Being prepared

Preparations for a pandemic of influenza

The Boy Scouts have an admirable motto: Be Prepared. 'Be prepared for what?' someone asked their founder Lord Baden-Powell. 'Why for any old thing', he replied. These surely are words of wisdom at a time when the spectre of biological warfare has become a grim reality and the next influenza pandemic might be lurking around the corner. Being prepared is surely the lowest common denominator

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in successfully dealing with an outbreak of any infectious disease, and whatever public health measures are in place for one can only benefit the others. 'We

Transmission electron photograph of influenza A. Photo courtesy of Dr Erskine Palmer, US Centers for Disease Control and Prevention

should be worried less about a specific pathogen or about whether an infectious disease emergency is naturally-occurring or deliberately-induced and more about the type of health systems we want to build to deal with the spread of infectious

disease in a rapidly shrinking world' said Monica Schoch-Spana from the Center for Civilian Biodefense Studies at Johns Hopkins University (Baltimore, MD).

Indeed, no one knows which organisms have fallen into the terrorists' hands or which other diseases may naturally re-emerge and spread. Influenza, on the other hand, is an all too familiar enemy that returns every year with admirable reliability. But, for all its mundaneness, influenza is a killer and has the potential to cause global havoc. The first pandemic was documented in 1580, a further 31 have been described since and it is just a matter of time until the next. These sporadic worldwide epidemics are characterised by their high morbidity and their high mortality: up to 40 million people died in the 1918–1919 pandemic and 1.5 million in the 1957 and 1968 outbreaks combined. If a virus of comparable virulence to the strain circulating in 1918 was to emerge today, it is estimated that 100 million people would die. In order to pre-

Originally given its name by 18th Century Italians who believed it to be due to the influence of heavenly bodies, the understanding of influenza is now extensive at the molecular and clinical level. The causative agents for the annual human misery are influenza A and B, two types of an RNA virus that have, crucially, a segmented genome and a lack of proof-reading ability. Influenza A is further classified into subtypes according to the presence of two surface antigens, one of 15 possible haemagglutinin (H) and one of nine neuraminidase (N) proteins; this diversity enables the virus to also infect species other than humans, such as horses, pigs and birds. Small changes in these surface antigens during replication make it possible for the virus to constantly subvert the host's immune system, so immunity developed one year is of reduced value the next. Since 1977, various strains of A(H3N2), A(H1N1) and B have been in circulation, generated through this antigenic drift. The major

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empt such a formidable scenario, the World Health Organization (WHO) has established one of the most effective surveillance systems, which might serve as a model for other infectious diseases such as AIDS or tuberculosis, as well as help to counter an attack with biological weapons. While treatment and prophylaxis are obviously specific to each pathogen, it would nevertheless be timely to assess the existing measures for coping with a sudden and widespread outbreak of influenza, since the management of any bioweapon or unanticipated disease depends on systems that are already in place.

problems arise when the virus undergoes antigenic shift and acquires a completely new antigenic make-up, which may increase virulence and enable the virus to evade existing vaccines. The dogma was that strains containing H1, 2 or 3 were considered to be human viruses and H4 and 5 were avian. Pigs, being susceptible to all, can act as viral blenders, releasing a completely novel strain by genetic reassortment if co-infected with a human and avian strain, as was thought to have occurred in 1918. In addition, the strains causing the 1957 and 1968 pandemics and the recent A(H5N1) isolated in Hong Kong are now thought to be due to an

avian strain directly crossing the species barrier, adding a further dimension to the evolution of the virus.

The yearly requirement for a vaccine tailored to the current circulating strains prompted the WHO in 1948 to establish a global surveillance network that comprises 110 centres in 83 countries. They record the local incidence of 'influenza-like illness' (ILI) via an internet database (FluNet), culture and type 175 000 isolates of influenza each year and send a representative 6500 of those to one of four major research centres in London, Atlanta, Tokyo and Melbourne for more detailed characterisation. Data is gathered throughout the year and the WHO meet in February to recommend the influenza strains to be included in the following season's Northern Hemisphere trivalent vaccine (similarly in September for the Southern Hemisphere). This recommendation is passed on to vaccine manufacturers together with the provided stocks, two strains of influenza A and one of influenza B, which are injected into fertilised chicken eggs. The virions are harvested from the allantoic fluid, purified, inactivated and finally blended together with a carrier fluid. Vaccine production is generally completed by the following August for distribution ideally by October. This unavoidable time delay is one of the major

constraints in dealing with influenza: by the time the vaccine is administered it is already almost a year out of date, and in some years the failure of one of the strains to replicate causes notorious delays in production and distribution.

Global surveillance is obviously the key to producing an effective vaccine, but it is also essential for detecting new and potentially dangerous strains that could lead to a

possible pandemic. This system was severely put to the test in Hong Kong in 1997 when six people died from an exceptionally virulent strain of A(H5N1) that crossed the species barrier from birds to humans. Fortunately, the virus could not

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spread between humans themselves, and a mass slaughter of 1.6 million chickens ensured that the disease was stamped out before the virus acquired the capability to do so. A further 1.2 million chickens were slaughtered as a precaution this year when another A(H5N1) strain was detected in the chicken markets. The early detection in

identified and further characterised. A major gap thus exists between surveillance and public health. Robert Hudson, the managing director of ZymeTx Inc. (Oklahoma, OK), is hoping to go some way towards filling that gap through their instigation of the National Flu Surveillance Network. The company manufactures ZstatFlu, a 20-min point-of-care neuraminidase assay for influenza, and the 6300 physicians who routinely use the test form a comprehensive American surveillance network whereby they record their cases daily via the internet (www.fluwatch.com). 'What WHO and the CDC pushes is vaccine, vaccine, vaccine and not really a comprehensive disease management program', Hudson said. 'The CDC reports what's happened. We're trying to report what's happening'. This real-time surveillance of influenza can also provide early warnings of other emerging diseases, as the first symptoms of other infections such as anthrax, smallpox and plague, can

be confused with influenza. 'If we're doing flu-like illness and flu, and if flu-like illness incidence goes up but flu doesn't, then we know something else is going on', said Hudson. The company is expanding the network to include 11 200 physicians next year and states that Japan is also interested in implementing a similar scheme.

Indeed, if an unusually virulent influenza case presents itself, or if a cluster

of unexplained influenza or ILI occurs, alarm bells will ring pretty quickly. To bolster this surveillance even further, an international group of leading influenza researchers recently proposed in *Science* a new US\$ 50 million 'global laboratory' to increase the capacity for definitive characterisation of isolates. But being concerned with the provenance of the disease is only one side of the equation. The incidents in

The global WHO surveillance network

1997 and again this year, this is the success of surveillance', commented Robert Webster of the St Jude Children's Research Hospital (Memphis, TN).

Despite the success of the WHO global network, at the end of the day, its major goal is viral surveillance in order to prepare the next season's vaccine. Moreover, the centres report ILI, not influenza itself, and only a subset of isolates are positively

Hong Kong have shown that the systems needed to detect new emerging strains are effective but not necessarily sufficient to deal with the consequences. 'If there was an influenza pandemic, we wouldn't have a hope in hell', Webster put it bluntly. 'It's all very well to have the global surveillance—it's a great idea—but we need to look at the infrastructure of the vaccine preparation and the stockpiling of antivirals'. Indeed, there are bottlenecks, mainly to quickly churn out a completely new vaccine and to distribute and administer it in the event of a pandemic. Furthermore, nations will need a significant quantity of stockpiled drugs for prophylaxis and treatment.

Vaccine research is urgently needed in order to reduce the dependency on fertilised eggs, the stocks of which currently limit vaccine production. PowderJect (Oxford, UK), the leading UK influenza vaccine producer, will increase investment in vaccine production by £13 million over the

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next 3 years, but this will simply address the increasing demands in the community as more groups are routinely recommended for vaccination. Despite the fact that this company supplies 35% of the UK and 20% of the US markets and were the first to actually complete production of this year's vaccine, they are still extremely limited in the event of a huge surge in demand. 'The current egg-based production is a biological process that you can't just turn on there and then to any kind of level', commented Rob Budge, PowderJect's Director of Corporate Affairs. The preparation of 'seed' stocks of all possible subtypes of the virus has been proposed, but, although this would inevitably speed up production of the vaccine if and when required, it would obviously not be tailored against a specific strain. 'It would not stop you getting infected, it would perhaps stop you from dying', said Webster. A live attenuated influenza vaccine (LAIV) is being developed by Aviron (Mountain View, CA) but was recently sent back to the drawing board by the US Food and Drug Administration for safety reasons. And while promising higher efficacy and easier intranasal administration, production time is unfortunately equally protracted.

PowderJect also have an 'ongoing programme' investigating the development of DNA vaccines. 'For DNA vaccines, the expression system will be in place and so you could scale-up production quite straightforwardly', said Budge. And the other encouraging aspect of this approach is that preclinical trials have shown cross-strain protection, which obviously could be relevant in a pandemic situation. The US National Institute of Allergy and Infectious Diseases has recently awarded grants to Aviron for further research, as well as to Aventis Pasteur (Swiftwater, PA) and Novavax (Rockville, MD) to investigate DNA vaccines and alternatives to egg-based production, respectively. But, for the foreseeable future, if there is a major antigenic shift in the virus, public health is still back to square one.

Antivirals are the other line of defence against a pandemic. There are currently four anti-influenza drugs: amantidine, rimantidine, zanamivir and oseltamivir, the latter two of which are recently developed neuraminidase inhibitors. However, due to side-effects and fear of resistance, it is not recommended that they are widely distributed, let alone stockpiled for an emergency. The drugs are expensive and only slightly reduce symptoms in otherwise healthy adults. But antivirals could literally be life-savers if taken prophylactically. As it can take up to 2 weeks for full immunity to develop, often requiring a second immunisation, stockpiled antivirals may be crucial to slow the spread of influenza in high-risk groups. However, supplies of these drugs are woefully inadequate, and GlaxoWellcome even withdrew Relenza (zanamivir) from the UK market this year due to the relatively low incidence of influenza during last winter. 'No thought has been given to stockpiling antivirals. That's something we could really do', lamented Webster.

Of course, these issues are specific to an outbreak of influenza. Common to an outbreak of any kind, whether deliberate or natural, are the thorny public health issues it would inevitably raise. Who would preferentially receive treatment in light of anticipated vaccine and drug shortages? Should the drugs, if manufactured in time, be available over the counter? At the most basic level, who will distribute all those pills? Moreover, global public health infrastructures are simply too inadequate for prompt mass prophylaxis and do not

have the capacity to care for mass casualties. In this harsh economic climate, hospitals even struggle to cope with a nominal increase in demand during an 'average' influenza season. And the impact of a pandemic must also be considered in terms of its social and economic consequences. If doctors and nurses become ill,

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who will care for the sick? If local police forces are struck down, public safety will plummet and failure of public infrastructures will lead to economic chaos. These are issues that will arise with a sudden, highly contagious disease of any kind. Plans for pandemic influenza have been prepared by some countries, e.g. the US and the UK, but while certainly identifying areas of weakness, they do not commit to any measures to address them.

The recent anthrax attacks have merely hinted at the consequences of a sudden outbreak of any infectious disease. The

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huge demand for and hoarding of Cipro, the paralysed mailrooms, the need for prophylaxis in a certain subset of the population and the need for training and education amongst health workers are just some of the issues which have confronted the US government. If anything beneficial emerges from the experience, it is that awareness of the logistics of such a situation will now be heightened. 'Maybe we should learn from these events for the future. Because Nature may be the terrorist next time', concluded Webster. So, as Lord Baden-Powell said, it's a question of being prepared for any old thing.

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DOI: 10.1093/embo-reports/kve259