Innovation, Policy, and Public Interactions in the Management of Infectious Diseases**

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Summary

This paper focuses on preparedness planning for an influenza pandemic, particularly the impact of specific policies on national health-related and economic outcomes. The case fatality rate (CFR) of a new influenza strain is likely to be the primary determinant of public behavior, leading to actions including individuals absenting themselves from work due to fear of infection (i.e., prophylactic absenteeism [PA]). Such behaviors impact the effectiveness of preparedness plans. Synthetic biology is a promising approach for the rapid development of improved diagnostics and vaccines, with enormous potential savings to national economies. Regulatory innovations are needed to enable rapid development of these technologies to address the emergence of a new pandemic strain of influenza. Throughout this paper, the United Kingdom is used to exemplify preparedness planning in a real-world setting. Similar points would apply to any other country operating, or planning to operate, a similar system of contingency planning and decision-making.

Current realities

The emergence in East Asia of a new strain of H5N1 avian influenza at the end of the 20th century has been a major concern among health authorities globally because, although it is only rarely transmitted to humans, it has a very high CFR. If it should mutate to a form that can readily infect humans while retaining this high CFR, it could cause a global pandemic of potentially devastating proportions. National and international health authorities have been developing preparedness plans for addressing the H5N1 threat since before 2005. Thus, in 2009, the unexpected emergence of an H1N1 strain of the influenza virus (frequently referred to as “swine flu”) encountered a relatively well-prepared response. Indeed, given that the CFR of the new H1N1 strain turned out to be low, the response provided a useful test of these preparedness plans in a context where any weaknesses that were revealed did not result in serious health or economic outcomes.

Preparedness planning in the U.K. is based on two largely irreconcilable objectives: minimizing direct health impacts and minimizing the indirect impact on the economy. Policies to achieve the first of these objectives include actions such as closing schools and more general “social distancing” (i.e., encouraging the public to avoid crowded places and prolonged contact with large numbers of people). On the other hand, policies to achieve the economic objective, described as “business as usual,” encourage uninfected people to behave normally (e.g., going to work). These two key objectives thus result in ambiguity in official advice in the event of a pandemic. Figure 1 explores potential economic outcomes from the tension between these two objectives, and examines perceived weaknesses in specific parts of the preparedness planning system related to factors such as risk communication, maintaining transport systems, delivery of food and fuel, coping with the demands on the health care system to diagnose disease, and delivery of drugs and vaccines.

Public response in the early stages of the 2009 H1N1 pandemic, before it was clear that the CFR was similar to a normal winter influenza epidemic, suggests that serious flaws in current preparedness plans would have been magnified if the H1N1 CFR had been higher. For example, there was evidence of some panic buying of drugs, stockpiling of face masks, and healthy people absenting themselves from work because of PA. There was also considerable controversy and some confusion around decisions to close some schools.

Based on the scenario in Figure 1, and building on standard epidemiological and U.K.-based economic modeling, an analysis was conducted to determine the potential impact of various combinations of mortality and morbidity from influenza, vaccine efficacy, school closures, and PA on the U.K. economy (Smith et al., 2009). The analysis found that the costs related to illness alone ranged between 0.5% and 1.0% of the gross domestic product (GDP) (UK£8.4 billion to UK£16.8 billion) for low-fatality scenarios, 3.3% and 4.3% (UK£55.5 billion to UK£72.3 billion) for high fatality scenarios, and larger still for an extreme pandemic with a CFR of up to 10% (e.g., as was the case for SARS). School closure increased the economic impact, particularly for mild pandemics, but had only a modest impact on infection rates. Vaccination with a pre-pandemic vaccine was calculated to save 0.13% to 2.3% of GDP (UK£2.2 billion to UK£38.6 billion); a single dose of a matched vaccine could save 0.3% to 4.3% (UK£5.0 billion to UK£72.3 billion); and two doses of a matched vaccine could limit the overall economic impact to about 1% of GDP for all disease scenarios.

One of the main drivers of economic impact in any pandemic is likely to be PA, assumed to be driven by the size of the CFR rather than by the infection rate, related to having an acquaintance die from the disease (the threshold being a CFR of 2.5%–5%). In this analysis, the impact of PA on the economy was more than quadruple the effect of the aforementioned factors. Even without PA, vaccine development and production will likely result in economic savings that outweigh the cost. The additional role of vaccination in providing reassurance and reducing the extent of PA will also greatly magnify these benefits.

Scientific opportunities and challenges

The above factors place a high premium on faster development of disease diagnostics (to characterize the nature of the organism for an emerging infectious disease and to distinguish infected from uninfected individuals) and on vaccines (to reduce both the infection rate and the extent of PA). Synthetic biology — combining large-scale DNA sequencing, artificial gene synthesis, and vaccine development using synthetically produced antigens — could allow for the rapid deployment of a new vaccine in response to a novel infection outbreak, as in the recent H1N1 influenza outbreak (Burbelo et al., 2010).

Artificial gene synthesis offers a shortcut to immunoassay development to detect human antibodies with high levels of sensitivity and specificity, resulting in a better diagnostic performance than natural proteins and increasing the spectrum and quality of immunodiagnostics. One technique is to generate a repeating peptide in a single protein to develop antibody-based tests for antigens, which leads to improved diagnostic performance compared to testing individual, natural, strain-specific proteins.

In vaccine development, bioinformatics can be used for engineering artificial proteins that match highly complex antigenic strain variations to induce a greater immune response. Two promising techniques currently in development are: 1) the creation of bioengineered antigens representing diverse strains of an organism to provide broad vaccine protection and 2) the use of synthetic attenuated viral engineering to produce live vaccines (modified viruses with proteomes identical to the virulent one, but with less than optimal codons and codon pairs, which renders the pathogenic viruses unable to grow or replicate efficiently and allows the infected host to mount a powerful immune response against the weakened virus). Synthetic biology will also have a role in the engineering of microorganisms for more rapid large-scale manufacture of these novel vaccines.

Policy issues

Planning for civil contingencies, including pandemic preparedness, aims to integrate the maintenance of key public services (e.g., health care, schooling, food distribution, transport, energy provision, banking), based on encouragement of community resilience and plans for maintenance of law and order. As noted above and in Figure 1, this will require an unprecedented degree of national-level policy collaboration, based on a good understanding of likely human behavior in response to a pandemic; there is room for improvement in both of these areas. In addition, the ability of synthetic biology to deliver better diagnostics and vaccines more quickly will require matching policy innovation at national and international levels to facilitate more rapid regulatory approval of these tools (EMA, 2011). Policy developments in civil contingency planning and product regulation will provide the physical and biological tools to minimize the health impacts of a pandemic or epidemic and will create an optimal societal environment for their application.

- *A coordinated national socioeconomic research strategy* is needed, well informed by an understanding of disease processes and of relevant scientific developments, to improve understanding of the likely behavior of members of the public and of official and unofficial responders in a range of pandemic scenarios. One outcome of this should be improved public communication plans based on the insights gained. **Proposed leads:** government research funders.

- *An open and robust planning and communication strategy for pandemic preparedness planning* must be developed that takes account of the views of those who will implement the plans, considers the outcomes of the socioeconomic analyses recommended above, and is able to integrate regional and local plans at a national level within clear and workable decision-making structures (including decision-making frameworks and designated decision-making powers). **Proposed leads**: local, regional, and national government officials across all functions involved in addressing a pandemic.

- *A science and innovation strategy* should be created and implemented to build on developments in synthetic biology to develop better methods for rapid characterization of novel disease organisms and more rapid development of effective vaccines matched to these organisms. **Proposed leads:** government bodies that fund basic science and medical science research.

- *Policy innovation* to support more rapid passage of new diagnostics and vaccines through safety and efficacy testing, including development of new, improved approaches to safety and efficacy testing (potentially also based on synthetic biology) and appropriate revisions of policy processes. **Proposed leads:** the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), and national regulators.

References

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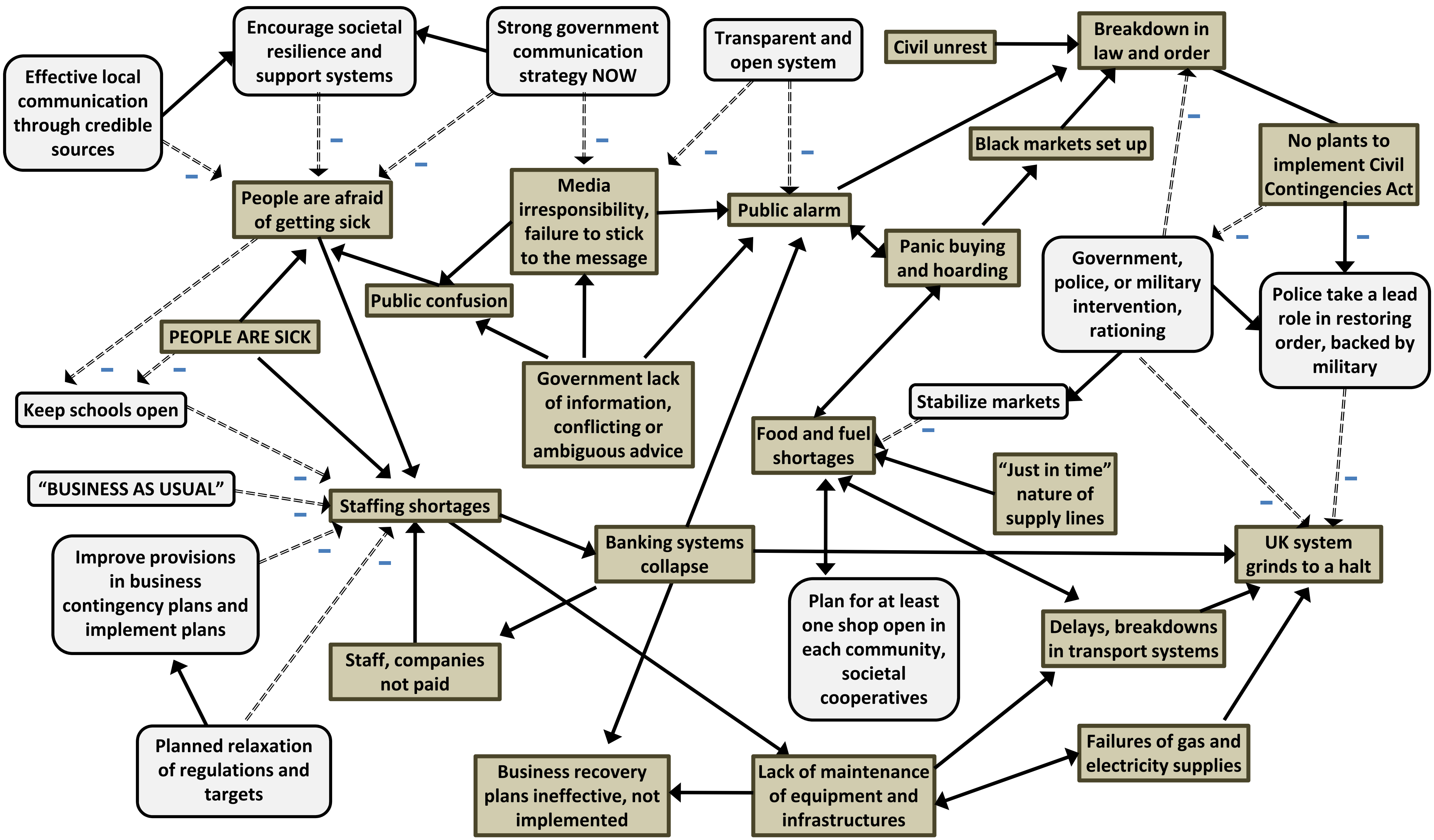
Figure 1. Preparedness Planning for Pandemic Influenza — Factors Impacting Mainly on the Economy



Note: In this figure, concepts colored dark grey are "problem-related" and those colored light grey are "solution-related"; arrows represent causal links and a dotted arrow with a negative sign indicates an inverse causal relationship.