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STREAM 4
Background document

OPTIMIZING TREATMENT

Optimizing the treatment of patients

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Introduction

The influenza A viruses continue to present challenges for the treatment of influenza disease. These challenges relate to the substantial impacts of seasonal influenza infections, uncommon but serious avian influenza A(H5N1) and other zoonotic influenza infections, and pandemic (H1N1) 2009 influenza infections. Studies of experimental infection in animal models and human infections have increased our understanding of the pathogenesis of human disease, particularly serious life-threatening disease. However, our knowledge about the viral and host factors leading to severe influenza illness is incomplete, and improved clinical management strategies are needed. Comparison of the reconstructed 1918 pandemic A(H1N1) virus, avian A(H5N1) viruses and the pandemic (H1N1) 2009 virus with seasonal viruses has identified viral factors which enhance pathogenicity and the risk of secondary bacterial infections. In addition, careful analysis of pandemic H1N1 infections in previously healthy persons as well as persons with underlying medical conditions has provided new insights. However, these analyses also have raised new questions about the treatment of serious disease, particularly for 'at risk' patients such as pregnant women and individuals who are obese.

Evaluation of rapid diagnostic testing for avian A(H5N1) and pandemic (H1N1) 2009 influenza viruses has highlighted the shortcomings of existing assays and stimulated research into new and improved point-of-care diagnostics. Improved diagnostics could help in optimizing antiviral treatment and supplementing current surveillance schemes. Currently available antivirals include the M2 inhibitors, oral amantadine and rimantadine, and the neuraminidase inhibitors (NAIs), oral oseltamivir and inhaled zanamivir. Early treatment particularly with the NAIs has proved beneficial in uncomplicated influenza. Oral oseltamivir also has shown some benefit in treating patients hospitalized with seasonal influenza or with serious avian A(H5N1) infections. However, parenteral formulations of antivirals are needed for treating serious life threatening disease. In addition, the development of resistance to some of the licensed antiviral drugs has emphasized the need for new antivirals against alternative viral targets and for combination antiviral therapy, particularly for the management of severe infections.

The initial detection of human infections with avian A(H5N1) in 1997, as well as continued sporadic zoonotic infections related to other avian influenza viruses, led to the development of pandemic preparedness and response plans in many countries including stockpiling of antivirals. In response to the pandemic (H1N1) 2009, novel approaches such as telephone hotlines and triage systems have been implemented in some countries to identify and treat ill persons.

This document will review the factors associated with influenza pathogenesis and disease severity, current approaches for clinical management of influenza, and healthcare capacity and response.

Factors associated with pathogenesis and clinical severity

Clinical spectrum and pathogenesis of human infections

The clinical spectrum of influenza infections in humans is broad. It can include a non-febrile, mild upper respiratory tract infection, a febrile influenza-like illness, and severe or even fatal complications, including rapidly progressive pneumonia. Disease severity is influenced in part by the virus and its replication patterns, the presence of secondary bacterial infections, and host factors such as age, immune status, underlying medical conditions, and possibly genetic factors.

In seasonal, pandemic and zoonotic influenza A infections, case fatality is related to the virulence of the infecting influenza virus. The high mortality (≥60% case fatality) characteristic of A(H5N1) infections is linked to very high levels of viral replication, particularly in the throat and lower respiratory tract, and is frequently associated with detection of viral RNA in the stool and the blood (de Jong 2005). These high viral loads are associated with an intense pro-inflammatory cytokine and chemokine response that likely contributes to illness severity. The duration of A(H5N1) viral replication in humans is prolonged and has been documented to last up to 15–17 days after illness onset (de Jong 2005). Extra-pulmonary dissemination of virus occurs in some experimentally infected animals (i.e. mouse, ferret); pathological studies of a limited number of fatal A(H5N1) infections have sometimes found dissemination of the virus to the intestine and brain as well as penetration of the placental barrier and infection of the foetus (Kortweg 2008, Kuiken 2008). However, administration of corticosteroids has been a confounding factor in some cases with documented dissemination (Gu 2007).

Levels of viral replication in the respiratory tract have been associated with disease severity in seasonal influenza virus infections as well (Nicholson 1998). The peak titers of virus in the upper respiratory tract occur within 24-48 hours of the onset of symptoms, are lower than titers for A(H5N1) and drop below the limit of detection within 4-5 days in uncomplicated infections in adults. Hospitalized adults often have evidence of viral replication lasting 5 days or longer after symptom onset (Lee 2009, Leekha 2007). This observation corresponds with evidence that delayed antiviral treatment may be effective in such patients (McGeer 2007, Lee 2009, Hanshaoworakul 2009). Hypercytokinemia (of proinflammatory and T helper 1 cytokines) has been detected in hospitalized patients with severe seasonal influenza which correlates with clinical illness and virus concentrations (Lee 2007). Early viral suppression may attenuate these potentially deleterious cytokine responses. Upper respiratory tract viral titers are on average higher in children compared with those in adults and persist for 6-8 days or longer. Virus replication may persist for several weeks and sometimes months in the immunocompromised host.

Estimates of population clinical attack rates for the pandemic (H1N1) 2009 virus from a number of countries range from 7% to 15% (WHO Transmission dynamics and impact of pandemic influenza (H1N1) 2009 – Update. *Weekly Epidemiological Report [WER], 2009*). Most persons experience an uncomplicated influenza-like illness with full recovery within a week even without medical treatment. Approximately 1-10% of persons with clinical illness require hospitalization. Preliminary estimates of the overall case fatality ratio are <0.5% (WHO, WER 2009). Compared to seasonal influenza, pandemic H1N1 virus replication is more prolonged in adults with uncomplicated illness and may persist for a week or longer, sometimes after fever and most symptoms have resolved (De Serres 2009, Liang 2009, Witkop 2009). Patients with severe illness generally deteriorate 3-5 days after the onset of symptoms and may rapidly progress to respiratory failure in 24 hours (WHO. Clinical features of severe cases of pandemic influenza. Pandemic (H1N1) 2009 briefing note 13. 16 October 2009). High and sustained levels of viral replication have been found in the lower respiratory tract of such patients. These high lower respiratory tract viral loads, like those observed for avian (H5N1) pneumonia, may relate in part to the ability of the pandemic H1N1 virus to bind to both alpha 2,6 (human like) and alpha 2,3 (avian like)-linked receptors, the latter being located in the distal airways and alveoli. Viral RNA and, uncommonly, infectious virus has been detected in the stool, but there has been little evidence of extra-pulmonary virus replication to date (WHO Research priorities. Informal Meeting on Pandemic (H1N1) 2009 on 2 September 2009 at WHO SEARO, New Delhi).

Secondary bacterial infections associated with influenza

Serious influenza infections are often complicated by secondary bacterial infections, particularly pneumonia. Complex interactions exist between the infecting influenza virus and co-infection with bacterial respiratory pathogens. Multiple mechanisms exist by which influenza virus infection can predispose to bacterial co-infections (Brundage 2008). These include breakdown of the physiological barriers to tissue invasion, decreased mucocilliary clearance, increased adherence of cell receptors due to viral NA mediated activity, and inhibitory effects on immune effector cells.

Re-evaluation of stored post-mortem samples from the 1918/19 pandemic has revealed histological evidence of serious bacterial pneumonia in virtually all cases (Morens 2008). Microbiological studies found that over 90% of lung samples were positive for bacteria including *Streptococcus pneumoniae*, *Staphlococcus aureus*, *Streptococcus pyogenes*, *Neisseria meningitidis* and *Haemophilus influenzae*. Evaluating the role of bacterial infections during the 1957 and 1968 influenza pandemics and seasonal epidemic influenza is partly masked by the use of antibiotics which can reduce bacterial isolation rates. *S. pneumoniae* has been the most frequently detected secondary pathogen in most studies. However, several studies have documented the importance of *S. aureus* in past pandemics (Kuiken 2008, Hers 1958, Oswald 1958, Robertson 1958). Methicillin-resistant (MRSA) strains have been associated with severe, rapidly progressive and sometimes necrotizing disease. Primary viral pneumonia and associated acute respiratory distress syndrome (ARDS) have been observed in about 50% of severe infections with pandemic (H1N1) 2009 influenza (ANZIC Investigators 2009); secondary bacterial infections have been found in approximately 30% of fatal cases. In addition, ventilator-associated pneumonia or other hospital-acquired infections caused by typical nosocomial pathogens have complicated the course of patients with severe illness. Bacterial complications may present as a clinical deterioration after initial improvement, a prolonged fever and refractory clinical course, or as a change in respiratory secretions.

Many questions regarding prevention strategies and the detection and management of secondary bacterial infections remain unanswered. For example, in a murine model of sequential influenza and *S. pneumoniae* infection, treatment with a cell-wall active antibiotic (ampicillin) was associated with significantly greater pulmonary inflammation and worse outcomes compared to treatment with an antibiotic inhibiting protein synthesis (azithromycin, clindamycin), even though both inhibited bacterial growth (Karlstrom 2009).

Fatal avian H5N1 infections have been associated with primary viral pneumonia leading to ARDS and, on occasion, shock and multi-organ failure. Evidence of bacterial pneumonia has been uncommon at the time of hospitalization, but nosocomial infections have developed during subsequent care (Kuiken 2008).

Possible role of host genetic pre-disposing factors

Pathogens such as influenza have to overcome multiple host defense barriers to establish infection. These barriers include mucociliary clearance, inhibitory molecules in respiratory secretions (e.g., defensins, mucins, surfactants, mannose-binding lectin [MBL]), and innate immune responses within the upper and lower respiratory tract to reach sialic acid-bearing receptors on susceptible cells. The types and distribution of receptors have been postulated to play important roles in severe lower respiratory disease associated with avian H5N1 infection.

However, inter-individual variations in receptor patterns are not well characterized in humans. Similarly, the levels of inhibitory molecules like MBL differ among persons and may play a role in susceptibility. Innate immune responses include the action of natural killer cells and the induction of cytokine and chemokine responses through various cell receptor signaling pathways such as those induced by the Toll-Like Receptors. Antigen presenting cells, mainly dendritic cells, process viral fragments including internal viral proteins, and migrate to the regional lymph nodes where activation of memory T-cells occurs. T-cell memory and recall elicit cross-reactive anti-influenza responses based on previous influenza infections. These include the cytotoxic action of antigen-specific memory CD8 cells and cytokine production by CD4-helper cells. Lastly, development of humoral antibodies occurs against hemagglutinin (HA) and other viral proteins, which eliminate any free virus and protect against future infection with the same virus. Many stages of innate and adaptive cell immunity involve interactions with the different classes of major histocompatibility antigens classes I, II, and III, which are important in fighting disease. Human leucocyte antigens (HLAs) are polygenic, and may be associated with reduced or enhanced immunological responses to infection in apparently healthy individuals and those with underlying medical conditions. Whether specific immunoglobulin deficiencies may be associated with severe influenza, as suggested by one report of low serum IgG2 levels in patients with severe pandemic (H1N1) illness (Gordon 2009), requires further study.

Viral-specific pathogenic factors may target some of these immunological mechanisms, leading to enhanced replication and perhaps immune-pathological responses to infection, either of which could result in severe disease. The NS1 protein has multiple effects on the immune system including blocking type 1 interferon production and the induction of antiviral responses in dendritic and respiratory epithelial cells (Haye 2009). The anti-interferon effects may serve to upregulate viral replication. The NS1 of both pandemic 1918 A(H1N1) and A(H5N1) possess a PDZ domain ligand which binds to cellular PDZ domains involved in cell signaling pathways for cytokine production (Garten 2009). In addition, the PB1-F2 protein of the 1918 A(H1N1) virus and the avian A(H5N1) virus have been associated with increased pathogenicity through stimulation of pro-inflammatory cytokine responses and the development of severe bacterial pneumonia (McCullers 2008, Garten 2009). In contrast, both the NS1and the PB1-F2 proteins in the pandemic (H1N1) 2009 virus are truncated which could explain in part the milder clinical picture observed in most patients. However, this would not explain the higher levels of viral replication and more severe disease observed in animal models of pandemic (H1N1) compared to seasonal H1N1, as well as the serious life threatening disease observed in some patients (Brookes 2009, Lange 2009, Streta 2009). This suggests that other viral virulence factors remain to be identified and that serious disease associated with pandemic A(H1N1) may be linked more closely with host genetic factors and underlying risk conditions, which may be critical in the absence of pre-existing protective immunity.

Possible effect of concurrent medical conditions

Risk factors for severe disease associated with pandemic (H1N1) 2009 infection appear to be similar to those identified for seasonal influenza. These include:

- Infants and young children, in particular <2 years
- Pregnant women
- Persons of any age with chronic pulmonary disease (e.g. asthma, COPD)
- Persons of any age with chronic cardiac disease (e.g. congestive cardiac failure)
- Persons with metabolic disorders (e.g. diabetes)

- Persons with chronic renal disease; chronic hepatic disease; certain neurological conditions (including neuromuscular, neurocognitive, and seizure disorders); hemoglobinopathies; or immunosuppression, whether due to primary immunosuppressive conditions such as HIV infection, or secondary conditions such as immunosuppressive medication or malignancy
- Children receiving chronic aspirin therapy
- Persons aged 65 years and older

A higher risk of severe complications from pandemic (H1N1) 2009 virus infection has also been reported in individuals who are obese (particularly in those who are morbidly obese) and among disadvantaged and indigenous populations.

On average, about 50% of hospitalized patients have had at least one or more underlying medical conditions[1] (WHO, WER 2009). However, about 1/3 of patients with very severe illness admitted to an intensive care unit were previously healthy persons.

Improved Clinical Management of Patients

Improvement of rapid, point-of-care diagnostic tools

Commercially available rapid influenza diagnostic tests (RIDTs) have been widely used to detect virus antigen in respiratory clinical specimens for seasonal influenza. The reported sensitivity of these tests ranges between <20% and 90% compared with virus culture or reverse transcriptase polymerase chain reaction (RT-PCR). The sensitivity of the test can vary by patient age, duration of illness, sample type, and influenza strain (Petric 2006, Chan 2007, Uyeki 2009). These tests have low sensitivity (18% - 69%) in adults with seasonal influenza and in patients with A(H5N1) virus or pandemic H1N1 infection (Chung 2007, Chan 2009, CDC 2009, Ginocchio 2009, Hurt 2009, Balish 2009). A negative rapid test result does not exclude infection and a positive test does not distinguish avian H5N1 or pandemic H1N1 influenza from infection with other influenza viruses (WHO H5N1 Clinical Management). Similarly, many pandemic H1N1 infections may be missed, especially in specimens with low viral titres (Balish 2009). Therefore, both positive and negative rapid test results should be interpreted with caution for pandemic (H1N1) 2009 influenza (WHO. Clinical management of human infection with new influenza A (H1N1) virus: initial guidance 21 May 2009). There is an urgent need for improved point-of-care diagnostics for individual patient management and public health surveillance.

Initial treatment decisions should be based on a patient's clinical presentation and available epidemiological data. Treatment should not be delayed while awaiting laboratory confirmatory testing (WHO. Guidelines for Pharmacological Management of Pandemic (H1N1) 2009 Influenza and other Influenza Viruses 20 August 2009). It is not yet known which clinical specimen gives the best diagnostic yield for pandemic H1N1 infection; however, lower respiratory samples test positive more often in patients with severe illness or pneumonia. Confirmatory diagnostic testing can be done by specialized laboratories in many countries. RT-PCR provides the most timely and sensitive evidence of pandemic (H1N1) or avian H5N1 infection. Further advancements of RT-PCR diagnostic technologies, such as the availability of test results within an hour and the need for minimal operator training, may lead to improved patient care, detection of antiviral resistance,

[1] Reports from several countries describing hospitalized cases have noted varying proportions of patients with co-morbid conditions; this likely reflects differences in how these conditions were defined.

and the potential for therapeutic monitoring in severely ill patients. Development of simple low-cost diagnostic tests for susceptibility as a marker of past infection (i.e. dried blood spot) would have epidemiological benefits as well. In addition to improved viral diagnostics, better methods to determine the presence and cause of bacterial co-infections would greatly improve clinical care and antimicrobial practices.

Development of new antiviral drugs and drug formulations

There are important limitations regarding the use of currently available antiviral drugs for treatment and prophylaxis of all types of influenza:

a) pandemic (H1N1) 2009 and seasonal A(H3N2) viruses have high-level resistance to the M2 inhibitors; avian A(H5N1) viruses are variably resistant;
b) most seasonal A(H1N1) viruses and a small number of pandemic (H1N1) isolates have high-level resistance to oseltamivir; oseltamivir resistance has emerged during treatment of some patients with avian H5N1 and pandemic H1N1 and may be associated with poor prognosis;
c) the efficacy of oral oseltamivir is uncertain in patients with severe avian A(H5N1) or other influenza infections;
d) parenteral agents for the treatment of severe infections are not widely available;
e) adult and paediatric antiviral formulations that are easy to store and use, particularly in under-resourced setting, are lacking.

New drugs

Several investigational antiviral drugs are in development including agents directed against currently used and alternative viral targets and host receptors and drugs with long retention times to facilitate reduced dosing schedules (Hayden 2009). These include laninamivir (CS-8958), an inhaled long-acting NAI in Phase 3 development, favipiravir (T-705), an oral influenza RNA polymerase inhibitor in Phase 2 development, and DAS181 an inhaled sialidase fusion protein which targets host sialic acid containing receptors to block virus attachment in Phase 1 development. Results from Phase 2 and 3 studies showed that a single dose of CS-8958 was as effective as a 5-day course of oseltamivir in uncomplicated influenza infection in adults and children (Biota Press Release, 2008).

Other early developments of note include novel siRNA which switches off viral proteins important for virus replication, and structural studies on key viral targets such as polymerase that may allow design of further new drugs. Novel inhibitors should increase the options for combination therapy which may be critical to suppress resistance development.

New formulations

Current antivirals are administered either orally or by inhalation, routes which may not achieve adequate drug levels at the sites of infection in seriously ill patients. Parenteral administration would rapidly and reliably deliver high levels of drug to the blood and consequently to different organs. An intravenous (IV) form of oseltamivir is under development to help meet this need. In addition, IV peramivir, originally developed but not adequately absorbed as an oral NAI, is currently in Phase 3 clinical studies in hospitalized patients. IV peramivir achieves much higher peak plasma drug levels (>40,000 ng/ml) than standard oral dose oseltamivir (~350 ng/ml). Also, peramivir binds to the neuraminidase enzyme's active site for up to 24 hours and has a prolonged

plasma elimination half-life in humans which allows once daily dosing regimens. Efficacy with single dose IV peramivir was superior to placebo (Kohono 2008) and comparable to 5-day treatment with oral oseltamivir in uncomplicated influenza in adult outpatients (Kohono, ICAAC 2009). However, it is much less active against oseltamivir-resistant N1-containing viruses with the H275Y mutation. IV peramivir is currently available for treating hospitalized patients with pandemic H1N1 illness in the USA under a Food and Drug Administration emergency use authorization mechanism.

Zanamivir, approved as an inhaled drug, has also been tested as an IV formulation in a phase 2a clinical study of experimentally infected volunteers and was found to be highly protective against virus challenge (Calfee 1999). Further studies are planned to test IV zanamivir in patients hospitalized with pandemic (H1N1) or avian A(H5N1) viruses. Zanamivir retains full inhibitory activity against oseltamivir-resistant N1-containing viruses, and IV zanamivir has been used on a compassionate basis in cases of severe pandemic (H1N1) illness with suspected or proven resistance (Kidd 2009, MMWR 2009). In addition, plans are underway to develop an IV formulation which may be diluted to allow nebulized administration of the drug.

Management of pregnant women, children and other persons at increased risk of severe disease and complications of influenza infection

Antivirals

Pregnant women, infants and children less than 5 years (especially those less than 2 years), the elderly (>65years), nursing home residents and patients with chronic co-morbidities as indicated previously are at increased risk for severe/complicated disease and should be treated with currently available antivirals.

Early administration of NAIs to at risk patients with pandemic (H1N1) illness is recommended to reduce the severity and duration of illness and the risk of progression to severe disease and death. In addition, any patient with severe or progressive illness due to suspected or proven pandemic H1N1, irrespective of underlying conditions, should receive early, empiric therapy with oseltamivir or another systemic NAI. Higher oseltamivir doses (150 mg bid in adults) and more prolonged therapy (e.g., 10 days) are reasonable because of prolonged lower respiratory tract viral replication in patients with severe pandemic (H1N1) illness. Antivirals may be used at any stage of active disease when ongoing viral replication is anticipated or documented. Some patients, particularly those with severe disease or immunosuppressive conditions, can experience viral replication for a prolonged period of time.

Pregnant women are known to be at increased risk of complications from influenza based on experience from seasonal, A(H5N1), and pandemic influenza. An increased risk of hospitalization and fatal outcomes have been reported in pregnant women infected with the pandemic (H1N1) 2009 virus (Jamieson 2009, Rasmussen 2009), especially during the third trimester of pregnancy. Pregnant women with suspected or confirmed pandemic (H1N1) 2009 infections warrant close observation and early treatment with antivirals. Peripartum infections have been documented with pandemic (H1N1) 2009.

The pharmacology of oseltamivir has not been studied in obese (BMI>30) individuals, but doubling the dose of oseltamivir to 150mg has been suggested until data become available. Severely ill obese patients appear to consist of two groups: those with additional risk conditions

such as cardiovascular disease and those with increased pressure on the lungs due to their obesity, which in turn is associated with an increased risk of developing ARDS. Adults ≥65 years appear to have a lower risk of infection with pandemic (H1N1) 2009 probably due to some long term immunity. However, persons in this age group experience a higher risk of complications if they develop infection and should be treated.

Nebulized zanamivir has been used in a small number of hospitalized patients with seasonal influenza and has been shown to be adequately tolerated in non-intubated patients but of uncertain benefit (Ison 2003). Virologic failure with inhaled zanamivir has been documented in those with pneumonic disease and nebulized zanamivir may be poorly tolerated in some patients who are mechanically ventilated. Nebulization of solutions made from the lactose-containing powder from the commercial inhaler may cause lethal ventilator dysfunction and this practice should be avoided. Appropriate infection control measures must be used during administration of nebulized antivirals to prevent possible transmission of influenza viruses by aerosol.

Investigational, intravenously administered NAIs now in clinical development (e.g. IV zanamivir or peramivir) provide high drug levels and reliable delivery. Given their activity in A(H5N1) animal models and good tolerability in initial human studies, either IV zanamivir or peramivir would be a reasonable alternative to oral oseltamivir for initial treatment of pandemic H1N1 or avian A(H5N1) virus infection, if available and approved by appropriate national regulatory authorities.

Other treatment considerations

Corticosteroids are not recommended for routine use, but low dose (e.g. hydrocortisone 50mg q6H) may be considered for septic shock with suspected adrenal insufficiency requiring vasopressors. Prolonged or high dose corticosteroids can result in serious adverse events including opportunistic infections and prolonged virus replication (Tang 2009).

Aspirin or salicylate containing products should not be used as an anti-pyretic for influenza in patients under 18 years old because of the risk of Reye Syndrome. In addition, observations from the 1918 pandemic suggest that salicylate use may have increased mortality, perhaps by increasing the risk of pulmonary edema (Starko 2009). Administration of convalescent blood products in 1918 may have reduced mortality in pneumonia patients (Luke 2006); administration of anti-H5N1 specific antibodies either as neutralizing antibodies or polyclonal serum has shown efficacy in animal studies and possibly in some patients. Such interventions require controlled clinical studies with virological and clinical monitoring. Similarly, although epidemiological or animal studies of various immunomodulating agents (e.g., statins, fibrates, glitazones, cyclooxygenase 2 inhibitors) have suggested that they may offer some possible benefit in treating influenza, careful prospective clinical studies are needed. Such agents should only be explored after independent preclinical studies have shown benefit and proven safety.

Management of severely ill patients

A minority of patients infected with pandemic (H1N1) develop rapidly progressive viral pneumonia, often leading to ARDS. In addition, exacerbations of pre-existing lower respiratory tract disease and secondary bacterial infection can lead to respiratory failure and the need for ventilatory support (Napolitomo 2009, WHO Clinical features of severe cases of pandemic influenza Pandemic (H1N1) 2009 briefing note 13. 16 October 2009). Australia and New

Zealand experienced a 15-fold increase in intensive care unit admissions related to pandemic (H1N1) 2009 influenza; pandemic (H1N1) patients occupied up to 20% of ICU beds at the peak of the pandemic's first wave (ANZIC 2009). Influenza A(H5N1) virus infection often causes severe, rapidly progressive respiratory failure. Many patients also develop multi-organ failure with a high proportion of patients requiring advanced organ support. Supportive therapy for critically ill patients infected with avian A(H5N1) or pandemic (H1N1) 2009 influenza, or, more rarely seasonal influenza, have been published (WHO Clinical Management of human infection with avian influenza A(H5N1) Updated advice 15 August 2007; WHO Guidelines for Pharmacological Management of Pandemic (H1N1) 2009 Influenza and other Influenza Viruses 20 August 2009). Key elements of supportive therapy include oxygen and invasive and non-invasive ventilation. New techniques, including extracorporeal membrane oxygenation (ECMO) and high frequency oscillation ventilators, have been used in situations when severely ill patients infected with pandemic (H1N1) were difficult to treat with conventional ventilators.

Health Care Capacity and Response

Managing surge capacity

Early clinical intervention strongly correlates with a better prognosis for patients with influenza. Interventions include not only administration of early antiviral treatment and antimicrobials for suspected bacterial co-infections, but also provision of the correct level of health care, especially critical care.

There are two important points during the continuum of care for patients with influenza when the need for a possible surge in capacity can be anticipated; advance planning is critical to help meet these needs. Firstly, when patients develop influenza-like illness, they require accurate and easy-to-understand information about the disease, its expected course and warning signs for severe disease that require immediate medical attention. Secondly, when infected patients develop life-threatening disease they require hospitalization and intensive care unit facilities and equipment. Triage systems for influenza-like illness must determine the correct diagnosis, including exclusion of other treatable conditions, assess if risk factors for serious disease are present, and determine if antiviral treatment and/or consultation with a doctor is needed.

Innovative approaches have been developed to help reduce pressures on hospital emergency departments and general practitioner at these two resource-intensive points. For example, the Department of Health in England implemented a national telephone hotline and internet based service that authorizes patients who are not in a specified risk group access to antivirals without the need to see a general practitioner (Elliot 2009). The technology to create a pandemic hotline and the methodology to build a workforce of home-based volunteers and/or call centres has also been put into practice in 2009 in the USA (CDC toll-free hotline; Hwang, 2007). These systems also have links with web-based expert information on triage such as the Centers for Disease Control and Prevention (CDC) website and with influenza experts. The effectiveness of such public health interventions requires careful study.

Assessing the surge capacity of intensive care unit facilities during a pandemic is critical. Electronic packages such as FluSurge and FluAid have been developed and are available to estimate the required surge capacity and to aid in planning (Nap 2007). Many countries have found that their capacity is insufficient to meet the demands of a pandemic including shortages of hospital beds, hospital staff, ventilation equipment and more specialized equipment such as

ECMO. Scenario planning and development of appropriate triage systems in advance of a pandemic can help identify resource gaps and ways to allocate scarce resources.

Development of alternative health delivery systems for care of patients

Home care will be especially important if most cases of pandemic (H1N1) 2009 remain relatively mild and patients can be managed at home with advice from pandemic hotlines or other resources like WHO and CDC websites. If the pandemic virus evolves and begins to cause severe disease with greater frequency, home or alternative site care with the aid of health care providing organizations may be required. Other public setting such as school gymnasiums, churches, or convention centres may be used with local health care and government administration. Local amenity workers including the police force, fire brigade, retired nurses, and other volunteers may be required to provide additional health care (Levin PJ 2007). Evaluation of alternative health care delivery systems is needed to identify effective approaches that did not result in increased patient morbidity and mortality.

Protection of health care workers and other care-givers

Protection of frontline healthcare workers should be the first priority, and WHO currently recommends pandemic H1N1 immunization of such persons, who represent approximately 1–2% of the population in many developing countries. In many countries vaccine will not be available or in short supply. Hence, consistent and correct use of infection control precautions is essential. Although WHO and many countries have developed guidance, there are many information gaps and a firm evidence base is lacking in critical areas including the effectiveness of hand washing, masks and respirators and the types of procedures likely to generate infectious aerosols. Behavioural research to increase seasonal influenza vaccine uptake and adherence to recommended infection control precautions is sorely lacking.

Research to underpin evidence-based recommendations for community settings is also needed, including recommendations for mask/respirator use in patients, their carers or contacts

Health care delivery in low resource settings

Disadvantaged populations such as minority groups and indigenous populations appear to be disproportionately affected by severe disease when infected with the pandemic (H1N1) 2009 virus. Although the reasons for this heightened risk are not yet fully understood, greater frequencies of co-morbidities, such as diabetes and asthma and lack of access to care are being explored (WHO. Clinical Features of severe cases of pandemic influenza. Pandemic (H1N1) 2009 briefing note 13. 16 October 2009). In developing countries several factors such as population density, under nutrition, care seeking from traditional healers, and delays in treatment may affect clinical attack rates, severity and case fatality. Establishment of surveillance in schools or worksites to monitor influenza-like illness-related absences and in sentinel hospital for patients with severe acute respiratory infections (SARI) can help in characterizing the risks of clinical disease, severity and death, and in identifying risk groups and risk settings. The ratio of symptomatic to asymptomatic infection can be estimated by conducting surveys of selected communities (e.g. schools, work-sites, households) combined, if possible, with serological testing; sentinel surveillance in voluntary blood donors is an alternative. Follow up of sample populations needs to be done to measure communicability, i.e., attack rates, secondary attack rates, the serial interval and other key parameters.

These epidemiological parameters can then be used in mathematical modeling to estimate disease burden and the effect of interventions (WHO_CDS_ H1N1_2009_Research_priorities. Informal Meeting on Pandemic (H1N1) 2009 on 2 September 2009 at WHO SEARO, New Delhi).

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