Critical Care Pandemic Preparedness Primer

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Introduction

The first half decade of the 21st century has brought with it infectious outbreaks such as severe acute respiratory syndrome (SARS) [1], bioterrorism attacks with anthrax [2], and the spread of H5N1 influenza A in birds across Asia and Europe [3, 4] sparking concerns reminiscent of the days of the Black Plague. These events, in the context of an instantaneous global-media world, have placed an unprecedented emphasis on preparing for a human influenza pandemic [5, 6]. Although some argue that the media have exaggerated the threat, the warnings of an impending pandemic are not without foundation given the history of past influenza pandemics [7], incidence of H5N1 infections among humans [8], and the potential impact of a pandemic. Reports of the 1918 pandemic vary, but most suggested that approximately one third of the world's population was infected with 50 to 100 million deaths [9]. Computer modeling of a moderate pandemic, less severe then in 1918, in the province of Ontario, Canada predicts 73,252 admissions of influenza patients to hospitals over a 6-week period utilizing 72% of the hospital capacity, 171% of intensive care unit (ICU) capacity, and 118% of current ventilator capacity. Pandemic modeling by the Australian and New Zealand Intensive Care Society also showed that critical care resources would be overwhelmed by even a moderate pandemic [10]. This chapter will provide intensivists with a review of the basic scientific and clinical aspects of influenza as well as an introduction to pandemic preparedness.

Influenza Virology and Pandemic Pre-requisites

Influenza is a RNA virus of the family orthomyxovirus. There are three types of influenza: A, B, and C, although only A and B are pathogenic to humans [11]. Influenza viruses are sub-typed based on two of their surface proteins; hemagglutinin and neuraminidase. Hemagglutinin facilitates viral cell entry via the sialic-acid receptor whereas neuraminidase plays a role in the cleavage of glycosidic linkages allowing release of viral progeny. Influenza A has 15 distinct hemagglutinin subtypes (H1-H15) and 9 neuraminidase subtypes (N1-N9). Human strains of influenza A are referred to by a combination of their hemagglutinin and neuraminidase subtype along with the city and year in which the virus was first identified, i.e., 'A/Sydney/97 H3N2'. Nomenclature for influenza B is much more straightforward as influenza B only has a single subtype of hemagglutinin (H1) and neuraminidase (N1).

Birds, in particular water fowl, are clearly the species with the greatest diversity of influenza A infections. All subtypes of influenza A (H1–15 and N1–9) have been

found in aquatic birds. In contrast, among mammals fewer subtypes have established sustained transmission (humans H1–3/N1,2; pigs H1,3/N1,2; horses H3,7/N7,8) [11]. Avian influenza is further subdivided into 'low pathogenic' or 'highly pathogenic' strains. Low pathogenic infections are less virulent because they are restricted to the respiratory (usually upper) and gastrointestinal (GI) tracts. This is because their hemagglutinin precursor can only be cleaved to produce its active form by extracellular proteases found in the respiratory and GI tracts. Conversely, the significantly increased virulence seen in highly pathogenic viruses is attributable to systemic infection which occurs because alterations in the hemagglutinin allow cleavage by intracellular proteases found in all organ systems [12].

To understand how novel influenza viruses evolve with the potential to cause a pandemic, one must consider the concepts of 'drift' and 'shift' [9, 11, 13]. Drift refers to point mutations occurring in the surface hemagglutinin or neuraminidase leading to a slight modification of the antigenic properties of the virus. Where drift is a minor change in viral genome, shift is a major change in the genome that results from the reassortment of genes from two influenza viruses leading to a 'new' virus with antigenically distinct glycoproteins. Until Taubenberger and his colleagues recently sequenced the genome of the virus responsible for the 1918 influenza pan-

Table 1. Pandemic definitions and resources

Pandemic Conditions	WHO Pandemic Phases	Links to Selected Pandemic Plans
1. a new influenza A virus arising from a major genetic change i.e., an antigenic shift 2. a susceptible population with little or no immunity 3. a virus that is transmitted efficiently from person to person 4. a virulent virus with the capacity to cause serious illness and death.	**Interpandemic period** *Phase 1.* No new influenza virus subtypes have been detected in humans. An influenza virus subtype that has caused human infection may be present in animals. If present in animals, the risk of human infection or disease is considered to be low. *Phase 2.* No new influenza virus subtypes have been detected in humans. However, a circulating animal influenza virus subtype poses a substantial risk of human disease. **Pandemic alert period** *Phase 3.* Human infection(s) with a new subtype, but no human-to-human spread, or at most rare instances of spread to a close contact. *Phase 4.* Small cluster(s) with limited human-to-human transmission but spread is highly localized, suggesting that the virus is not well adapted to humans. *Phase 5.* Larger cluster(s) but human-to-human spread still localized, suggesting that the virus is becoming increasingly better adapted to humans, but may not yet be fully transmissible (substantial pandemic risk). **Pandemic period** *Phase 6.* Pandemic: increased and sustained transmission in general population.	WHO: www.who.int/csr/disease/influenza/pandemic/en Canada: www.phac-aspc.gc.ca/cpip-pclcpi U.S.A.: www.pandemicflu.gov European Union Plans: www.ecdc.eu.int/Influenza/National_Influenza_Pandemic_Plans.php Australia/New Zealand Intensive Care Society: www.anzics.com.au/uploads/influenza_pandemic_report.pdf Ontario, Canada: www.health.gov.on.ca/english/providers/program/emu/pan_flu/pan_flu_plan.html Toronto Academic Health Science Network: http://portal.sw.ca/tahsn

demic [a], it was felt that pandemics resulted from reassorted viruses (shift) whereas small epidemics and mismatches with influenza vaccines resulted from drift [11]. Taubenberger's group showed that the 1918 human H1N1 influenza virus differed from the H1N1 avian influenza virus of the day in only 10 amino acids, the result of drift. Although this new knowledge increases concern that H5N1 avian influenza may drift into a strain that fulfills the conditions necessary to produce a pandemic (Table 1), it also allows the World Health Organization (WHO) to monitor for key changes in H5N1 viral sequence which may enable human-to-human transmissions.

Clinical Presentation and Complications

Influenza presents with a variety of general symptoms familiar to most clinicians. These may include: Fever, headache, malaise, cough, sore throat, rhinitis, nausea and vomiting. Symptoms can vary with the specific strain of influenza [14] or host factors such as age [15]. Avian influenza H5N1 presents with a similar constellation of symptoms which also vary between family clusters [8]. Given this variability, it is difficult to determine *a priori* what symptoms a potential pandemic strain of influenza may produce. Complications produced by influenza are more predictable and include pneumonia (bacterial or viral), myositis, rhabdomyolysis, encephalitis, aseptic meningitis, transverse myelitis, and exacerbation of any underlying chronic condition particularly cardiac, pulmonary, or renal disease. Complications from H5N1 human cases to date are similar to H1N1 only more severe. High risk groups for complications of seasonal influenza include patients with cardiac, pulmonary or renal disease, diabetes, hemaglobinopathies, immunosuppression, and residents of nursing homes or those over 65 years old.

A review of H5N1-infected patients who required intensive care unit (ICU) support suggests a very virulent disease [16], although these data may be skewed by reporting bias. Of the 41 patients reported, 68% developed multiple organ failure (MOF) with a mortality rate of 90%. The time to ICU admission was rapid at 2 days (IQR 0.75 to 3.25 days) with a median time from hospital admission to death of 6 days. The majority of patients developed respiratory failure, but of note 44% developed hemodynamic compromise and 24% renal failure. Pneumothorax occurred in 17%, a rate higher than that noted in most series of acute respiratory distress syndrome (ARDS).

Diagnosis

The diagnosis of influenza can be challenging. While it may be possible to differentiate a viral from bacterial infection based upon features of the history and clinical exam [17], it is difficult to differentiate influenza from other respiratory viral infections, making laboratory diagnostics essential. Immunoflorescent antibodies (IFA), direct immunofluroesence, ELISA and molecular methods such as real-time polymerase chain reaction (PCR) are the most commonly used diagnostic methods in non-pandemic settings. During pandemics, clinical diagnosis may be more useful due to the increased pre-test probability, particularly if few other respiratory viruses are co-circulating at the time [18].

Prophylaxis and Treatment

Prophylaxis for influenza includes vaccination [19] or antiviral use [20, 21], both of which are currently available for seasonal influenza strains. It is unlikely, however, that vaccination will play a significant role in the early days of a pandemic scenario due to the lag time in production once a pandemic strain is identified [5, 22]. Although much effort is being directed toward developing a H5N1 vaccine [23–25], variations in the strain, when hemagglutinin mutations necessary for more efficient human-to-human transmission occur, may decrease the efficacy of the vaccine. Further, it is possible that the pandemic strain may not even be H5N1. A significant focus has, therefore, been placed on the potential role of antivirals for treatment or prophylaxis during a pandemic. The antivirals currently available are the adamantanes (amantadine and rimantadine), which block fusion of the virus and host-cell membranes, and the neuraminidase inhibitors (oseltamivir and zanamivir) which block the release of viral progeny from the infected cell [20]. Computer modeling shows that antivirals could play a role in both containment of an early outbreak through prophylaxis [26] or treatment [27], which has been favored in cost-analyses [28]. The primary limitation of antivirals is the development of resistance [29, 30] against influenza A, particularly for the adamantanes [31] which also lack activity against influenza B.

Transmission and Infection Control

The incubation period for influenza varies with age and ranges from 1–4 days (averaging 2 days) for adults. Adults are typically infectious from the day prior to the onset of symptoms to day 5 of their illness whereas infants and children can be infectious several days prior to symptom onset and continue to shed virus for weeks [32]. Influenza is transmitted primarily via respiratory droplets although the previous 'black and white' distinction made between droplet and airborne transmission of respiratory viruses was oversimplified [33]. There is evidence that airborne (aerosol) transmission of influenza does occur in some circumstances [21, 32]. None the less, except under select circumstances, hand-hygiene and droplet/contract precautions (mask, gloves, gowns, and eye protection) remain the mainstay of infection prevention for influenza [34]. Readers should note that airborne precautions with the use of 'N-95' (EU FFP2) masks are recommended for avian influenza (H5N1) [35]. It remains uncertain what precautions will be most appropriate during a pandemic. The precautions used may in fact change over time as the response evolves from efforts to slow the spread by controlling the very first cases in a region to later in a pandemic when the infection is broadly established in the community.

Some have questioned the utility of personal protective equipment for health care workers during a pandemic given that health care workers' largest exposure risk will not be at work but rather when they are outside of work in the community. This argument neglects to recognize that exposure risk is additive and health care workers who treat patients with influenza would have an additional risk above that of non-health care workers. Reasonable efforts should be made to mitigate this additional risk through the provision of appropriate personal protective equipment, while recognizing that it will not be possible to prevent all transmissions to health care workers. Honest communication and efforts to protect health care workers will be essential to ensure they will continue to report for duty during a pandemic [36].

In addition to protecting health care workers during a pandemic, vulnerable non-influenza patients admitted to hospitals must be protected against nosocomial transmission. Strategies to prevent nosocomial transmission include cohorting infections patients separately from non-infectious patients and surveillance for symptomatic patients. This presents a greater challenge since influenza is infective prior to the onset of symptoms [21, 33, 37]. Thus, cohorting should not be relied upon as a fool-proof method of infection control. However, it can still significantly decrease the exposure of highly susceptible critically ill patients to potential infection.

Pandemic Planning Activities

Governments, organizations and businesses of all sizes have developed or are in the process of developing pandemic response plans. Links to a selection of pandemic plans can be found in Table 1. A review of European Union pandemic plans revealed a strong commitment by governments to the planning process but coordination was lacking between countries [38]. Most pandemic plans are based on several basic assumptions. The first assumption is that a pandemic will occur in a series of waves, each lasting 6–15 weeks, occurring over the span of a year or more. The clinical attack rate assumed by most plans ranges from 15–35% and represents a less severe pandemic then in 1918. Plans also assume that transmission will primarily occur in communities, as opposed to within health care facilities as occurred in SARS [1]. The primary focus of pandemic plans is system capacity, whereas in SARS the objective was containment. Pandemics are by definition widespread, affecting many areas at once, thus plans must focus on self sufficiency since support from neighboring countries or communities is unlikely.

The following sections review key issues for a hospital response to a pandemic, followed by issues specifically related to critical care.

Preparing Hospitals to Respond

Patient flow and clinical pathways

Capacity will be the primary issue during a pandemic. In order to optimize capacity there must be a well coordinated influx and efflux of patients through the system as a whole and through individual hospitals. Figure 1 illustrates the proposed flow of patients with influenza through the Ontario health care system in a pandemic. The premise behind this model is that each decision point differentiates those patients who need to receive advanced care while diverting those who are able to care for themselves thus decreasing the burden on the health care system. Within health care pandemic planning, much attention has been paid to admission criteria, however discharge criteria are even more important [39]. Clinical pathways [39] can facilitate patient flow through hospitals, improve patient safety, and support health care workers performing in expanded scopes of practice.

Communication

Communication is always a challenge in any disaster. SARS highlighted communication challenges within hospitals [40, 41]. Hospitals must develop a communication plan. During a pandemic senior hospital leadership must be visible, supportive, communicate frequently and transparently with staff, patients, family members, and

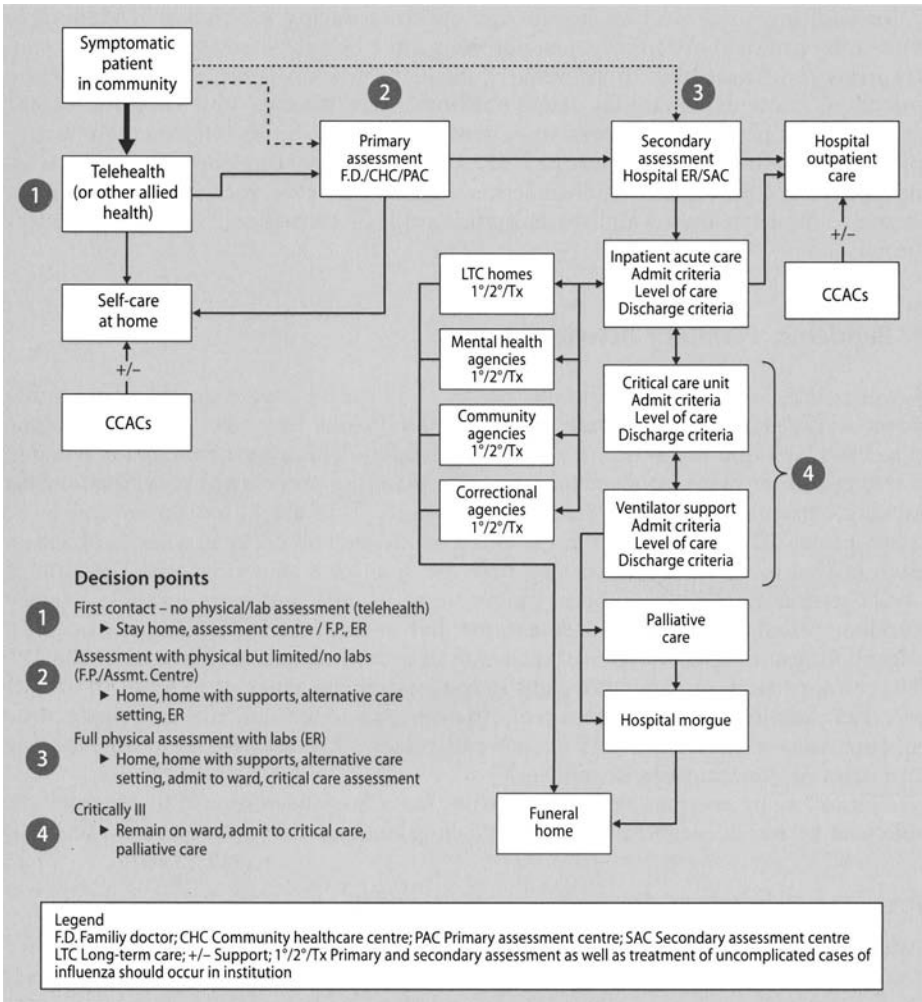

Fig. 1. Proposed flow of influenza patient through health care system

the media. Communication plans should be coordinated with other health care facilities, public health and all levels of government.

Command and control

Clear lines of command are critical to mounting an effective response, but traditional organizational structures used in health care are not intended for managing crises such as a pandemic. The Incident Management System (IMS) is rapidly being adopted by health care systems [42] and is ideal for structuring a response to a pandemic.

Human resources

Human resources shortages pose the greatest threat to a successful pandemic response. With expected absenteeism rates in the private sector of up to one third, health care organizations can anticipate similar if not higher rates at a time when system demands will be several fold higher then normal. Plans must be in place to scale back non-essential work and focus on 'essential work'. In doing so, it is important to remember that every health care worker will be essential and mechanisms must be in place to redeploy staff from non-essential to essential activities. Human resource plans must extend beyond the response phase into recovery. We have learned from SARS that the impact of personal and co-worker illness or death during an outbreak can have lasting effects on health care workers, long after the event [43].

Ethics

Many difficult issues must be confronted during a pandemic. When seeking to address such issues decision makers must be guided by both science and ethics. The complexities of these issues are beyond the scope of this chapter and readers are directed to a very thoughtful review [44].

Critical Care Response to a Pandemic

Accommodating influenza and non-influenza patients

When confronted with an overwhelming situation, people have a tendency to focus only on this issue (i.e., influenza) until it is resolved. However, in a pandemic we will still have an equal duty to care for the patient who happens to have a motor vehicle accident or myocardial infarction as well as those with influenza. A single pool of critical care resources exists that must be accessed by all. Thus, intensivists must plan to deal with both influenza and non-influenza patients during a pandemic which may last 12 months or more. Strategies to increase capacity include transforming non-ICU care areas, such as post-anesthetic care units, step-down units, endoscopy units, into ICUs and then assigning some units to deal with cohorts of either influenza or non-influenza patients. This task can be facilitated by creating and maintaining an inventory of all areas in your hospital that have the key requirements for conversion to an ICU: Oxygen, suction, medical gas, and electrical power, and adequate physical space to accommodate staff, equipment and patient care. Regional coordination is necessary to ensure that all essential health care needs are met within a region when individual hospitals scale back their routine services to meet the surge in patients.

Surge capacity

Plans and processes to deal with surges in critical care patients during a pandemic need to be developed. Involvement of intensivists in this planning process is essential. Most ICUs are capable of dealing with small surges (i.e., $<20-30\%$ above their day to day capacity) without exceeding their ability to cope. Various strategies such as a mass critical care and triage may be required to cope with larger surges. Collectively these concepts are referred to as surge response strategies. Hick and colleagues [45] differentiate between two important concepts: Surge capacity – making available adequate resources to deal with increased number of patients; and surge capability – the ability to manage increased number of patients. These definitions illustrate the need to plan for staff resources in addition to equipment and facilities.

For further information on surge capacity see the article by Hicks et al. [45] and web resources available at the Centre for Excellence in Emergency Preparedness (www.ceep.ca).

Care teams

One strategy that can be utilized to increase capacity is to modify the bedside staffing structure through the use of care teams. In a care team, a group of health care workers work together to care for a defined group of patients, usually in a fixed geographical area. This system makes use of a pyramid supervisory structure with less skilled or experienced staff being supervised and assisted by a small number of more skilled or experienced health care workers. This allows resources to be used more efficiently and allows less skilled health care workers working in expanded roles to function safely and effectively. A 50% increase in the critical care human resources capacity could be obtained by supplementing experienced ICU staff with non-ICU staff in care-teams. This structure is also consistent with the IMS organizational structure. ICU outreach teams for hospital wards and telephone support from academic intensivists for community intensivists may also help to maintain system capacity [40].

Mass critical care

Mass critical care is a different model and a different standard of critical care from what is practiced under normal circumstances. Simply stated, the goal of mass critical care is to provide a few key interventions (those with the highest impact and potential to save lives) to many people rather then providing very resource intense interventions to a few [40, 46, 47]. All processes and procedures are open to modification and must be considered from a new perspective including standards of care, staffing, equipment, and the allocation of resources. Although there certainly is a need to modify the standard of care during a pandemic, one must always keep in mind the primary objective of ensuring that the maximum number of people possible, survive. Thus, caution must be exercised when expanding clinical roles or modifying management to ensure that care is not compromised beyond the point where more harm is being done than good. For instance, it is of little use to move to a ventilation strategy such as long term manual ventilation with bag-valve-masks that may allow many more people to be ventilated but results in an increased number of deaths due to barotrauma than would have occurred if fewer patients were ventilated using a less harmful ventilation strategy. Striking an appropriate balance requires monitoring treatment outcomes during the response. In order to comply with medicolegal and ethical standards, plans to alter the standard of care during a pandemic should be publicly discussed and documented in advance with clear, objective criteria defined for the institution of mass critical care [44]. For these same reasons it is critical that all hospitals within an area adhere to the same standards of care.

Triage

During a pandemic, surge capacity may be maximized, yet resource scarcities will still occur [46, 47]. In such situations it is necessary, and in fact mandated by international law [47, 48], to utilize methods for allocating resources that are both equitable and maximize the benefit to the population at large [45]. Such methods are referred to as triage. Human rights, humanitarian laws [48] and strict adherence to ethical practices, such as transparency and accountability, must be observed when triage protocols are being developed [46, 47]. A full exploration of the ethical issues

Table 2. The prioritization tool for use in the critical care triage protocol. Adapted from [49]

Colour Code	Initial Assessment	48 hour Assessment	120 hour Assessment	Priority/Action
Blue	Exclusion criteria* **or** SOFA >11*	Exclusion criteria **Or** SOFA >11 **Or** SOFA 8–11 no Δ	Exclusion criteria* **or** SOFA >11* **or** SOFA <8 no Δ	Medical management +/– palliate & d/c from CC
Red	SOFA≤7 **or** Single Organ Failure	SOFA score <11 and decreasing	SOFA score <11 and decreasing progressively	Highest
Yellow	SOFA 8–11	SOFA <8 no Δ	SOFA <8 with <3 point decrease in past 72 h	Intermediate
Green	No significant organ failure	No longer ventilator dependent	No longer ventilator dependent	Defer or d/c, reassess as needed

* If exclusion criteria or SOFA >11 occurs at anytime from initial assessment to 48 hours change triage code to Blue and palliate. CC: critical care; d/c: discharge; Δ: change

related to triage can be found in the framework developed by the Joint Centre for Bioethics [44].

Prior to recent pandemic planning initiatives, no triage systems had been developed for use in critical care for medical illnesses. Illness severity scoring systems used in critical care research have a reasonable ability to predict ICU outcome. However, they are not intended to predict mortality in the individual patient and are cumbersome to use and impractical when human resources are scarce. Although validated for predicting outcome, they have not been validated for guiding, or more specifically restricting, treatment. Christian et al, have recently published the first comprehensive triage protocol designed for use during a pandemic [49]. This protocol has been incorporated into the Ontario Pandemic Influenza Plan [39]. The triage protocol utilizes the Sequential Organ Failure Assessment (SOFA) score [50] and has four main components: Inclusion criteria, exclusion criteria, minimum qualifications for survival, and a prioritization tool (Table 2).

A challenge in developing critical care triage protocols for a pandemic is that many prognostic factors, such as the natural history and response to treatment, are unknown. Given the highly complex nature of triage protocols, it is impossible to create a triage system *de novo* during a pandemic [46, 47]. The best way to prepare for critical care triage during a pandemic is to develop general triage guidelines [49] in advance of the pandemic and then modify the protocol once variable factors, such as probability of survival and available resources, are known. The infrastructure and training necessary to allow effective triage must also be addressed.

Conclusion

Although influenza is an illness we contend with every year, a great deal of uncertainty exists as to what an influenza pandemic would have in store for the world. This uncertainty makes specific planning difficult and increases anxiety among both

the public and health professionals. It is important to remember however, that as a pandemic draws nearer our knowledge will increase, dissipating the uncertainty. Although our plans must remain general, we must initiate the planning process now. Firstly, we do not know when the next pandemic may begin. Moreover, once a pandemic does begin, there will be insufficient time to lay the foundation upon which to mount a response. Critical care will play an instrumental role in the response to a pandemic, thus intensivists must be involved in planning the response. Intensivists bring to pandemic planning a unique understanding of treating critically ill patients and managing ICUs. Having read this chapter, intensivists should feel more comfortable engaging their colleagues in public health, infectious disease, and emergency medicine in planning together to prepare their community to respond to a pandemic.

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