STREAM 2
Background document

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RESEARCH AGENDA
FOR INFLUENZA

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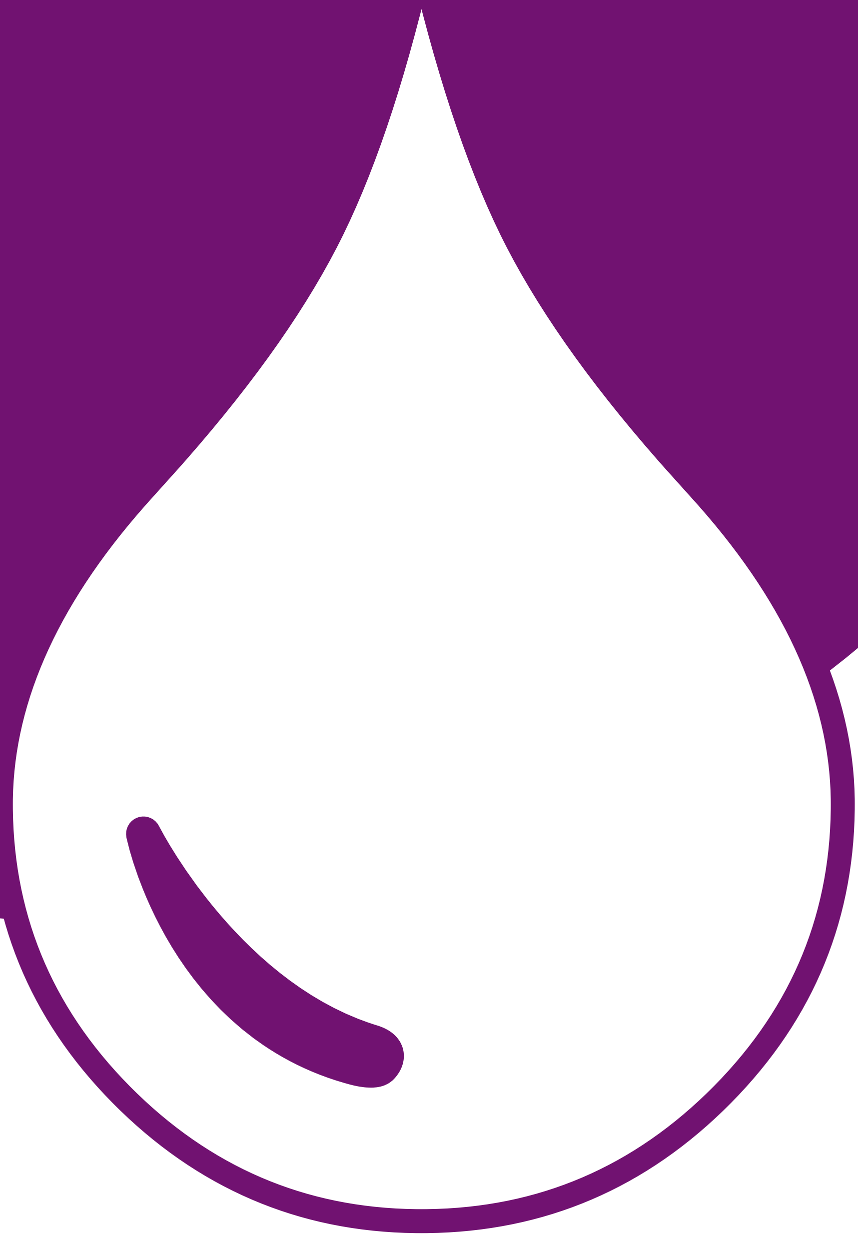

LIMITING SPREAD

Limiting the spread of pandemic, zoonotic, and seasonal epidemic influenza

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Introduction

Influenza causes substantial disease burden worldwide. An estimated 10%-20% of the world's population is affected each year by seasonal epidemic influenza. Pandemics arise through antigenic shifts resulting in a new virus that is not related to previous human seasonal influenza viruses. Widespread infection results due to the lack of immunity in the population to the pandemic virus. Influenza pandemics and epidemics can have substantial health (e.g. clinical illness, hospitalization and death) and socio-economic (e.g. absenteeism from work and decrease in travel and trade) impacts.

Globalization and increased travel and trade within and between countries have resulted in the rapid spread of disease. This was typified by the rapid spread of Severe Acute Respiratory Syndrome (SARS) across three continents within weeks in 2003 (Skowronski, 2005) and by pandemic (H1N1) 2009 influenza. Preparedness, early detection and outbreak response are critical elements in limiting the spread of seasonal and pandemic influenza at the local, national, and global levels.

However, limiting the spread of influenza has been challenging. There is limited scientific evidence on important aspects of disease transmission and on the effectiveness of different strategies to limit transmission. Expansion of the current evidence base is critical for formulating evidence-based preparedness and response measures that are effective and minimally disruptive to individuals and communities.

To assist in identifying key research questions related to the control of influenza, this document highlights available information as well as gaps in our knowledge in three main areas: 1) factors affecting human-to-human transmission of influenza; 2) the effectiveness of public health measures to limit the spread of influenza; and 3) the dynamics of virus spread at the global and local levels. This will lay the foundation for discussion of research that can lead to improvements in limiting the spread of influenza.

1. Factors affecting person-to-person transmission

To formulate and implement effective influenza control measures such as personal hygiene measures, social distancing and infection control, it is critical to understand the factors affecting transmission of influenza among humans. However, sufficient evidence is lacking in key areas such as how influenza spreads and transmission patterns in different settings. In this section we discuss existing knowledge on the transmission of influenza among humans and identify important knowledge gaps.

1.1. Key factors affecting human-to-human transmission

1.1.1. Mode of spread of influenza

Influenza is thought to spread by droplet, contact and airborne routes. However, the relative likelihood of spread due to each of these modes is not well understood. Respiratory droplets are currently thought to be the main mode of transmission (Bridges, 2003). There is also some suggestion that influenza may spread through airborne aerosols that are expelled through coughing or sneezing or aerosol generating procedures such as bronchoscopy or intubation (Tellier, 2006; Cate, 1987; Moser, 1979). However, the clinical impact of aerosol spread is

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thought to be low (Brankston, 2007). Influenza can also likely be spread via direct or indirect contact of the respiratory mucosa with contaminated fomites such as hands or towels (Bean, 1982; Morens, 1995).

1.1.2. Distance of close contact

Droplet transmission is assumed to be the main mode of transmission for influenza. Since, droplets travel only a short distance through the air, close contact with an infected person has been often cited as a risk for exposure and subsequent infection. Public health policies for tracing close contacts or infection control guidance often use a distance of up to 2 meters or 6 feet. Some experts believe that aerosol spread may also occur at close range. However, the correlation between the distance of exposure and the corresponding risk of infection is unknown.

1.1.3. Viral properties

Viral properties such as the fitness for replication in the respiratory tract and the relative preference for localization of replication in the upper respiratory tract versus the lower respiratory tract, affect the likelihood of individual infection and transmission (Nicholls, 2008; Nicholls, 2007). Upper respiratory tract infections (the usual route of infection for seasonal and pandemic influenza) may be more likely to result in viruses being expelled and circulated through coughing or sneezing compared to lower respiratory tract infections. It is therefore important to assess the fitness for replication of influenza virus strains in the human respiratory tract to help determine viral infectiousness.

<u>1.2. Evaluation of transmission patterns and infectivity co-factors in different settings</u>

1.2.1. Transmission in different settings

The risk of influenza transmission can vary by setting. However, it can be difficult to determine the exact mode of transmission in many outbreak investigations. Increased mixing and contact among individuals, poor hygiene and individual characteristics such as susceptibility to infection and immunity from previous exposure may be contributing factors that facilitate transmission. Further studies should explore transmission within these settings to allow for targeted interventions.

Household transmission

In several observational studies seasonal influenza transmission within households has ranged from 13% to 32% (Philip, 1961; Hall, 1973; Foy, 1976; Longini, 1982). Determinants of the attack rate in households include age (children have higher attack rates compared to adults) and the number of susceptible occupants in the household (Longini, 1982).

Schools

Transmission in schools is fueled by higher attack rates among children. This may reflect their increased susceptibility to infection and opportunities for congregation and spread within the school environment. During the 2005/06 influenza season, the overall attack rate in schools in England and Wales was 24.1% with a range of 14.6% to 44.9% across different regions (Zhao, 2007). One Taiwanese study found that the R_o (i.e. the average number of secondary cases that results from one infected person) in schools ranged from

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2.8 to 16.9 compared to a R_o of 1.2 to 2.4 in community settings (Chen, 2007). Pandemic (H1N1) 2009 influenza has been notable for explosive outbreaks in school settings. During an outbreak in New York City, USA, 33% of students reported influenza-like symptoms (Frieden, 2009). In another pandemic-related outbreak in England, 31% of students and staff reported influenza-like symptoms of whom 37% tested positive for pandemic (H1N1) 2009 influenza (Health Protection Agency, 2009).

Closed environments

Closed environments such as boarding homes, nursing homes and military facilities have one of the highest rates of transmission for influenza. One study in a boarding school found a 71% overall attack rate (Delbin, 1979). Military ships and facilities have experienced similarly high attack rates ranging from 42% to 58% within a short period of time (e.g. 1 month) (Earhart, 2001; Liu, 2009). Nursing homes also experience attack rates of about 40% (Patriarca, 1987).

Healthcare facilities

Attack rates between 30% and 50% have been reported for seasonal influenza among healthcare workers and hospitalized patients (Horcajada, 2003; Balkovic, 1980). The spread of influenza in healthcare facilities is likely influenced by the movement of healthcare staff and patients, compliance with appropriate infection control precautions and susceptibility among hospitalized patients. Vaccination of healthcare workers is recommended to assist in reducing the spread and impact of influenza in the healthcare setting (Salgado, 2002).

Airplanes

One study of transmission of influenza during air travel found that 72% of passengers developed respiratory symptoms within three days of exposure to an ill passenger on an airplane (Moser, 1979). Influenza A (H3N2) virus was isolated from some passengers and 20 of 22 ill persons who were tested had serologic evidence of infection with this virus. Two comprehensive reviews of the risk of influenza transmission in an aircraft found only two other instances of transmission (Mangili, 2005; Leder, 2005). One was an outbreak of seasonal influenza A (H1N1) among 60 military personnel who travelled in two aircraft in the United States (Klontz, 1989) and the other was an outbreak of influenza-like illness among 15 individuals aboard a 75-seat Australian plane (Marsden, 2003). Given the recent advances in aircraft technology and the larger size of aircraft, new studies should explore the spread of influenza in this setting.

1.2.2. Age-dependent spread and risk of infection

Influenza usually transmits much more intensely among children. This may be due to increased viral replication in children and poorer respiratory hygiene in this age group. While transmission of influenza is often amplified among preschool and school-aged children (Neuzil, 2002), this can occur in any group living in close proximity (Morens, 1995). The very young (<2 years) are also at risk for developing severe illness and complications (WHO, 2009). The mechanisms of transmission and age-related differences in illness severity are not well understood. More studies are needed to determine the roles played by contact patterns, age-specific susceptibility to influenza and other determinants. In general, conditions which amplify outbreaks have been poorly researched.

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1.2.3. Effect of co-morbid conditions on spread and risk of infection

Influenza may spread more readily among those with pre-existing medical conditions. Slower viral clearance has been shown to occur among individuals with co-morbid conditions and those on corticosteroid therapy (Lee, 2009). Individuals who are immunocompromised also have a higher frequency of influenza infections (Kunisaki, 2009). Pandemic (H1N1) 2009 influenza has been shown to result in more complications and increased hospitalisations and mortality among pregnant women compared to previous influenza epidemics (Jamieson, 2009). Those with chronic lung diseases are also at higher risk for severe illness (WHO, 2009).

1.3. Transmission of influenza during different stages of infection in humans

1.3.1. Infectivity after illness onset

Influenza is most infectious during the first three days of illness (Nicholson, 2003; Bell, 2006a). There is one report suggesting transmission may occur during the incubation period (Sheat, 1992). Although many studies have explored the duration of viral shedding, the relationship between viral shedding and actual infectiousness is unclear. Virus has been isolated 24-48 hours before onset of clinical symptoms (Frank, 1981; Davis, 1961; Khakpour, 1969) to about 5 days after onset of symptoms in adults (Frank, 1981; Philip, 1969; Hayden, 1980). Isolation of virus can occur for up to two weeks in children and longer in immunocompromised individuals (Nicholson, 2003). Shedding usually ceases once illness has resolved (Frank, 1981; Monto, 1985). Early studies of pandemic (H1N1) 2009 influenza suggest that the virus may be shed for a longer period of time; one study cultured viable viruses in 24% of samples taken seven days after illness onset in adults (Witkop, 2009).

1.3.2. Asymptomatic and sub-clinical infection

Influenza viruses have also been isolated from respiratory samples in persons with sub-clinical or asymptomatic infection and in persons with mild symptoms. However, it is unclear how infectious persons with pre-symptomatic, mildly symptomatic, asymptomatic and subclinical infections are, and how the amount of virus shed correlates with infectiousness over time.

1.4. Stability of human influenza viruses on varying environmental surfaces and conditions

Influenza viruses can survive for about 24 to 48 hours on hard, nonporous surfaces such as steel and plastic and for up to 12 hours on porous surfaces such as cloth and paper at 28°C and humidity levels of 35% to 40% (Bean, 1982). Viruses could be transferred for 24 hours after initial contamination of non-porous surfaces, while transfer could occur for 15 minutes after contamination of tissues. Influenza virus concentrations decreased by 100 to 1000 fold on hands within 5 minutes of transfer and could only be recovered during the first 5 minutes. In another study, influenza A viruses were also found on over 50% of fomites tested in homes and day care centers during the influenza season (Boone, 2005). None of these studies, however, explored actual infections resulting from fomite or hand contact on different surfaces.

Higher humidity levels were shown to reduce viral survival (Bean, 1982). Animal models have shown that influenza virus transmit better in conditions of lower temperature and lower humidity

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(Lowen, 2007). Lowen also hypothesized that transmission of influenza in temperate regions is primarily by aerosol spread, while transmission in the tropics is by contact (Lowen, 2009).

Key Brainstorming Questions

What are the modes of influenza transmission and what is the relative importance of each?

Does the importance of different transmission routes differ by environmental setting (home, healthcare, work, school) or by patient characteristics such as age, co-morbidity and immune status?

What are the patterns of virus deposition on touched and respired environments (as opposed to virus excretion measured by nasal swabs) in patients infected with influenza?

What is the risk of transmission associated with asymptomatic or pre-symptomatic disease?

2. Public health measures to limit transmission

Public health measures have been the mainstay for the prevention of infectious diseases for centuries and remain important and relevant today. Pharmaceutical interventions such as anti-viral dugs and vaccines are additional prevention and control measures that have come into prominence in recent decades; however, other than in well-resourced settings, they may not be available in sufficient or timely quantities. Public health measures may be the only measures available for the control of influenza in many countries.

Individual and community-level measures have been adopted to reduce the spread of influenza within households and institutions, in the general population and across borders. Although these practices have been widely adopted, the mechanisms of their action are often not well understood and there is limited evidence to support their effectiveness in the field. Much of the anecdotal evidence has been based on observations made during previous pandemics. Studies of the 1918 pandemic suggest that early and sustained implementation of non-pharmaceutical public health measures were effective in reducing the impact of the pandemic (Bell, 2006a; Merkel; 2006; Merkel, 2007; McLeod, 2009). Additional observational and experimental research is needed to develop a more complete evidence base to support the use of these measures.

It is difficult to discern the relative importance and effectiveness of individual measures as they are often used in combination. The independent and combined effectiveness of intervention measures should be studied when opportunities arise. In addition, mathematical modelling can aid policy- and decision-makers in planning for the implementation of these measures under varying conditions. However, mathematical models are only as good as the epidemiological and clinical data available for input variables.

2.1. Effectiveness and feasibility of individual-level measures

2.1.1. Personal hygiene

Personal hygiene measures such as covering the mouth and nose when coughing or sneezing, avoiding touching of the mouth or eyes with unwashed hands, washing of hands with soap and

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water, and other similar hygiene and etiquette measures have long been recommended. A systematic review by Jefferson and colleagues found that simple measures such as frequent handwashing, barriers such as masks, gloves and gowns, and isolation of individuals with suspected respiratory infections were effective in reducing viral transmission, especially during the SARS outbreak (Jefferson 2008). Hand washing has been shown to reduce non-specific respiratory infection risk by 6% to 44% in various settings (Rabie, 2006) and was highly effective in preventing transmission of SARS (Fung, 2006). A study in Pakistan found that providing soap and education about handwashing reduced the incidence of pneumonia by 50% (95% CI 34-65%) among children below the age of 5 years (Luby, 2005).

Virucidal tissues are widely available commercially and have been shown to be effective in interrupting transmission of rhinoviruses (Jennings 1987). Commercial alcohol hand disinfectants have also been shown to be effective in inactivating influenza viruses (Schurmann, 1983). However, evidence on the effectiveness of these measures in preventing the transmission of influenza is lacking.

2.1.2. Masks

Many countries have stockpiled masks and recommended their use in community and healthcare settings. However, there is little available evidence on their effectiveness. One randomized control trial (RCT) in Australian households found that mask use (either surgical or non-fit-tested FFP2 masks) significantly reduced the risk of influenza-like illness, but adherence proved to be a major problem (MacIntyre, 2009). Another household study in Hong Kong found that surgical masks and hand hygiene decreased transmission if started within 36 hours of the onset of illness in the index patient, although compliance was a problem (Cowling, 2009). A recent RCT in Canada showed that there was no significant difference in influenza infection rates among hospital nurses who wore surgical masks compared to nurses who wore N-95 (FFP2) masks while caring for potential influenza patients (Loeb, 2009). One limitation of the study was the lack of a comparison group of nurses that did not wear masks or respirators. Additional studies are needed in a variety of community and healthcare settings to determine the technical effectiveness of masks.

In addition to the technical effectiveness of these measures, social and behavioral aspects are equally as important, as shown by the household studies of MacIntyre and Cowling. A hospital-based simulation exercise in the United Kingdom reinforced that ongoing training and education for healthcare workers are also required (Phin, 2009). However, there is a lack of studies exploring factors that foster the correct and consistent use of these individual-level measures.

2.2. Effectiveness and feasibility of community-level measures

There are a myriad of community-level public health measures that have been used during influenza epidemics and pandemics. These include contact tracing, school and workplace closures, reduction of mass gatherings, temperature screening and travel restrictions (discussed in greater detail in Section 3).

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2.2.1. Contact tracing and quarantine

Contact tracing and quarantine of close contacts have been used in an effort to contain and delay the spread of influenza within countries. However, there is no clear evidence for the effectiveness of these measures.

2.2.2. School and workplace closures

One of the key decisions that policy makers often consider during epidemics and pandemics is the closure of schools and possibly workplaces to reduce the spread of influenza. However, there is no clear epidemiological evidence for the effectiveness of school closures in delaying the spread and overall impact of influenza. Some modelling studies have tried to address these issues. One study showed that total closure of schools and workplaces could reduce the overall population attack rate by 95%; however, this had devastating socio-economic consequences that could outstrip the impact of a pandemic (Sadique, 2008; Carrat, 2006). A United Kingdom model showed that if the R_0 for a pandemic virus was <2, early closure of schools could reduce the overall population attack rate by >20%; however, this would decrease to a <10% reduction in the attack rate for pandemic viruses with higher R_0 values (Vynnycky, 2008). A French modelling study showed that early and prolonged school closure and limiting contact among children outside school could reduce the overall attack rate by 17% and the peak attack rate by 45% (Cauchemez, 2008). In practice, the actual timing and length of school closures remain difficult to determine. Policy makers must therefore consider the benefits of closures in reducing spread versus the socio-economic cost (Cauchemez, 2009).

2.2.3. Reducing mass gatherings

Reducing mass gatherings and avoiding crowded places have also been recommended during epidemics and pandemics. However, the evidence to support these recommendations is not clear, as these measures are often undertaken in the context of several other interventions and compliance is difficult to determine.

2.3. Factors to consider in the selection and timing of public health measures

Public health professionals and policy makers face challenges in selecting the most appropriate public health measures for a given influenza epidemic or pandemic. Many factors must be considered to ensure that the response is appropriate for the situation and does not result in greater impact compared to the disease itself. In addition, the timing of these measures is important to maximize their effectiveness while minimizing any collateral damage.

The rate and extent of spread and severity of disease will determine the urgency and scope of the response. A severe epidemic with high morbidity and mortality which spreads quickly across the world may warrant more extreme measures compared to a 'mild' pandemic. Systems for surveillance coupled with focused investigations can help to assess these key parameters and guide the most appropriate response. Research is needed to determine the effectiveness of different surveillance strategies and recommend the best approaches for different local settings.

The timing of the response measure is also important to maximize its effectiveness. For example, one model that evaluated the spread of pandemic influenza among healthcare workers found that anti-viral pre-exposure prophylaxis was effective in maintaining essential services only if it was

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timed to include the peak of the pandemic; poorly timed prophylaxis had no or a negative impact (Lee, 2007).

The demography, socio-cultural determinants and geopolitical framework are also important determinants. These factors must be studied in the local context to facilitate compliance with the selected measures. Acceptance and compliance by the affected population is as important as the technical effectiveness of the measure.

Finally, it is important to ensure that scare resources are optimally utilized given the wide range of possible scenarios and solutions available. Health services research such as resource optimization studies and economic evaluations should be done in local settings to determine the relative cost- and resource-effectiveness of the available measures. Policy decisions can then take into account the results of these types of studies along with the range of factors described previously.

2.4. Identification of barriers and solutions for implementation

Barriers that hinder implementation of response measures must identified and addressed. Some of these, such as acceptability by the community and resource affordability have been noted previously. In addition, many of the pharmaceutical and non-pharmaceutical measures require access to healthcare and effective risk communication messages. Solutions are available but research is needed to determine their effectiveness.

Surge capacity is important to ensure that access to health care is maintained throughout an influenza epidemic or pandemic. However, the amount of surge capacity that should be built and maintained must be addressed in advance.

Modelling studies can also provide information about the possible effectiveness of some approaches. For example, global collaboration can circumvent the relative lack of resources in certain areas through redistribution. One modeling study suggested that redistribution of anti-viral stockpiles to countries lacking antivirals could contain a pandemic with an R_0 of up to 1.9; however, if there was no redistribution of antivirals, containment might only be possible for a pandemic virus with an R_0 of less than 1.5 (Colizza, 2007).

Other solutions to address issues that arise as a result of response measures include home education to prevent children from congregating outside of school during school closures and subsidies for individuals who are quarantined.

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Key Brainstorming Questions

What is the relative effectiveness of hand and respiratory hygiene, face masks, and fit-tested respirators in preventing the spread of influenza?

Does the relative effectiveness of these measures change according to setting (healthcare versus home) or by patient type (children versus adults)?

What is the actual impact of school and workplace closures and holidays in different settings?

What is the effectiveness of border screening and use of health declaration cards in detecting cases and preventing spread?

3. Dynamics of virus spread at global and local levels

Influenza is a global disease that does not respect borders. It spreads quickly through travel and trade. Experience with pandemic (H1N1) 2009 influenza in many countries has demonstrated the importance of schools in amplifying transmission of the pandemic virus -- both within schools and the wider community. While research studies have demonstrated the effectiveness of influenza control measures, most of these were undertaken in limited local settings. In addition, different local characteristics such as the geography, socio-cultural-economic framework, demographics and population susceptibility all affect the spread of influenza locally and across borders. It is important to understand the dynamics of virus spread at global and local levels to optimize the use and effectiveness of public health measures.

3.1. Seasonality of influenza virus infection and implications for global virus spread

Influenza epidemics exhibit clear seasonal patterns although the mechanism for this is not well understood. In temperate countries, seasonal influenza epidemics occur during colder winter months; influenza activity can remain above baseline levels for six to eight weeks and typically peaks as a single peak (Nicholson, 1998). However, in the tropics which lack defined seasons, influenza can have a high baseline level of activity with multiple peaks (Chew, 1998). One hypothesis for these different patterns relates to the timing of the global circulation of influenza viruses. Influenza viruses continually circulate in the tropics, especially in East and South-East Asia, resulting in overlapping epidemics and seeding of epidemics in temperate regions in both northern and southern hemispheres (Russell, 2008). This is a key area for further research; understanding when and how influenza viruses spread across regions is important in guiding the selection of vaccine strains and anticipating epidemics in local settings.

3.2. Assessing spread of influenza under different epidemiological settings

Gaining a better understanding of how influenza spreads in different settings can assist in planning appropriate response measures. For example, few data are available to characterize the spread of influenza in rural versus urban settings, in temperate versus tropical climates, or in closed versus open environments.

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3.2.1. Pre-existing immunity in the population

Pre-existing immunity may explain in part the different rates of infection observed across age groups and will influence strategies to reduce the spread and impact of influenza. For example, up to a third of older adults ≥65 years have cross-reactive antibodies to the pandemic (H1N1) 2009 influenza virus in contrast to <10% of younger adults and almost no children (Hancock, 2009). This partial immunity may be responsible for the relative sparing of older adults and the preponderance of cases of pandemic (H1N1) 2009 influenza in children and younger adults. The potential for transmission and spread of specific subtypes and strains in different populations may therefore be related to pre-existing immunity and cross-protection to various strains.

3.3. Utility and timing of different response strategies during early spread of human cases of an animal or pandemic influenza virus

The timing and effectiveness of response strategies have not been comprehensively studied due to the complexities of performing randomized trials during an epidemic. Mathematical modelling studies can help evaluate different strategies under varying assumptions.

3.3.1. Containment of influenza at its source

Two key modelling studies (Ferguson, 2005, Longini, 2005) suggested that a combination of pharmacological and public health measures under favorable conditions (e.g. early detection and low R_0) had the potential to successfully contain the initial emergence of a pandemic virus. Ferguson found that combined antiviral prophylaxis, school and workplace closures and area quarantine provided a 90% chance of containing a virus with R_0 of 1.9. Longini suggested that a combination of pre-pandemic vaccination, household quarantine and antiviral prophylaxis could contain a virus with R_0 of 2.4. These studies were based on the emergence of a novel strain of influenza in rural areas of South-East Asia. Additional studies in urban areas and different regions are needed to determine the feasibility of containment under different assumptions.

3.3.2. Border control measures

Entry screening and quarantining of travellers crossing international borders have not been shown to reduce the spread of a pandemic and are generally not recommended by WHO (Bell, 2006a). Screening of travellers was implemented by many countries in response to the 2009 pandemic. However, the positive predictive value for detecting febrile passengers is very low when the prevalence of fever among travellers is low (Bitar, 2009; Pitman, 2005). In addition, travellers infected with influenza may not be febrile if they are in the incubation phase, have subclinical infection or are using anti-pyretics. A modelling study in New Zealand suggested that border controls have the potential to prevent the entry of influenza entry into a country (Roberts, 2007); studies to systematically evaluate the feasibility of border screening have been initiated (Duncan, 2009). Although WHO has suggested traveller education and exit screening during the early phases of a pandemic (Bell, 2006a; Bell, 2006b), such measures have not been proven to be effective and can be disruptive (Epstein, 2007).

3.3.3. Delaying the spread of influenza and mitigating its impact

Given the inherent difficulties in rapidly detecting and stopping the spread of an emerging pandemic virus, delaying spread and mitigating impact may be more feasible strategies. However,

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measures such as contact tracing, quarantine of close contacts, reduction in travel and border screening are difficult to implement and require extensive resources. Instead, pharmaceutical and public health measures are more often used. These approaches are not mutually exclusive, however, and can be implemented concurrently if sufficient resources are available. Mathematical modelling studies have shown the synergistic effectiveness in reducing the impact of influenza if these measures are used in combination rather than singly (Ferguson, 2006; Halloran, 2008; Duerr, 2007; Germann, 2006). The pandemic (H1N1) 2009 influenza virus has a R_0 of 1.2 to 1.6 (Fraser, 2009) which makes controlling its spread easier than viruses with higher transmissibility.

Key Brainstorming Questions

How is the spread of virus affected by social structures and behaviors (population density, living conditions, interactions)?

What are the implications of seasonality and differences in transmission (temperate versus tropical countries) on the timing of vaccination?

What is the impact of local practices on delaying the spread of virus between and within countries?

What is the impact of delaying the onset of a pandemic at global and country levels?

How does replacement of influenza viruses in circulation occur?

What makes a novel virus successful – viral strain, pre-existing population immunity, proportion of the population vaccinated?

Summary

There has been substantial research on influenza over the decades, yet it is apparent that many unknowns still abound. The 2009 influenza pandemic has been the most closely studied of all pandemics. It offers an opportunity to gain new insights into the transmission of influenza, the dynamics of spread in different settings and the effectiveness of various prevention and control measures. This information in turn can be used to refine and improve influenza preparedness and response at global and country levels.

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