EU, and 3) strengthening EU coordination and contribution to global health. The EU is emphasizing the significance of vaccination as a public health tool, both internally and externally, and trying to develop tools to assist member states, healthcare workers and the public to reinforce the credibility of vaccination. In addition, the EU is making investments into a small number of targeted projects looking at clinical development of particular influenza-related products, including the potential for a universal flu vaccine, as well as collaborating internationally to push forward research on new generation vaccines.

### Added value of joint procurement

| Better preparedness, availability of vaccines in sufficient quantities |
| Strengthened purchasing power and better contractual conditions |
| Equal treatment of Member States |
| Greater exchange of best practices and pooling expertise |
Added value of joint procurement
- Better preparedness, availability of vaccines in sufficient quantities
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“The EU emphasizes the significance of vaccination as a public health tool”
Regulatory requirements of (pre-)pandemic preparedness

Dr Marco Cavaleri, Head of Anti-infectives and Vaccines, European Medicines Agency

THE EMA HAS MULTIPLE STRATEGIES IN PLACE IN PREPARATION OF PANDEMIC TIMES. SEVERAL REGULATORY TOOLS AND A REVISED HEALTH THREAT PLAN ALLOW FOR RAPID DECISION-MAKING IN TERMS OF APPROVAL FOR MEDICAL COUNTERMEASURES. DEVELOPING EFFICIENT VACCINES IS ESPECIALLY ENCOURAGED, PARTICULARLY THE INVESTIGATION OF STRAINS WITH PANDEMIC POTENTIAL. ACCORDING TO DR MARCO CAVALERI, HEAD OF ANTI-INFECTIVES AND VACCINES, EUROPEAN MEDICINES AGENCY, ‘APPROVAL OF PREPAREDNESS VACCINES CAN SPEED UP THE APPROVAL OF PANDEMIC VACCINES, BUT CERTAIN REQUIREMENTS WILL REMAIN.’

The EMA has recently published its revised health threat plan, based on its experiences during the 2009 pandemic, as well as during the Ebola and Zika outbreaks. In addition, the EMA has a number of regulatory tools that allow for rapid decision-making in terms of approval for medical countermeasures in both pandemic and interpandemic times. These include specific legislation, conditional market authorization and authorization under exceptional circumstances.

In 2003, the EMA started working on pandemic preparedness planning, focusing on vaccines. This resulted in the registration of three mock-up vaccines between 2006-9, which were approved for use in a pandemic based on an H5N1 dataset. This allowed the easy switching of the vaccine strain during the 2009 H1N1 pandemic and enabled relatively quick decision-making from the point of declaration of a pandemic to the approval of vaccine for mass production. Some may say that the process was still too slow and needs improvement.

The EMA is interested in the development of broadly cross-protective, novel vaccines so long as they show efficacy. This could be shown through field trials in the context of seasonal influenza. Extrapolation to strains that are different than the ones currently circulating will have to be discussed. It may be complicated if cellular immunity is the most important pathway for protection, as defining a correlate of protection could be challenging, but there is still potential to find alternative ways of advancing the development of novel vaccines.

Such a vaccine should target adults, particularly the elderly but also young children, and the overall size of the safety database should be of at least 3,000. The EMA encourages the investigation of more than one strain with pandemic potential because of studies showing that different strains require different levels of boosting to be protective. Although approval of preparedness vaccines can speed up the approval of the pandemic vaccine, some post-authorization requirements will remain in terms of collecting effectiveness and safety data, particularly for adverse events of special interest.

“The EMA has a number of regulatory tools that allow for rapid decision-making in terms of approval for medical countermeasures in both pandemic and interpandemic times.”
In Europe currently, four vaccines have been approved as H5N1 pandemic preparedness vaccines, using different platforms. Meanwhile, the previously approved H1N1 vaccines have been withdrawn, as H1N1 has become a seasonal strain. With regard to antivirals, there are several products in development with different mechanisms of action and different routes of administration. It will be important to have a diversified portfolio of antivirals available given the potential for emergence of resistance and strain-specific needs. These antivirals have been approved in uncomplicated influenza, but not yet in the context of severe influenza, including hospitalized patients. However, because NAIs are the standard of care, it is difficult to demand a placebo-controlled trial.
Industry as a key player

Dr Beverly Taylor,
International Federation of Pharmaceutical Manufacturers & Associations (IFPMA)

THE CONTRIBUTION OF THE PHARMACEUTICAL INDUSTRY IN PANDEMIC PREPAREDNESS CANNOT BE UNDERESTIMATED. AN EFFECTIVE RESPONSE TO A PANDEMIC RELIES ON THE DEVELOPMENT AND AVAILABILITY OF VACCINES, WHICH REQUIRES STRATEGIC PREPARATION AND IMPLEMENTATION. TO ADDRESS VARIOUS ISSUES SURROUNDING PANDEMIC PREPAREDNESS, BEVERLY TAYLOR OF THE INTERNATIONAL FEDERATION OF PHARMACEUTICAL MANUFACTURERS & ASSOCIATIONS (IFPMA) NOTES, INDUSTRY RELIES ON WHO TO GIVE THEM A CLEAR SIGNAL ON WHEN AND WHETHER IT IS NECESSARY TO START MANUFACTURING PANDEMIC VACCINES. DR TAYLOR EMPHASIZES THE IMPORTANCE OF A GLOBAL STRATEGY AMONGST INDUSTRY, WHO AND OTHER STAKEHOLDERS TO ENSURE VACCINE AVAILABILITY DURING A PANDEMIC.

The pharmaceutical industry is a key player in pandemic influenza preparedness and response. An effective widespread pandemic response is reliant on robust and growing seasonal influenza vaccination programmes in order to support growth in manufacturing capacity. Key to an effective response is improving the processes for developing vaccines, licensing vaccines, and subsequent surveillance.

Several elements are required for rapid response to a pandemic caused by an identified strain. These include early supply of viruses and plasmids, the rapid determination of the appropriate bio-containment level, timely supplies of calibrated reagents and antigens, simple and aligned regulatory pathways, the resolution of any issues related to low yields or stability, and ongoing, timely and consistent communications and robust collaborations throughout.

Currently, global manufacturing capacity exceeds seasonal demand, but this is very difficult to sustain, even for high-income countries. One way to ensure that companies maintain this capacity is to increase demand through increased seasonal vaccination rates, based on public health need and the burden of disease. Increased capacity may even allow improved preparation for a better response during a pandemic: building country preparedness infrastructure through seasonal vaccination campaigns will also benefit pandemic preparedness and response.

Industry uses the same manufacturing facilities to manufacture both seasonal and pandemic vaccine. The decision to switch is mostly undertaken by national governments and therefore global coordination is difficult to achieve. This means that the industry requires a very clear signal, such as the declaration of a public health emergency of international concern (PHEIC) by WHO, to cease the manufacture of seasonal vaccine and begin manufacturing pandemic vaccine.

WHO Switch meetings were initiated to develop a global strategy and operational mechanism for pandemic vaccine response at the start of a pandemic when seasonal influenza vaccine may still be needed in some parts of the world. These meetings have been particularly valuable because of the presence of the range of stakeholders, including WHO, vaccine manufacturers, regulatory agencies, governments, clinicians and vaccine programme managers, who have many different perspectives on what is needed at the beginning of a response to a pandemic. These meetings developed into three Switch Implementation Teams: 1) looking at validation of the pandemic switch decision process; 2) looking at the process from surveillance to candidate virus vaccine generation and testing, and 3) looking at the process from candidate vaccine virus to registered vaccine.

The industry is working towards a strategic partnership with WHO on both seasonal and pandemic influenza countermeasures. It is also looking to develop solutions to influenza vaccine immunogenicity problems.
“The industry is working towards a strategic partnership with WHO on influenza countermeasures”
Government challenges

Dr Tanya Scanlon, Head of High-Consequence Infectious Diseases and Pandemic Flu Policy, Department of Health and Social Care, UK

FOLLOWING A UK GOVERNMENT SIMULATION IN 2016 OF AN INFLUENZA PANDEMIC, VARIOUS CHALLENGES IN RESPONDING TO THE PANDEMIC WERE IDENTIFIED. ACCORDING TO DR TANYA SCANLON, HEAD OF HIGH-CONSEQUENCE INFECTIOUS DISEASES AND PANDEMIC FLU POLICY IN THE DEPARTMENT OF HEALTH AND SOCIAL CARE, UK, TO OVERCOME THESE CHALLENGES NATIONAL GOVERNMENT AND LOCAL-LEVEL PREPAREDNESS SHOULD BE PRIORITIZED. AMONGST OTHER STEPS THAT SHOULD BE TAKEN, ‘COLLABORATION BETWEEN GOVERNING BODIES SHOULD BE DEVELOPED AND ADEQUATE LEGISLATION AND GUIDELINES SHOULD BE IMPLEMENTED’, SHE SAID.

Pandemic threats are very high on the UK National Risk Register, produced in 2017, which acknowledges that such threats require bespoke planning and cross-sector coordination and collaboration. The most recent simulation using a worst-case scenario, similar to the 1918 pandemic in terms of severity and proportion of people affected, was held in 2016. It focused on week seven of the pandemic and involved 950 representatives, ministers, and devolved administrations at the local level. The simulation found a good level of readiness on clinical countermeasures, but only partial readiness on workforce absence, health service (such as bed supply) and excess death management.
The results were not bad, but there was still more to do: in February 2017 the Prime Minister chaired a meeting that resulted in a number of recommendations, the formation of a cross-government board and several work programmes. Key focus areas include: healthcare; adult social care and community care; excess deaths; sector resilience; cross-cutting enablers such as legislation and communication; updating the pandemic flu strategy; restructuring online documentation; and developing a pandemic flu resilience standard for local-level planning in England. These tools are intended to assist local clinicians and responders.

There are many challenges. These include questions around prioritizing pressures in hospitals, dealing with excess dead bodies, ethical decision-making with public buy-in, and introducing emergency legislation across all four UK nations. To overcome these challenges, one of the keys is to prioritize pandemic influenza preparedness across government departments and the health sector, which is not easy.

Local-level preparedness is another challenge, as there are lots of other competing priorities and limited funding at that level. Local authorities are also unlikely to have specialized knowledge and thus might rely on military assistance or mutual aid, which are both likely to be unavailable during a pandemic.

Devolution is challenging in the UK, requiring collaboration across legislation while maintaining respect for devolved powers and processes, coordinated public communications to prevent divergent messaging, and internal mechanisms that maintain open communication channels between policy officials. Vaccine security and stockpiling present additional challenges, and stockpiling must be balanced with public perceptions, political risks and cost effectiveness.

Current work includes finalizing an excess death strategy that will be made public; revising the 2011 influenza strategy; and setting up an ethics group to consider and test difficult decisions before a pandemic happens.
Planning for a pandemic: what is necessary for the way forward?
World Health Organization (WHO) leadership

WHO is focused on ensuring that all countries have their own capacity to undertake national risk assessments. However, it is clear that a WHO headquarters declaration of a pandemic, or PHEIC, would remain crucial for seeding the necessary global response, particularly for making the switch from seasonal to pandemic vaccine manufacturing. Consistent communication from WHO is needed early and often.

Cross-sector collaboration

Pandemics must be seen as a civil emergency, not just a health emergency. This is particularly important because political awareness of pandemic influenza has declined considerably since 2009. The UK takes an ‘all of government’ approach to pandemic preparedness; this approach could be replicated in other countries to ensure appropriate preparedness measures are undertaken by all potentially affected sectors, and to improve cross-sector communication and collaboration.

Research

It is essential that research be integrated into pandemic preparedness and response. This research should include monitoring for vaccine immunogenicity and safety, antiviral efficacy, and non-pharmaceutical countermeasures. Maintaining pandemic research teams in interpandemic years is difficult but this challenge can be overcome through multi-year contracts with clauses that require the prioritization of pandemic research in the case of a pandemic declaration. Pre-approved research projects that can be activated within two to three weeks of a pandemic declaration are also an option. Developing pre-pandemic standards and protocols can help ensure that research data are produced in a timely manner that effectively informs the response; these processes are currently underway through the Platform for European Preparedness Against (Re-)emerging Epidemics (PREPARE).

Early discussion of ethical dilemmas

In the event of a severe pandemic, intensive care unit capacity is likely to fall, as is the availability of hospital beds, and moral/ethical decisions will likely have to be made over aspects such as which patients would be admitted to hospitals and who should the scarce ventilators be used on. Arrangements should be agreed during the inter-pandemic period, involving a wide group of stakeholders (including community representatives, faith groups and judges) in the discussion to ease public acceptance of the resulting strategy. The suggestion was made for countries to appoint a decision-making board that convenes both before a pandemic to plan, as well as during a pandemic to make decisions on such issues.

Novel approaches to the influenza vaccine

Pandemic vaccines come too late for countries that can afford them and those that cannot. This raises a need to prioritize the development of a universal influenza vaccine. A number of countries and organizations, including the EU and India, are looking into this.

Joint procurement of vaccines and antivirals

Joint procurement of vaccines and antivirals provides a way of ensuring that all member states, regardless of size, are treated equally. Negotiations for procurement of pandemic influenza vaccine will be finalized in the next few months.
To be continued....

Much has happened in all areas since the 1918 and 2009 H1N1 pandemics, but the world remains underprepared, and in some cases austerity measures may have left some countries worse off. The cornerstone of pandemic preparedness is seasonal preparedness. Cross-sector collaboration and communication, systems capacity building and research protocol development in the interpandemic periods are essential for improving Europe’s capacity to respond to the next influenza pandemic.

ESWI is looking forward to continuing this discussion at the occasion of the 7th ESWI Influenza Conference, 13-16 September 2020, Valencia Spain