HPA Global Health

Assessment of the Impact of Pandemic (H1N1) 2009 Influenza in sub-Saharan Africa

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Executive Summary

In April 2009, WHO declared the first influenza pandemic of the 21st century. Although the impact of the pandemic has been relatively moderate in many developed countries, concern has been raised that the pandemic will have a disproportional impact on populations in the least developed countries.

The purpose of this report is, given the current evidence base, to assess the impact of pandemic (H1N1) 2009 on the least developed countries in sub-Saharan Africa and to estimate the possible impact of the pandemic on progress towards achieving the health related Millennium Development Goals (MDGs).

The aim of this report is to provide information to assist with policy making and to provide information to supplement the initial assessment of the potential impact of the pandemic in least developed countries that was laid out in the joint WHO/UN report 'Supporting Developing Countries' Response to Pandemic H1N1' released in September 2009.

This assessment has been produced by the UK Health Protection Agency (HPA) with the help of the South Africa National Institute for Communicable Diseases, the Medical Research Council Centre for Outbreak Analysis and Modelling at Imperial College London and the London School of Hygiene & Tropical Medicine. It incorporates information about the impact of the pandemic on First Nation, Aboriginal and Torres Strait Islander populations shared by Canada and Australia**.**

Although surveillance systems are weak in many parts of Africa, it appears that many of countries in sub-Saharan Africa have yet to experience any significant pandemic activity. There is no evidence to suggest that populations in sub-Saharan Africa have any significant pre-existing immunity to pandemic (H1N1) 2009 influenza and as such it seems feasible that the pandemic virus will spread through sub-Saharan Africa at some point in the near future, possibly following seasonal influenza patterns with increased activity during the next rainy season.

With the exception of the comprehensive data that was collected from South Africa during the Southern Hemisphere winter pandemic waves, there is currently very little data on the impact of pandemic (H1N1) 2009 influenza in sub-Saharan Africa. Due to the scarcity of information, the assessments undertaken in this report are based on extrapolation from data collected in developed countries and with models that have been developed to take into account risk factors that could increase the vulnerability to severe disease outcomes of populations in sub-Saharan Africa.

Three key vulnerability issues were taken into account when modelling likely impact on sub-Saharan Africa:

- Age distribution: Based on what has been seen in developed countries, people under 25 years of age appear to be the most vulnerable to infection with pandemic (H1N1)2009. This age group represents the highest proportion of the population in sub-Saharan Africa. There is evidence of immunity in people over 65 years of age in developed countries. However, due to the age demographics, this potential protective factor is unlikely to play a significant role in sub-Saharan Africa.

- Prevalence of co-morbidities: Chronic respiratory diseases including Tuberculosis (TB), immunosuppression and untreated HIV have been shown to be risk factors for severe disease and mortality in developed countries. The population of sub-Saharan Africa has a high prevalence of these risk factors and they often co-exist, resulting in modelling challenges.

- Factors related to very low income: Evidence from aboriginal populations suggest a possible four-fold increase in mortality ratios for Least Economically Developed Countries (LEDC) countries. Regression analysis of 1918 mortality data by per capita gross domestic product (GDP) (presumably reflecting factors such as malnutrition and access to healthcare) may be translated to the current pandemic to suggest an inflation in deaths for the classification of countries.

Given the available evidence base the key findings reported here were:

- Populations in sub-Saharan Africa are likely to be disproportionately impacted by pandemic (H1N1) 2009. Observed numbers of deaths per million from pandemic (H1N1) 2009 for a developed country is 10, on average, but for sub-Saharan Africa it was estimated that a reasonable planning limit of 100-200 deaths per million could occur as a result of pandemic (H1N1) 2009.

- Maternal mortality: A reasonable limit suggests planning for an increase of 3-6% in the maternal mortality rate in sub-Saharan Africa equating to an additional 30 to 60 deaths per 100,000. This could increase the 2007 MDG reported ratio of 900 to 930-960 per 100,000 resulting in a rate greater than the baseline rate reported in 1990 upon which progress towards the MDG target is measured.

- Child mortality in under 5 year olds: A reasonable limit suggests planning for an increase of 0.1%, compared to the reported 2007 MDG ratio 14,500 per 100,000 live births (an additional 8 to 17 deaths per 100,000).

- Mortality rate in patients with TB: A reasonable limit suggests planning for a possible increase from the reported 2007 MDG ratio of 48 to 49 per 100,000 general population.

- Mortality rates for HIV/AIDS: A reasonable limit suggests planning for a possible 0.7 to 3.9 deaths per 100,000 general population.

- With the next wave of pandemic (H1N1) 2009 expected to begin in sub-Saharan Africa in May, or perhaps even earlier, there is still time to prepare; in particular improving surveillance and making medical countermeasures available to the most at risk populations.

- The gaps identified in knowledge and understanding of the progress of pandemic influenza in Africa are considerable. In the longer term actions need to be taken to improve Africa's capability and capacity to respond to future threats to health; in particular strengthening surveillance and monitoring

- This report has not directly considered healthcare systems in sub-Saharan Africa and access to them because of time constraints but we recognise that they will add to the impact of pandemic (H1N1) 2009 in its next wave.

Recommendations

Immediate/short term

1. There is an urgent need for international bodies to facilitate data sharing between countries in sub-Saharan Africa. A special project should be established now.

2. Serological surveillance for evidence of exposure to pandemic (H1N1) 2009 in sub-Saharan Africa is essential to understand the impact of the first wave. This could be carried out by the testing of blood samples already collected and stored. In the absence of surveillance this is the only way this information can be obtained.

3. Studies to monitor the impact of the next wave of pandemic (H1N1) 2009 are proactively developed and ready for use.

4. In addition to the recommendation to vaccinate healthcare workers there is an opportunity to reduce the impact on the identified high risk groups through opportunistic vaccination as those risk group patients attend already established clinics in existing programmes.

5. Access to antivirals and antibiotics for high risk groups will make a difference by reducing the impact of disease and secondary bacterial infections. Those providing care should be made aware of this report.

6. Collect data to improve our understanding of the effect of multiple risk factors/co-morbidities on influenza outcome.

Mid-term

7. Surveillance systems must be strengthened to provide a better understanding of current and future health threats due to influenza and other emerging diseases.

8. South Africa should be considered as a regional resource centre for sub-Saharan Africa and the strengthening of its capacity through international aid should be accelerated.

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Introduction

The Urgent Needs Identification and Prioritisation (UNIP) report sets out the urgent needs of 77 low income countries, including 44 countries in Africa, in terms of urgent response needs and priorities for pandemic (H1N1) 2009.[1] The Secretary General of the United Nations and the Director General of the World Health Organization are concerned about the possible impacts of pandemic (H1N1) 2009 on the millennium goals, particularly maternal mortality, HIV/AIDS and TB. There is therefore an urgent need to carry out an assessment of the impact of pandemic (H1N1) 2009 in Africa and other low income countries in order to evaluate whether there has been or there is likely to be a significant impact of the pandemic on achievement of the United Nations' Millennium Development Goals. This information will assist with planning and the allocation of scarce resources, such as vaccines and antivirals, and has to ensure maximum benefit.

The overall aim of this paper is to try to assess the impacts of pandemic (H1N1) 2009 on health outcomes relevant to the Millennium Development Goals. It is intended therefore to focus the work on childhood and maternal mortality in the world's least resourced countries, whilst taking into account co-morbidity factors: HIV/AIDS, TB and potentially the overall poorer health outcomes that are seen more generally in such countries.

Background

This project brings together experts from the United Kingdom's Health Protection Agency, experts in South Africa, Canada and Australia, academic colleagues at Imperial College and the London School of Hygiene and Tropical Medicine with the guidance of the United Nations System Influenza Coordination (UNSIC) and the World Health Organization (WHO) to provide an assessment of the impact of the pandemic on developing countries (particularly in sub-Saharan Africa) both during the first waves of the pandemic in 2009 and in the expected next wave(s) in 2010.

The HPA has implemented a pandemic (H1N1) 2009 workstream with the National Institute for Communicable Diseases (NICD) in South Africa to

[1] World Health Organization. Urgent Support for Developing Countries' Responses to the H1N1 Influenza Pandemic. 1 October 2009.

enable sharing of surveillance data and to provide support to further improve their capabilities to respond.

The first wave of pandemic (H1N1) 2009 is over in South Africa but the country is preparing for the next wave which is expected at the beginning of their winter in late May or early June 2010 (see graph on page 8). A considerable amount of data about the first wave in South Africa has been gathered but there is little available data from other sub-Saharan African countries and few opportunities to obtain further data because the capabilities and capacity for laboratory diagnosis and surveillance are limited. There is an urgent requirement to identify future actions that will further elucidate the impacts as they occur.

The impact of pandemic (H1N1) 2009 on the aboriginal populations in Australia and Canada gave some cause for concern and the enhanced surveillance and response implemented provides further insight into the potential impact in sub-Saharan Africa.

Millennium Development Goals

In September 2000, at the meeting of the United Nations General Assembly, 189 nations made the commitment to make "the right to development of a reality for everyone and to [free]_the entire human race from want."[2] While many countries have made solid progress towards meeting the Millennium Development Goals, regions, such as sub-Saharan Africa, are at risk of not reaching their goals by 2015.[3] Whilst the reasons for falling behind are multi-faceted, the primary threat to the achievement of the goals is HIV/AIDS, the fourth-leading cause of death worldwide.[4] The impact of HIV/AIDS on the health status of populations is well understood but too often the impact the disease has on the socioeconomic status of populations and their ability to achieve the targets in the Millennium Development Goals is not fully recognised.[5]

MDG 4: Child mortality

Children under five years of age face a high risk of infection and significant risk of serious illness. A widespread outbreak with a high attack rate, particularly in children with pre-existing medical conditions, could result in a significant increase in excess child mortality.

MDG5: Maternal mortality

Pregnant women are at a high risk of developing severe disease and death from pandemic (H1N1) 2009. It is likely that in countries where a high proportion of pregnant women have underlying medical conditions, excess maternal mortality could be observed during the pandemic.

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[2] United Nations General Assembly, 55th Session. Resolution adopted by the General Assembly: United Nations Millennium Declaration (A/RES/55/2) 2000. http://www.un.org/millennium/declaration/ares552e.htm.
[3] United Nations Millennium Project. Investing in development: A practical plan to achieve the Millennium Development Goals – Overview. United Nations Development Program. 2005.
[4] World Health Organization. Health in the Millennium Development Goals. Geneva, 2005.
[5] Alban A, Anderson NB. Putting it together: AIDS and the Millennium Development Goals. International AIDS Vaccine Initiative, New York, 2005. http://www.iavi.org/viewfile.cfm?fid=33078.

Whilst also considering HIV and TB prevalence in these populations, this project has not looked specifically at access to the healthcare system nor access to essential medicines in assessing the impact of pandemic (H1N1) 2009.

Understanding the challenges (cultural, social, economic, health) in sub-Saharan Africa

The first challenge is in obtaining an accurate diagnosis of influenza. Fever is a characteristic of a number of infectious diseases – tropical as well as non-tropical – resulting in obvious challenges to the diagnosis and treatment of the influenza virus throughout the world. In countries where malaria is endemic, as in many countries in sub-Saharan Africa, this difficulty becomes even greater. In at least one of the native languages in Uganda, the word for fever is identical to the word for malaria. Due to the prevalence of malaria, standard treatment is usually to treat childhood fevers with antimalarial medications. Given that fevers due to infectious diseases generally only last a few days, even without treatment, healthcare workers are presumed to have successfully treated malaria even when this was not the cause of the fever.[6]

The second challenge is the different population responses to pandemic influenza in sub-Saharan Africa in that in developed countries we have observed that there is immunity in the over 65 year-old group with the highest attack rates in the young population. Looking at the demography of sub-Saharan Africa, it is clear that the whole population is susceptible. There is evidence from an influenza vaccination trial in Gabon which clearly shows lower immunological responses among rural versus semi-urban children. These differences were thought to be due to underlying medical conditions and malnutrition in the rural populations.[7] In addition, thirty years after work conducted in Gambia, the clinical relevance of the varying antibody levels and antibody responses and influenza-like illnesses remains incomplete when trying to understand antibody reactivity in African populations versus populations of European descent.[8] There is very little information about the impact of influenza on sub-Saharan populations apart from those in South Africa.

Seasonal influenza in Africa

The actual impact of influenza in developing countries remains an unanswered public health question. Lack of influenza surveillance and a lack of awareness of the virus have resulted in a very limited understanding of the epidemiology and impact in many developing countries, particularly those in sub-Saharan Africa. Compounding the problem are the socio-economic challenges confronting these countries where access to healthcare and

[6] Yazdanbakhsh M, Kremsner PG. Influenza in Africa. 15 December 2009. PLoS Med 6(12):e1000182. http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.1000182.
[7] van Riet E, Adegnika AA, Retra K, et al. Cellular and humoral responses to influenza in Gabonese children living in rural and semi-urban areas. J Infect Dis 2007. 196:1671-1678.
[8] McGregor IA, Schild GC, Billewicz WZ, Williams K. The epidemiology of influenza in a tropical (Gambian) environment. Br Med Bull 1979. 35:15-22.

limited communicable disease surveillance vie with access to clean water and nutrition as public health priorities. The ability of a developing country to support influenza vaccination programmes simply is not seen as a priority when other public health challenges, such as prevention and treatment of HIV/AIDS and malaria, are more urgent needs, irrespective of the challenges of economic and social development.

An outbreak of influenza A(H3N2) in Madagascar in July to September 2002,[9] highlights important considerations that need to be taken into account for controlling seasonal or pandemic influenza outbreaks in developing countries. An acute respiratory illness resulted in an unusually high number of deaths in the village of Sahafata, in a remote region of the country, approximately 450 to 500 km south of the capital. The isolation of the area resulted in a delay in the response by health authorities. Due to the remote location, no data were gathered to allow identification of the worst hit areas but it appears that transmission of the virus was exacerbated by over-crowded living conditions and a particularly cold and wet winter in addition to the country's civil unrest from December 2001 to June 2002.

A study indicated that mortality rates of influenza and pneumonia in people over 65 years of age were significantly higher in South Africa than the US. The study indicated that seasonal and pandemic influenza-related excess mortality could be significantly greater in the African continent than those observed in other developing countries.[10] In younger populations, although children infected with HIV have been found to be at greater risk of viral-associated severe lower respiratory tract infections caused by influenza (A and B), respiratory syncytial virus, parainfluenza (1-3) and adenoviruses, these viruses appear to be a less common cause of infection in HIV-positive children than in HIV-negative children although the viruses may be isolated with greater frequency in non-symptomatic children who are HIV-positive.[11]

Seasonality of influenza

The "influenza season" generally occurs in the winter months: in the Northern Hemisphere this is from November to February; in the Southern Hemisphere, this is from late May to August. Due to a lack of seasonal winters in tropical and subtropical regions, influenza can occur at any time of the year but often presents as distinct outbreaks two to three times a year rather than a constant level of circulation as described in Singapore and Hong Kong. A diffused seasonal pattern of influenza in tropical regions may mask the assessment of the actual clinical impact of the virus which may therefore result in the belief that influenza is a less important cause of serious illness and mortality.[12] To understand the true impact of influenza in tropical regions, the more diffused

[9] World Health Organization. Weekly epidemiological record. 15 November 2002. 77(46):381-388. http://www.who.int/wer.

[10] Cohen C, Viboud C, Simonsen L, et al. Estimation of influenza-related excess mortality in South African seniors, 1998-2005. Third European Epidemiology Congress, Vilamoura, Portugal, 14-18 September 2008.

[11] Madhi SA, Schoub B, Simmank K, et al.Increased burden of respiratory viral associated severe lower respiratory tract infections in children infected with human immunodeficiency virus type-1. J Pediatr, July 2000. 137(1): 78-84.

[12] Wong CM, Chan KP, Hedley AJ, et al. Influenza-associated mortality in Hong Kong. Clinical Infectious Disease. 1 December 2004. 39:1611-7.

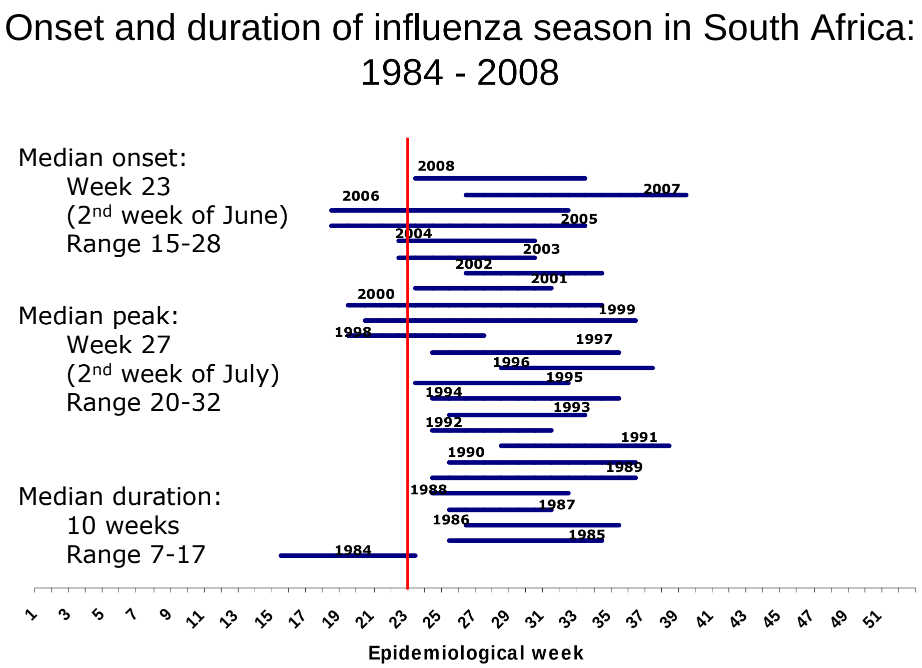
seasonal pattern of illness and co-circulation of other respiratory viruses must be considered.[13] The difficulties for calculating modelling estimates for excess influenza-associated disease are compounded by these geographic challenges.[14]

The timing of the appearance of the new pandemic was unexpected and at first was thought to be a continuation of seasonal influenza activity. It appeared in Mexico towards the end of their winter influenza season. It spread several weeks later to parts of the United States (California, Texas and New York) and Canada and thereafter spread rapidly to Spain and the United Kingdom leading to a first wave in the Northern Hemisphere's summer months, though this first wave did not occur in all European countries. This is similar to the pandemics of 1918 and 1957 where the first waves also appeared in the Northern Hemisphere's spring and summer seasons.

A second wave of pandemic (H1N1) 2009 appeared in late summer and early autumn in the Northern Hemisphere and now appears to be waning in early winter 2009/2010.

Whilst the first wave of pandemic (H1N1) 2009 appeared outside the traditional influenza season in the Northern Hemisphere, it is expected to fall into a seasonal pattern hereafter.

In the Southern Hemisphere, pandemic (H1N1) 2009 appeared during the traditional winter season and led to an influenza-free summer season. This part of the world is expected to experience its second wave with the arrival of their upcoming winter season beginning in late May and early June 2010.



[13] Chow A, Ma S, Ling AE. Influenza-associated deaths in tropical Singapore. Emerging Infectious Diseases, January 2006. 12(1):114-121.
[14] Simonsen L. The global impact of influenza on morbidity and mortality. Vaccine, 1999. 17:S3-10.

Time course of presentation of pandemic (H1N1) 2009

The update on influenza A(H1N1) (later renamed pandemic (H1N1) 2009) published by WHO on 29 May 2009 illustrates the presence of the virus in 53 countries but not in any African country.[15] On 19 June 2009, the first case of the pandemic strain was reported in South Africa.[16] The first case of the pandemic strain was reported in Kenya twelve days later, on 1 July 2009.[17] Due to the limited capability of surveillance and diagnostic capacity throughout the continent, there is scant understanding of the presence of the virus in many African countries. As of 18 December 2009, the predominant strain of influenza circulating in northern and eastern Africa is pandemic (H1N1) 2009, West Africa is currently experiencing a mix of the pandemic and seasonal strains (the seasonal strains are both seasonal H1N1 and H3N2).[18]

At the onset of pandemic (H1N1) 2009, the UK activated a system to study the first few hundred (FF100) early laboratory confirmed cases and their contacts in considerable detail in order to understand this novel disease and to inform policy decisions. It provided an early understanding of the key clinical, epidemiological and virological parameters of pandemic (H1N1) 2009. Of the 392 cases comprising the FF100 from the arrival of the first cases in the UK at the end of April 2009 through to 13 June 2009, when the system was closed to new cases, the symptoms experienced by those with the pandemic strain of influenza was found to be similar to seasonal influenza. The cases within the FF100 were predominantly children (59% under 18 years of age, median age 15, IQR 10-27), with few cases reported in those more than 65 years of age (0.3% cases >65 years). Cases reported a generally mild illness with symptoms similar to those seen in seasonal influenza. To be eligible for inclusion within the FF100, cases needed to have a fever ($\geq 38^{o}C$). Beyond fever, the most common symptoms were sore throat (73%), malaise (72%) and a greater than expected proportion reported diarrhoea (24%) and vomiting (24%). Underlying conditions were found in 11% but they did not appear to be at an elevated risk of infection or experience different symptoms to those without underlying illness. The majority (96%) of the FF100 cases took antiviral drugs as treatment for their illness and very few reported adverse effects. The duration of illness was similar to seasonal influenza (median 7 days, IQR 4-12): significantly shorter in those given treatment within 48 hours of onset of symptoms (median 5 days, IQR 3-10) compared with those treated after (median 10 days, IQR 5.5-14). A total of 14 cases were hospitalised, giving a case-hospitalisation ratio of 3.6% (95% CI 2.0-5.9%). No case in the FF100 group died.[19]

Pandemic (H1N1) in low- and middle-income countries and the increased burden in aboriginal communities

An increased relative risk of infection with pandemic (H1N1) 2009 has been associated with pregnancy and indigenous status. Using publicly available

[15] World Health Organization. Influenza A(H1N1) – update 41. http://www.who.int/csr/don/2009_05_29/en/index.html.
[16] World Health Organization. Influenza A(H1N1) – update 51. http://www.who.int/csr/don/2009_06_19/en/index.html.
[17] World Health Organization. Influenza A(H1N1) – update 56. http://www.who.int/csr/don/2009_07_01a/en/index.html
[18] World Health Organization. Influenza A(H1N1) – update 79. http://www.who.int/csr/don/2009_12_18a/en/index.html
[19] Health Protection Agency First Few Hundred Team. Pandemic influenza A/H1N1 in the UK: Clinical and epidemiological findings from the first few hundred cases. Unpublished data.

data available in Australia from May to October 2009 the relative risk of hospitalisation has been estimated as being 5.2 for pregnant women and 6.6 for indigenous populations. Admission to intensive care units has been estimated as 6.5 for pregnant women and 6.2 for indigenous populations. Risk of death has been estimated as 1.4 for pregnant women and 5.2 for indigenous populations. In Australia, both pregnancy and indigenous status were associated with severe influenza.[20]

Aboriginal and/or Torres Strait Islanders make up 2.4% of the Australian population, yet of more than 37,000 laboratory-confirmed cases of pandemic (H1N1) 2009 reported by the end of November 2009, 10%[21] were reported to be from one of these indigenous populations.[22] Indigenous Australians were more vulnerable to complications from pandemic influenza due to higher rates of underlying chronic illnesses, some of which had not been previously diagnosed, in addition to being at greater risk of being socially disadvantaged and having reduced access to healthcare due to social isolation and/or the remoteness of their community.[23]

On 17 June 2009, Australia moved into a pandemic phase called PROTECT focusing on the identification of people in whom pandemic (H1N1) 2009 may be severe and providing early medical care and interventions to reduce further complications. Indigenous populations are included in this target audience due to the following facts:[24]

- Indigenous Australians have a much greater burden of diagnosed chronic disease than non-indigenous Australians.
- Risk factors for chronic disease are more prevalent in indigenous Australians and they are more likely to have at least one risk factor for chronic disease.
- Indigenous Australians develop chronic disease at younger ages and pandemic (H1N1) 2009 preferentially infects younger people.
- Indigenous Australians are more likely to have undiagnosed chronic diseases.
- Approximately 50% of indigenous Australians live in outer regional and remote areas.
- Indigenous Australians in urban areas are more likely to live in conditions that predispose them to the spread of respiratory infections.
- Many indigenous peoples have limited access to primary healthcare and medicines.
- Indigenous Australians access primary healthcare through a range of services including both mainstream primary care and Aboriginal Community Controlled Health Services.

[20] Kelly H, Mercer GN, Cheng AC. Quantifying the risk of pandemic influenza in pregnancy and indigenous people in Australia in 2009. Euro Surveill. 2009;14(50):pii=19441. http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19441.

[21] Of the 37,000 laboratory-confirmed cases, 92% had indigenous status documented.

[22] Professor Jim Bishop, Chief Medical Officer, Department of Health and Ageing, Australia. Personal email communication received 3 January 2010.

[23] Professor Jim Bishop, Chief Medical Officer, Department of Health and Ageing, Australia. Personal email communication received 3 January 2010.

[24] Department of Health and Ageing, Australia. Appendix to the PROTECT Annex: Guidance for Primary Health Care Workers providing care to Aboriginal and Torres Strait Islander people. Version 1.0. 8 July 2009.

However, studies have been done in developed countries which indicate that indigenous populations carry a higher burden of diseases and mortality compared to other populations.

Investigators found that in Canada and the US, even though indigenous populations represented less than 5% of the general population, they accounted for a much bigger proportion of hospitalised cases of pandemic (H1N1) 2009 influenza: 17.6% in Canada and 17.5% in Arizona.[25] This population (Native Americans and Inuit) was also found to be at increased risk of death due to the pandemic influenza strain. Among ethnic groups in a given country, there may be variations in the risk of severe disease and death. For example, Inuit are estimated to have a sevenfold higher rate of hospital admissions and deaths associated with pandemic (H1N1) 2009 influenza as compared to any indigenous population in North America. Indigenous populations in Australia, Canada and New Zealand had a three to eight times higher rate of hospitalisation and death associated with infection with pandemic (H1N1) 2009 and four times greater risk of dying from their infection compared to all other racial and ethnic groups combined.[26] Native Americans and Alaskan Natives were four times more likely to die of pandemic (H1N1) 2009 compared to other population groups in the states where data was provided.[27]

Other risk factors for severe disease

One study examined the characteristics of patients who were hospitalised with pandemic (H1N1) 2009 influenza in the United States: of the 272 (approximately 25% of the hospitalised) patients reviewed, 45% were children under 18 years of age, 5% were aged 65 years and over.[28] The researchers found underlying medical conditions, including asthma, diabetes, heart, lung and neurological diseases and pregnancy in 73% (198) of the patients, similar to the pattern seen with seasonal influenza.[29] The underlying conditions were found in 60% of children and 83% of adults, with 32% having at least two such conditions. A total of 18 patients (7%) were pregnant and of these, 33% (6) had another underlying medical condition, 67% (12) were in the third trimester of their pregnancy. Among the 272 hospitalised, 25% (67) were admitted to intensive care units, 67% with an underlying medical condition, 18% had immunosuppression and 9% were pregnant. Seven percent (19) of the hospitalised patients died, 68% of whom had an underlying medical condition and 16% were pregnant.[30]

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[25] La Ruche G, Tarantola A, Barboza P, et al, for the epidemic intelligence team at InVS. The 2009 pandemic H1N1 influenza and indigenous populations of the Americas and the Pacific. Euro Surveill. 2009;14(42):pii=19366. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19366.

[26] Jain S, Kamimoto L, Bramley AM, et al. Hospitalised patients with 2009 H1N1 influenza in the United States, April –June 2009.N Engl J Med 2009; 361:1935-44.

[27] Centers for Disease Control and Prevention, Morbidity and Mortality Weekly Report. Deaths related to 2009 pandemic influenza A (H1N1) among American Indian/ Alaska Natives — 12 States, 2009. MMWR 2009;58:1341-1344.

[28] Jain S, Kamimoto L, Bramley AM, et al. Hospitalised patients with 2009 H1N1 influenza in the United States, April –June 2009.N Engl J Med 2009; 361:1935-44.

[29] Jain S, Kamimoto L, Bramley AM, et al. Hospitalised patients with 2009 H1N1 influenza in the United States, April –June 2009.N Engl J Med 2009; 361:1935-44.

[30] Jain S, Kamimoto L, Bramley AM, et al. Hospitalised patients with 2009 H1N1 influenza in the United States, April –June 2009.N Engl J Med 2009; 361:1935-44.

Individuals infected with HIV are at increased risk of developing complications following pandemic (H1N1) 2009 infection due to being immunosuppressed. Experts fear that the high HIV infection rates seen in Africa, especially sub-Saharan Africa, will have a significant impact on the disease burden presented by pandemic (H1N1) 2009 in these countries. Due to limited laboratory and surveillance services in the majority of African countries, data on the impact of both seasonal and pandemic (H1N1) 2009 influenza in these populations are incomplete. No published study was found describing the impact of pandemic (H1N1) 2009 on TB. However, studies suggest that seasonal influenza and TB co-morbidity have detrimental effects.[31] The only available data on mortality, co-morbidity and pandemic (H1N1) 2009 influenza in African countries is for South Africa and indicates that TB is a risk factor for severe disease.

Pandemic (H1N1) 2009 and maternal mortality in HIV-infected women

Understanding the causes of morbidity and mortality enables public health professionals, medical science and policy makers to focus efforts on alleviating the devastating impact diseases can inflict on populations. This knowledge is of prime importance when trying to ascertain a country's success towards attaining the Millennium Development Goals. The diverse challenges confronting developing countries results in the simple fact that death data is not recorded as completely as it is in more developed countries. This results in obvious problems in the early recognition of threats to human health. In India, approximately 33% of deaths are registered and of this number roughly 33% have data on the cause of death.[32]

Globally, over 500,000 women die during pregnancy, delivery or during the puerperium per annum, and at least 10 million suffer serious injuries or disabilities: over 80% of these deaths occur in sub-Saharan Africa and South Asia[33] but the preponderance (50%) of these deaths are in sub-Saharan Africa.[34] In sub-Saharan Africa, the maternal mortality ratio is nearly 1,000 per 100,000 live births versus 8 per 100,000 live births in developed countries.[35] In sub-Saharan Africa, lifetime risk of maternal death is 1 in 22 versus 1 in 8,000 in developed countries.[36] The fifth Millennium Development Goal is to have the global maternal mortality ratio reduced by 75% of what it was in 1990 by 2015; with five years to go, this looks unobtainable. From 1990 to 2005, global maternal deaths decreased 1% per annum; in sub-

[31] Jain S, Kamimoto L, Bramley AM, et al. Hospitalised patients with 2009 H1N1 influenza in the United States, April –June 2009.N Engl J Med 2009; 361:1935-44.

[32] Jha P, Gajalakshmi V, Gupta PC, et al. Prospective study of 1 million deaths in India: Rationale, design, and validation results. PLoS Medicine. February 2006. 3(2):e55-e56. DOI:10.1371/journal.pmed.0030018.

[33] United Nations Department of Economic and Social Affairs, Statistics Division. Progress toward the Millennium Development Goals, 1990-2005. United Nations Department of Economic and Social Affairs, New York, 2005. http://unstats.un.org/unsd/mi/mi_dev_report.htm.

[34] Menéndez C, Romagosa C, Ismail MR, et al. An autopsy study of maternal mortality in Mozambique: The contribution of infectious diseases. PLoS Med 2008. 5(2):e44. DOI:10.1371/journal.pmed.0050044.

[35] Menéndez C, Romagosa C, Ismail MR, et al. An autopsy study of maternal mortality in Mozambique: The contribution of infectious diseases. PLoS Med 2008. 5(2):e44. DOI:10.1371/journal.pmed.0050044.

[36] Menéndez C, Romagosa C, Ismail MR, et al. An autopsy study of maternal mortality in Mozambique: The contribution of infectious diseases. PLoS Med 2008. 5(2):e44. DOI:10.1371/journal.pmed.0050044.

Saharan Africa the annual reduction is even more worrying, only 0.1% per annum.[37]

Pregnant women are at an increased risk of developing serious complication of influenza. Evidence for this has come from studies of outbreaks of seasonal influenza and global pandemics prior to the current pandemic as well as the current pandemic. Previous epidemics and pandemics have shown that complications in pregnant women most commonly include acute pneumonia and cardio-respiratory disease[38,39] and that consequently pregnant women were at increased risk of influenza-related hospital admission compared with non-pregnant women. This risk increases with increasing length of gestation.[40] In the current pandemic, early evidence from the UK, North America and Australasia, has estimated that pregnant women were at a 4 times higher risk of being hospitalised for complications compared to the non pregnant population;[41] that pregnant women were over represented in the group of patients admitted to hospital requiring Level 2 (High Dependency Care) or Level 3 care (Critical/Intensive Care); and observations from the USA,[42] Canada[43] and Australasia[44] showed that pregnant women formed between 7% and 9% of admissions to Intensive Care Units. Safety of pandemic H1N1 vaccine in pregnant women comes from the study of over 2000 pregnant women who received influenza vaccine demonstrated no associated adverse fetal effects[45] additionally there is no evidence of risk from vaccinating pregnant women, or those who are breast-feeding, with inactivated viral or bacterial vaccines or toxoids.[46]

Maternal mortality ratios for women who are HIV-positive can be significantly higher than for women without HIV. Surveys in Malawi and Zimbabwe suggest that the risk of pregnancy-related death is eight to nine times greater in women who are HIV-positive.[47] In Uganda, the rate was found to be more than three times in women who were HIV-positive versus those who were not.[48] Suppressed immunity, secondary to HIV/AIDS, results in an increased risk of prenatal and childbirth complications including miscarriage, anaemia, postpartum haemorrhage, and puerperal sepsis, as well as increasing the likelihood of death from indirect causes during and after pregnancy from

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[37] Menéndez C, Romagosa C, Ismail MR, et al. An autopsy study of maternal mortality in Mozambique: The contribution of infectious diseases. PLoS Med 2008. 5(2):e44. DOI:10.1371/journal.pmed.0050044.
[38] Kort B. A., Cefalo R. C., Baker V. V. Fatal influenza A pneumonia in pregnancy. Am J Perinatol 1986, 3(3):179-182.
[39] Neuzil K. M., Reed G. W., Mitchel E. F., Simonsen L., Griffin M. R. Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women. Am J Epidemiol 1998, 148(11):1094-1102.
[40] Greenberg M, Jacobziner H, Pakter J. Maternal mortality in the epidemic of Asian influenza, New York City, 1957. Am J Obstet Gynecol 1958, 76:897-902.
[41] Jamieson DJ, Honein MA, Rasmussen SA et al. H1N1 2009 influenza virus infection during pregnancy in the USA. The Lancet on line 29 July 2009; doi:10.1016/S0140-6736(09)6134-0.
[42] Jain S, Kamimoto L, Bramley AM, Schmitz AM, Benoit SR, Louie J, et al. Hospitalized Patients with 2009 H1N1 Influenza in the United States, April-June 2009. N Engl J Med 2009; 361 (10.1056/NEJMoa0906695).
[43] Kumar A, Zarychanski R, Pinto R et al. Critically ill patients with 2009 Influenza A(H1N1) infection in Canada. JAMA online 12 October 2009 (doi:10.1001/jama2009.1496).
[44] The ANZIC Influenza Investigators. Critical Care Services and 2009 H1N1 Influenza in Australia and New Zealand. N Engl J Med 2009; 361.
[45] Heinonen OP, Shapiro S, Monson RR et al. Immunisation during pregnancy against poliomyelitis and influenza in relation to childhood malignancy. Int J Epidemiol, 1973. 2: 229-35.
[46] Plotkin SA, Orenstein WA and Offit PA (eds) Vaccines, 5th edition. Philadelphia: WB Saunders Company, 2008.
[47] Bicego G, Boerma JT, Ronsmans C. The effect of AIDS on maternal mortality in Malawi and Zimbabwe. AIDS, 2002. 16:1078-1081.
[48] Sewankambo NK, Gray RH, Ahmad S, et al. Mortality associated with HIV infection in rural Rakai District, Uganda. AIDS, 2000. 14:2391-2400.

diseases such as malaria and pneumonia.[49] A South African study demonstrated that the proportion of maternal deaths secondary to indirect infections (including HIV) was the most significant cause of maternal mortality as deaths increased from 23% to 31% during the period 1998 to 2001.[50] Pregnancy is known to be a risk factor in pandemic (H1N1) 2009.

Public health interventions

The purpose of the UNIP process is to identify interventions that may be implemented rapidly in order to help countries most in need to strengthen their capacities to reduce the health, humanitarian, economic and social impacts of the current influenza pandemic. Developed countries have identified those at particular risk in experiencing complications from pandemic (H1N1) 2009 and pregnancy is recognised to be of particular concern. The impact of pandemic (H1N1) 2009 is likely to be greater in countries with weak healthcare systems, inadequate access to essential medicines, large numbers of vulnerable citizens with underlying medical conditions, and insufficient resources to address these challenges without international support.[51]

For interventions designed to strengthen country readiness to respond to pandemic (H1N1) 2009, the decision was made to give priority to the Least Developed Countries (LDC) and the other Global Alliance on Vaccines and Immunisations (GAVI)-eligible countries. These countries have the least capacity and resources, and have populations that are likely to be the most vulnerable to the impact of pandemic influenza (H1N1) 2009. The assessment tool was sent to International Health Regulations (IHR) focal points in governments in the 77 LDC and GAVI-eligible countries.[52]

This work comes on top of broader efforts by WHO, the UN System as well as the International Federation of the Red Cross/Red Crescent (IFRC) to assist countries in responding to and preparing for pandemic influenza.[53]

Most African countries report having developed inclusive coordination mechanisms incorporating many key actors. The majority of African countries report strong engagement with civil society and the Red Cross on pandemic preparedness. Lack of finance and resources has limited the implementation of pandemic plans in Africa: more than half of African countries have not had the resources to implement their pandemic plans down to sub-national and local levels. Many African countries have made significant efforts to strengthen surveillance, although in some cases these are weak at local level. A number of African countries have developed national clinical care guidelines for pandemic influenza, in many cases strongly based on WHO

[49] Graham W, Hussein J. Measuring and estimating maternal mortality in the era of HIV / AIDS. United Nations Population Division, Department of Economic and Social Affairs, 2003. http://www.un.org/esa/population/publications/adultmort/GRAHAM_Paper8.pdf
[50] Moodley J. Saving mothers: 1999-2001. S Afr Med J, 2003. 93:364-366.
[51] World Health Organization. Urgent support for Developing Countries' Responses to the H1N1 Influenza Pandemic. 1 October 2009. p. 9.
[52] World Health Organization. Urgent support for Developing Countries' Responses to the H1N1 Influenza Pandemic. 1 October 2009. p. 9.
[53] World Health Organization. Urgent support for Developing Countries' Responses to the H1N1 Influenza Pandemic. 1 October 2009. p. 11.

recommendations. However, the ability to implement these guidelines may be compromised by limitations of healthcare infrastructure, medical supplies and staffing. In some countries these guidelines are still under development or have been disseminated to national and district levels but not the peripheral and community levels. While most African countries have developed a national communications plan – in many cases with support from UNICEF, WHO or CDC – very few African countries have developed business continuity plans for key sectors to ensure continuity of essential services. Most African countries have developed key public health messages and some are using innovative approaches to communicate pandemic messages, such as theatre and songs. However, in some cases, poor communications infrastructure (such as internet and email access) in addition to high rates of illiteracy, have limited the development and dissemination of important public health messages. In some cases, the messages relay information on how to minimise or prevent infection but overlook the steps to take when people become ill. A majority of African countries have trained staff in healthcare facilities about how to reduce disease transmission but in some cases, the training is still a work in progress and has not reached the local level or remote parts in a country. Few African countries have developed plans for continuing care for other patient groups when there is increased demand for alternative care facilities when hospitals cannot meet demand; in some cases these plans are underway but have not yet been completed. Very few African countries have plans in place for storage, distribution and delivery of vaccine when it becomes available.[54] WHO is requiring that countries must have workable plans in place for storing and distributing pandemic-specific vaccine in order to be eligible to receive vaccine from the donated supply.

Countries of humanitarian concern are amongst the countries that have made the least progress in pandemic preparedness to date. As a result, during the UNIP process, they were the group of countries who stipulated the most gaps and needs.[55]

Antivirals and antibiotics

Access to antivirals

Although the evidence is still being collected, there are indications that early treatment with antivirals can reduce the severity of illness and complications and may increase survival. Use of antivirals for prophylaxis and containment is not currently recommended. Two antivirals are currently recommended by WHO for treatment of pandemic influenza H1N1: oseltamivir and zanamivir. Oseltamivir is the drug of choice for severe illness due to its ease of administration. Several sporadic cases of oseltamivir resistant pandemic (H1N1) 2009 have been reported but are insufficient to justify a change in treatment recommendations at this time.[56]

[54] World Health Organization. Urgent support for Developing Countries' Responses to the H1N1 Influenza Pandemic. 1 October 2009. pp. 14-15.
[55] World Health Organization. Urgent support for Developing Countries' Responses to the H1N1 Influenza Pandemic. 1 October 2009. p. 18.
[56] World Health Organization. Urgent support for Developing Countries' Responses to the H1N1 Influenza Pandemic. 1 October 2009. p. 21.

Based on expected attack rates and rates of serious illness, WHO has estimated that between 3% and 6% of the population may require antiviral treatment. For the LDC and GAVI countries covered by the UNIP process (excluding India which has its own antiviral production capacity) it is estimated that around 78 million treatment courses will need to be provided to ensure that those with severe illness can be treated.[57]

Access to antibiotics

For people who develop bacteria-related complications, rapid treatment with antibiotics can be lifesaving during a pandemic. Data from past pandemics show that the majority of secondary bacterial pneumonias were associated with Gram positive cocci.[58] Severe illness in cases of pandemic (H1N1) 2009 has recently been strongly linked to co-infection with *Streptococcus pneumoniae*, an organism which in recent years has demonstrated increasing antibiotic resistance in countries where surveillance for antimicrobial resistance (AMR) is routinely performed.[59]

Most countries already have stocks of antibiotics but it can be assumed that there will be a surge in demand during a pandemic. There is inadequate information about the antimicrobial resistance patterns for the most likely agents causing secondary bacterial pneumonias in many developing countries, so the utility of a country's existing stocks of antibiotics for treatment of this complication cannot be assumed. Assumptions have been made that approximately 3% of the population will develop complications that may require antibiotic treatment. This implies that upward of 39 million antibiotic treatment courses may be required, though it is likely that the volume that will actually be needed to be supplied through this programme will be somewhat lower as existing domestic stocks can be utilized.[60]

Distribution

It is anticipated that support with shipment to each country may be required by some countries. However it is believed that no assistance, or very limited assistance, will be required by most countries with in-country distribution.[61]

Vaccines

The Strategic Advisory Group of Experts on Immunization (SAGE) held an extraordinary meeting on 7 July 2009 in Geneva to discuss various issues related to the pandemic strain vaccine.[62] SAGE stressed the importance of

[57] World Health Organization. Urgent support for Developing Countries' Responses to the H1N1 Influenza Pandemic. 1 October 2009. p. 21.
[58] World Health Organization. Urgent support for Developing Countries' Responses to the H1N1 Influenza Pandemic. 1 October 2009. p. 21.
[59] Palacios G, Hornig M, Cisterna D, et al. Streptococcus pneumoniae coinfection is correlated with severity of H1N1 pandemic influenza. PLoS ONE, 31 December 2009. 4(12):e8540.doi:10.1371/journal.pone.0008540.
[60] World Health Organization. Urgent support for Developing Countries' Responses to the H1N1 Influenza Pandemic. 1 October 2009. pp. 21-22.
[61] World Health Organization. Urgent support for Developing Countries' Responses to the H1N1 Influenza Pandemic. 1 October 2009. p. 22.
[62] World Health Organization. Weekly epidemiological record. 24 July 2009. 30(84):301-308.

achieving equity among countries and identified three different objectives that countries can adopt as part of their pandemic vaccination strategy:

- protecting the integrity of the healthcare system and the country's critical infrastructure
- reducing morbidity and mortality
- reducing transmission of the pandemic virus within communities.

In order to achieve these objectives, SAGE recommended that all countries immunise their healthcare workers as a first priority. As insufficient vaccine will be available initially, a stepwise approach to vaccinate particular groups may be considered. SAGE recommended that the following be considered as priorities:[63]

- pregnant women
- individuals aged >6 months with one of several chronic medical conditions
- healthy young adults (between 15 and 49 years of age) to reduce morbidity and mortality
- healthy children
- healthy adults between 49 and 65 years of age
- healthy adults over 65 years of age.

Access

Pandemic (H1N1) 2009 vaccines can potentially provide the means of protecting susceptible populations from infection and mitigating the impact of the disease. Several pandemic-specific vaccines have been produced, including non-adjuvanted, adjuvanted, live attenuated and recombinant vaccines.[64]

As the current global supply of pandemic (H1N1) 2009 vaccine is limited, the priority is to provide supplies to countries without access to vaccine and to provide quantities of vaccine to protect healthcare workers and those at greatest risk of severe complications of disease.[65]

The Director General of WHO has negotiated with several vaccine manufacturers to make a fixed proportion of their manufacturing capacity available to WHO for developing countries. This is generally in the order of 10%. Vaccines will become available to WHO from the fourth quarter of 2009, but initial supplies will be very limited.[66]

Based on realistic production projections, 10% would amount to around 300 million doses of vaccine, of which 150 million doses have already been pledged to WHO as donations by manufacturers, but a further 150 million would need to be procured. A total of 300 million doses is believed to be

[63] World Health Organization. Weekly epidemiological record. 24 July 2009. 30(84):301-308.
[64] World Health Organization. Urgent support for Developing Countries' Responses to the H1N1 Influenza Pandemic. 1 October 2009. p. 22.
[65] World Health Organization. Urgent support for Developing Countries' Responses to the H1N1 Influenza Pandemic. 1 October 2009. p. 22.
[66] World Health Organization. Urgent support for Developing Countries' Responses to the H1N1 Influenza Pandemic. 1 October 2009. p. 22.

sufficient to cover up to 10% of the population of the 96 countries currently lacking access to vaccines.[67]

There is an opportunity to vaccinate sub-Saharan African populations in the identified groups before the next wave when they are seen in healthcare settings for routine follow-up. This opportunistic vaccination will not require the setting pup f special infrastructures; cold chains already exist.

Vaccination response in HIV-infected patients

Vaccination of those most at risk from pandemic (H1N1) 2009 and seasonal influenza:

- the elderly,
- infants,
- patients with respiratory disorders,
- cardiovascular disease,
- immunodeficiency including those infected with HIV and the debilitated,

or vaccination of persons who can transmit the disease to high risk individuals is the most effective form of preventing infection.

Several studies have looked at the response to vaccination of HIV-infected children and adults, the impact of CD4+ count and viral load levels at vaccination. Even though the response in HIV-infected individuals is less than that seen in those not infected, HIV infection does not impair the ability to produce protective levels of antibodies. Further, vaccination does not affect HIV replication and the CD4+ levels.

Modelling the potential impact of pandemic (H1N1) 2009

The overall aim was to assess the impact of pandemic (H1N1) 2009 on health. The work focused on childhood and maternal mortality in the world's Least Economically Developed Countries (LEDCs) whilst taking into account the impact of HIV/AIDS, TB and the overall poorer health outcomes that are seen more generally in such countries.

The analysis was not conducted at the level of an individual country; instead countries were classified into a small number of representative groups based on their reported population age distributions, pregnancy rates and disease prevalence (particularly HIV/AIDS).

Reliable mortality data from pandemic (H1N1) 2009 was not possible to obtain directly from the least well resourced countries, at the present time. The intention was to obtain mortality data for pandemic (H1N1) 2009 from better resourced countries with better reporting and surveillance systems that have already completed their pandemic activity this year. Using these data the overall pandemic (H1N1) 2009 mortality ratio per million, the mortality ratio per million in the absence of co-morbidity, the excess risk posed by HIV/AIDS

[67] World Health Organization. Urgent support for Developing Countries' Responses to the H1N1 Influenza Pandemic. 1 October 2009. p. 22.

(particularly from South Africa and past experiences with seasonal influenza), and the excess risk by age group and pregnancy status was calculated and summarised, where available. These data were adjusted to take account of the specific demographics and HIV/AIDS prevalence related to the specific situations in each of the least well resourced country groupings from above.

Countries with a larger proportion of children and younger adults might be expected to experience overall higher attack rates compared to developed countries that have a larger proportion of their population in adult and elderly age classes (experience with pandemic (H1N1) 2009 and seasonal influenza indicates there are higher attack rates in children than in adults). Where available, data with which to parameterise this effect were sourced for the current pandemic, and incorporated into the mortality estimation. The relationship between GDP and excess mortality during the 1918-20 pandemic were recently analysed based on vital registry data showing that excess population mortality varied over thirty-fold across countries in that pandemic, with per capita income explaining a large fraction of the excess.[68] A similar analysis was extended to the current number of deaths reported by each country to investigate this potential factor in the overall estimates of childhood and maternal mortality for the least well resourced countries.

Demography analysis and classification

Summary

The population of each country was classified into three age groups, together with the per capita birth rate and estimates of HIV and TB prevalence. This data came from WHO[69] and UN[70] sources. Hierarchical cluster analysis allowed us to construct six categories of countries with common factors; four of these matched the majority of African countries (see Table 1 and Figure 1).

Methods

To simplify the analysis, demography of each country worldwide was characterised into relatively few indicative classes. This was performed by using key demographic indicators as follows. First, estimated populations for each country were sourced by 5 year age bins;[71] for the purpose of classification these were combined to give three factors (children [<15 years of age], adults [15-64 years of age], elderly [>65 years of age], other choices of factors were possible but at the expense of the parsimony of the final classification).

Second, data on live births[72] were collated from which it is possible to calculate birth rates for a population. Pregnancy is a risk factor for

[68] Murray et al. Estimation of potential global pandemic influenza mortality on the basis of vital registry data from the 1918-20 pandemic: a quantitative analysis. Lancet, 2006. 368, 2211-2216.
[69] World Health Organization. Global TB control : epidemiology, strategy, financing : WHO report 2009.
[70] United Nations, Department of Economic and Social Affairs, Population Division, World Population Prospects: The 2008 Revision.
[71] United Nations, Department of Economic and Social Affairs, Population Division, World Population Prospects: The 2008 Revision.
[72] United Nations, Department of Economic and Social Affairs, Population Division, World Population Prospects: The 2008 Revision.

complication and possible death from pandemic (H1N1) 2009 and children under 5 years of age are at higher risk of hospitalisation. Understanding the magnitude of people at risk is important; however, the number of live births and birth rates are only a proxy for the real problem of the number of pregnant women in the countries of interest.

In addition, data were sought on HIV[73] and TB[74] (following evidence from South Africa that these were important risk factors for cases developing complications and possible death[75]).

These six factors were used to categorise each country in the world into a number of clusters (five to six of these were of relevance to the countries under consideration). The classification was performed using hierarchic cluster analysis with a Euclidean dissimilarity metric and a complete linkage structure.[76] This choice of metric and linking structure leads to distinct, circular clusters ideal for creating this type of grouping. TB prevalence was so low that it was found to have negligible effect and was thus discarded from the analysis. This left five remaining factors (the proportions within the three age groups, HIV prevalence in adults and birth rates) on which the analysis was based. Countries for which complete data on all five factors were not available were also discarded so as not to bias the results. The mean characteristics of the resulting eight clusters of countries are given in Table 1 and the clusters are plotted on a world map in Figure 1.

The majority of More Economically Developed Countries clustered together in one group containing most of Europe, North America, Russia and Australia. This group was characterised by a low proportion of children, high proportion of elderly and low pregnancy rates. Qatar and the United Arab Emirates have unique demography and form a cluster on their own, but they are not of further interest in this analysis.

The Southernmost countries of Africa formed a cluster characterised by a very high prevalence of HIV. These countries were distinct in their demography from a small group of South East African countries including Zambia, Malawi and Mozambique which have HIV prevalence well in excess of the rest of Africa. The remainder of Southern Africa and some parts of Central Africa clustered together in a group characterized by a very high proportion of children, low proportion of elderly people, very high pregnancy rates but much lower HIV prevalence. There was a distinct Central African belt taking in parts of the Middle East, East Asia, Central and Southern America characterized by a lower proportion of children, higher proportion of adults and lower pregnancy rates. North Africa formed a group with much of South East Asia and South America (including India and Argentina), with a lower proportion of children, higher proportion of adults and elderly, lower birth rates and lower HIV prevalence. The remainder of Central and South East Asia and South

[73]UNAIDS. Report on the global AIDS epidemic, 2008.
[74] World Health Organization. Global TB control: epidemiology, strategy, financing. WHO report 2009.
[75] National Institute for Communicable Diseases, Situation Update Pandemic Influenza A(H1N1) 2009 South Africa.
[76] Krzanowski & Marriott. Kendall's Library of Statistics: Volume 2: Multivariate Analysis Part 2. Wiley. October 1995. ISBN: 978-0-340-59325-7.

America (including China and Brazil) formed a final group distinguished by a slightly older population and slightly lower birth rates.

Age-specific mortality data analysis

Summary

The observed mortality experienced in Argentina and the UK, whilst four-fold different as overall per million ratio, shows the distribution of deaths by age is broadly similar. Canadian data shows substantial variation from these patterns.[77] Analysis ignoring risk factors that may inflate overall mortality indicate that 15-22% of deaths may occur in the under 5 age group, 20-25% in 5 to 15 age group and 26-31% in women of childbearing age in the four country classifications of major interest. Assuming a wholly susceptible population reduced these estimates by 1-3%.

Methods

Age structured mortality data were collected for the UK[78] and Argentina[79] and redistributed into selected age categories. By combining mortality data with demographic data, pandemic (H1N1) 2009 deaths per million population were calculated. While the overall rates differed between the two countries, when applied to the hypothetical countries constructed via the classification process, the effect was qualitatively similar. Table 2 presents the combined deaths and rates per million population for Argentina and UK. Similarly structured data from Canada,[80] showed a different age stratification of deaths, with fewer children and more over 65 year olds. For this project the aim is to derive a planning assessment at a reasonable worst case scenario in countries that tend to have larger child populations and pregnancy rates. Therefore, the focus was on the Argentine and UK data for this first phase of analysis. High mortality ratios were reported in UK and Argentina in the 50-64 age group. This may be an artefact of the surveillance systems or due to 50 to 64 year old people in both countries being more likely to have co-morbidities, but given it is apparent in the data from both countries no further comment on this issue is made here. Investigation of the phenomena will be an important research question in later work.

Extrapolation of the mortality ratio per million provides a simple estimate of the burden in other country classifications. However, the presence of co-morbidities and prior immunity in the population needed to be taken into account. Table 3 uses the 2008 baseline data from the UK serology study[81] and adjusts the expected per capita mortality ratio per million to a wholly susceptible population. This process assumed that Argentina had similar background immunity prior to the current pandemic as the UK but enabled us to consider the effect on a totally naïve population. There was no evidence as

77 Pelletier, Personal Communication, 2009.
78 Donaldson, LJ, et al, Mortality from pandemic A/H1N1 2009 influenza in England: public health surveillance study, in press.
79 Ministerio de Salud de la Nación, Influenza Pandémica (H1N1) 2009. República Argentina: Informe Semana Epidemiológica Nº 46.
80 Pelletier, Personal Communication, 2009.
81 Miller, et al. Tracking the incidence of pandemic influenza A/H1N1v infection in England: a serological evaluation, in press.

to whether it was more appropriate to consider LEDCs as totally susceptible or to have equivalent prior immunity to countries like the UK. It was important to note that a wholly susceptible population may suffer more infections than one might linearly extrapolate from a population with some prior immunity due to the inherent nonlinearity of contact. This project however, was not trying to model infections as too little is known about the mixing patterns in the countries of interest and so its scope is limited to mortality. Future work will be required to provide evidence based evaluation of infections.

The results of applying the combined age structured death rates from Table 2 to the hypothetical countries appear in Table 4. This shows the proportion of total deaths which might occur in each age category without taking into account any explicit co-morbidity. Due to the fact that most LEDCs had a relatively low proportion of older adults and elderly people (aged 50 and over), the comparator cluster was unique in having over one third of deaths in these age groups. Most LEDCs were likely to experience around 20% of deaths in young children, 25% in older children, 15% in young adults, 30% in 25-49 year olds and only around 10% in older adults and the elderly. Due to gender biases often found in the populations of LEDCs, this also means that around 25% of deaths are likely to occur in women of childbearing age (15-49 years of age). Removing the effects of prior immunity as illustrated in Table 3 only changed relative proportions by a few percentage points, decreasing expected mortality in those ages groups we are most interested in bounding (the proportion of deaths in children under 15 is reduced by about 1% consistently and deaths 15-45 year old women were reduced by 3% overall).

Mortality evident in risk groups

Summary

Analysis of South African and UK mortality data suggest a relative risk of dying of pandemic (H1N1) 2009 of around 10 if a co-morbidity was present compared to not, and around 40 if that co-morbidity was TB. The overall size of risk groups was difficult to estimate but reasonable estimates do not alter the order of magnitude of the relative risk due to pre-existing co-morbidity. Tables 6 and 7 show the proportions of total deaths likely in the age and risk groups of interest given these relative risks.

Methods

One may expect LEDC countries to experience a greater number of deaths than apparent in the comparator cluster due to a number of factors. First, their populations had higher prevalence rates of specific co-morbidities (such as HIV and pregnancy). Second, their access to healthcare was likely to be lower. Third, other risk factors (such as malnutrition) may be evident for which developed countries cannot provide clear proxies.

Unfortunately, data on the effects of co-morbidities on pandemic (H1N1) 2009 infections and outcomes was scarce, even amongst mortality data. The only data currently available in the Southern Hemisphere comes from South

Africa[82] and is presented in Table 5; other data is available from the UK[83] and Canada[84]

The South African data presented in Table 5 shows the co-morbidities recorded in 91 confirmed fatal cases of pandemic (H1N1) 2009. There was limited data on cases with multiple conditions which made determining the risk associated with individual conditions difficult. Subject to the constraints described above, the data revealed the probability of having a co-morbidity, given that one died of pandemic (H1N1) 2009. It would have been preferable to know the relative risk of dying of pandemic (H1N1) 2009 given the presence of a particular co-morbidity, compared to dying of the current pandemic if one did not have any co-morbidities. This is related by the expression:

$$P(Died \mid Condition) = \frac{P(Died) \cdot P(Condition \mid Died)}{P(Condition)}$$

and the relative risk (RR) compared with those patients without a co-morbidity is then given by:

$$RR = \frac{P(Died \mid Condition)}{P(Died \mid NoConditions)} = \frac{P(Condition \mid Died) \cdot P(NoCondtions)}{P(NoConditions \mid Died) \cdot P(Condition)}$$

The prevalence of HIV and TB and the probability of being pregnant were collected for the earlier demographic analysis. It thus remains to collect estimates of the prevalence of diabetes, obesity and cardiac disease in South Africa, from which it is possible to estimate the total proportion of the population who have one or more existing co-morbidities and the proportion that have none.

Estimates of diabetes prevalence are available from WHO[85] for most countries; in South Africa it is estimated to be 1.9%. The WHO Global InfoBase[86] contains two surveys with national coverage of South Africa which cover obesity (BMI>=30kg/m^2) and one “WHO Comparable Estimate”. These suggest prevalence of obesity in the range of 8.9%-21.1% with women at significantly greater risk than men. For the purposes of the initial analysis the mid point of 14.1% was chosen. It was not possible to locate any data on cardiac disease for South Africa so the UK figure of 3.7% from the British Heart Foundation[87] was used as an upper bound. Assuming that having a co-morbidity does not increase or decrease the chance of having others and so removing double counting naïvely between these groups leaves an estimate of the total high risk group for pandemic (H1N1) 2009 in South Africa of

[82] National Institute for Communicable Diseases, Situation Update Pandemic Influenza A(H1N1) 2009 South Africa.
[83] Donaldson, LJ, et al, Mortality from pandemic A/H1N1 2009 influenza in England: public health surveillance study, in press.
[84] Pelletier, Personal Communication, 2009.
[85] World Health Organization. Prevalence of diabetes worldwide: Country and regional data, 9 December 2009.
[86] World Health Organization., WHO Global InfoBase, 9 December 2009.
[87] Allender, Steven, et al, Coronary heart disease statistics: 2008 Edition.

around 30.4%. This was considered an upper bound as there was likely to be considerably more overlap between conditions than this naïve analysis allows.

Without taking into account the known overlap between the co-morbidities the following relative risks of death were obtained from the South African data: HIV 12.8, pregnancy 47.8, diabetes 22.6, obesity 4.4, cardiac disease 8.6 and TB 39.6 compared with those with no known risk factors. If the total size of the high risk groups were as suspected, (lower than 30.4%) this would increase the individual relative risks further.

In the situation of multiple co-morbidities it is assumed one is a dominant risk factor (i.e. TB dominates HIV [as it severely compromises the lungs], HIV dominates all others [due to general immunosuppression], etc.). Some clinical review will be needed to assess these assumptions. It is known that of the pregnant women in South Africa who subsequently died, 71% of those tested were HIV-positive[88] and 50% of TB sufferers in South Africa are HIV-positive.[89] There is some evidence that HIV is also a significant risk factor for diabetes;[90] the relative risk varying between around 8 in young adults to around 2 in the elderly compared to HIV-negative individuals. Using a mid-range value of 5 for diabetes and HIV prevalence levels in South Africa suggested that around 52.5% of diabetics in the country were also likely to have HIV. It is possible that this is not feasible in South Africa as the data being quoted was for the US which has a much lower prevalence of HIV and totally different healthcare system, social and other health problems, but alternative data sources are scarce. The low prevalence of diabetes in South Africa and high proportion of HIV-positive deaths means it has little effect on the calculated relative risk for H1N1. Assuming TB dominates all other conditions it was found that the relative risks reduce to: HIV 12.4, pregnancy 38.7, diabetes 20.5, obesity 4.0 and cardiac disease 7.8. Assuming HIV dominates the remaining conditions the relative risks reduce to: pregnancy 12.7, diabetes 10.9, obesity 2.1 and cardiac disease 4.2.

Of the relative risks remaining, pregnancy, diabetes, HIV and TB stand out as significant risks. Obesity and cardiac disease both appear to have significantly elevated risk levels however data on these conditions in South Africa was limited and they were likely to be significantly correlated with each other and with diabetes and possibly HIV.

To check for bias and reinforce the analysis presented here, based on the South African experience, other similar datasets of mortality by age and specific co-morbidities from UK[91] and Canada[92] were sourced. Detailed UK data suggests similar relative risks as the South African data, assuming 75% of the population have no co-morbidities: HIV 12.6, pregnancy 8.9, diabetes, 6.5 and obesity 1.3. However, as with the age specific analysis, the Canadian

[88] National Institute for Communicable Diseases, Situation Update Pandemic Influenza A(H1N1) 2009 South Africa.
[89][World Health Organization. Global TB control : epidemiology, strategy, financing : WHO report 2009.
[90] Currier JS, et al, Diabetes Mellitus in HIV-Infected Individuals, 9th Conference on Retroviruses and Opportunistic Infections, 2002.
[91] Donaldson LJ, et al, Mortality from pandemic A/H1N1 2009 influenza in England: public health surveillance study, in Press.
[92] Pelletier, Personal Communication, 2009.

data[93] was an exception to this trend with pandemic (HIN1) 2009 deaths in HIV-positive groups and pregnant women conformed to rates one might expect given the population level prevalence. To be risk averse it was assumed the relative risks suggested by the South African and UK data to provide upper estimates on mortality rates. Further work will be required to better understand the variation between the Canadian, UK and South African data.

This analysis was extrapolated to the chosen demographic classifications enabling the evaluation of: the number of deaths per million for the total population, the under 5 year olds, the under 15 year olds and women of childbearing age. This was done by assuming that a co-morbidity had a more dominant effect on influenza outcome than age and, in the absence of a co-morbidity, age was the dominant risk factor. A better evidence based understanding of the interactions of age and co-morbidity on influenza related health outcome would enable review of the impact of this assumption.

The challenge in applying this analysis was primarily in assessing the overall proportion of the population in each demographic classification (or each country) who have no co-morbidities since this was the comparison factor which determines the magnitude of the risks in the various risk groups. As was found when collecting data for South Africa, data on many co-morbidities was difficult to source accurately and what constituted a risk group varied from country to country. In the UK the risk groups for pandemic (H1N1) 2009 were defined as children under 5 years old, people aged 65 years or older, pregnant women, patients who have had drug treatment for asthma within the last three years, people with diabetes mellitus, people with immunosuppression and anyone with chronic respiratory, heart, kidney, liver or neurological disease.[94] Figures for some of these are readily available in many countries; however, data on asthma, immunosuppression and chronic disease are scarce for much of the world. Many of these conditions are however most prevalent in elderly people who represent only a small proportion of the population in LEDCs and are already removed by the over 65 year-old category. Immunosuppression is most commonly associated with HIV/AIDS, solid organ transplant and cancer survival, the later two of which will be even rarer in the developing world than in the developed world – in the UK cancer prevalence is less than 3.3%[95] and organ transplants number less than 3,500 per year.[96] Without proper treatment chronic liver and kidney disease are likely to be self-limiting in developing countries. While asthma kills more people in the developing world its prevalence is likely to be at least as high in the developed world due to poorer air quality and other factors. In all, since all these conditions effect only very small proportions of the adult (15-49 year old) population and are often highly correlated with one another, HIV and age, one might readily assume that their contribution to the overall size of the

[93] Pelletier, Personal Communication, 2009.
[94] National Health Service Flu Resilience Team, Swine Flu Pandemic: From Containment To Treatment - Guidance to the NHS, 2 July 2009.
[95] Cancer Research UK, Prevalence (Numbers of Cancer Survivors) UK, 16 December 2009 http://info.cancerresearchuk.org/cancerstats/incidence/prevalence/index.htm.
[96] National Health Service Blood and Transport, http://www.organdonation.nhs.uk/ukt/statistics/statistics.jsp, 16 December 2009.

high risk groups will be minimal in comparison to the factors which are known. This analysis is therefore carried out using only the factors for which data has been obtained – age, pregnancy, HIV, TB and diabetes – to estimate the total size of the risk groups in the demographic classifications.

For South Africa, this leads to a total high risk group of 29.1% of the population (individual group sizes are as follows <5 10.2%, >65 4.6%, HIV (5-65) 11.1%, pregnant 1.6%, diabetes 1.9%, TB 0.7%, giving a total of 30.1%, though after allowing for potential overlap we find a range of 27.4%-29.1%, even this is likely to be an overestimate) compared to the previous calculation of 30.4% resulting in a minimal increase in the risk ratios calculated earlier. Looking at the relative risks obtained in the analysis of the South African and UK data the risk due to pregnancy, HIV and diabetes appear of a similar order at around 10 times that of a person with no co-morbidities, TB appears significantly higher at around 40 whilst obesity and cardiac disease appear negligible in comparison. With the exception of Canada, data from around the world seem to suggest that the proportion of deaths where there were no co-morbidities is around 20-30%. A similar figure of 20-30% seems reasonable for the proportion of the population who have some co-morbidity given the calculation of the total size of South African risk groups at 30.5% and the proportion of the UK population targeted for pandemic (H1N1) 2009 vaccination (i.e. the groups identified as being ‘at risk’ of complications) of around 20.5%. Taking a midpoint figure of 25% it was found that the overall relative risk of dying of the current pandemic if a co-morbidity was present compared to no co-morbidity was around 9 (5.4 – 16.0). Therefore, a uniform relative risk of 10 for HIV and pregnancy, 40 for TB, and 10 for all other risk factors was adopted. A summary table of the estimated proportion of deaths attributable to each risk factor under these assumptions is presented in Table 6 along with the relative overall mortality rates of the different demographic clusters compared to the comparator cluster when risk groups were taken into account. The data suggested that whilst southern Africa can expect substantially greater mortality than seen in more economically developed countries, North Africa, Asia and South America may actually see less if healthcare and other factors were equal due to lower elderly populations and lower apparent prevalence of obesity, diabetes, etc.

The estimates for risk and for age were combined assuming that if a specific co-morbidity (HIV, TB or pregnancy) was present then it was responsible for the death, if no co-morbidity was present then deaths occur in proportion to the risk according to the age of the individual. Detailed tables are presented in Appendix 1 where the proportion of deaths expected due to the major risk factors was broken down by age group according to prevalence of the risk factor in the age groups where available. A summary of groups of particular interest is given in Table 7.

From the South African data it is known that of the pregnant women tested who subsequently died 71.4% were HIV-positive and 19.0% had active TB. Assuming as before that TB is a dominant factor, it is found that HIV with pregnancy gives a relative risk of dying of 141.6 compared to someone with no co-morbidities. This seems reasonable since one might expect relative risks to be multiplicative when combined so this compares favourably with these estimates of around 12 for pregnancy and HIV individually. This is likely to be an over estimate however since pregnancy and HIV infection may be associated and it is not possible to control for this, neither can the evidence seen in South Africa be corroborated since no HIV-positive pregnant women have died in countries for which data is available.

Applying this to the estimates of mortality by risk groups it is found that accounting for HIV and pregnancy together only significantly affects countries with very high HIV prevalence where 10-15% of deaths may occur in HIV-positive pregnant women. Correspondingly, the overall mortality in these countries may also rise by 10-15 percentage points higher than otherwise estimated. In terms of mortality rates the greatest effect is seen in countries with moderate HIV prevalence and high birth rates which attain mortality rates among pregnant women similar to those of countries with very high HIV prevalence such that demographic clusters 1-4 all estimate mortality rates of 70-80 per 100,000. While a significant increase over the single co-morbidity estimate this is still less than 10% of the expected maternal mortality rate. Further work is required to understand the effects of combinations of co-morbidities on individual outcomes following infection with influenza, the general prevalence of co-morbidities in appropriate communities and to develop methodologies to consider these problems.

Overall mortality ratio

Summary

The number of currently observed deaths suggest that a national level mortality rate might be 6.1 per million in the first year of pandemic activity. Crudely one might allow a further 60% of deaths to occur in later years as the pandemic strain becomes seasonal. Variations in the 1918 pandemic mortality, access to healthcare and evidence from aboriginal populations suggest a four-fold inflation in mortality ratios per million for each factor for LEDC countries. Regression analysis of 1918 mortality data by per capita GDP may be translated to the current pandemic to suggest an inflation in deaths given the classification of countries. Table 8 shows the possible upper bound on mortality arising from this pandemic by such classification of country.

Methods

No excess mortality has been observed in the UK. In other countries changes in excess mortality will not be known for some time. Existing knowledge of mortality is predicated on the surveillance network within each country, which may vary, leading to a different measure of mortality than is available in the literature.[97] A simple translation from previously published work cannot be made. Some of the observed variation in the currently observed deaths may be a result of different reporting practises in the countries supplying the data.

[97] Murray, et al. Estimation of potential global pandemic influenza mortality on the basis of vital registry data from the 1918-20 pandemic: a quantitative analysis. Lancet, 2006. 368, 2211-2216.

The proportion of deaths arising in particular age groups and possible multipliers for the country classifications were considered given their different demographic structure to the comparator set, but to assess the likely numbers of deaths it is necessary to derive estimates of, and the variation in, mortality ratios. In those countries that are in South America and Oceania (it is expected their pandemic activity to have ceased for this season), 7.9 deaths per million were observed (3353 observed deaths in 7% of worldwide population, range of 1.9 to 14.8 deaths per million by country).[98] Extending this collection of countries to South East Asia, Central America and South Africa 3.7 deaths per million were observed (4,025 deaths in 18% of worldwide population, range 0.04 to 14.8 per million). However, many countries within South East Asia have reported very low mortality ratios in comparison to the other countries included, for example Indonesia has reported only 10 deaths for their population of over 230 million. Removing Indonesia, Vietnam, Laos, Cambodia and the Philippines from analysis provides 3,932 deaths in 11% of the global population or 6.1 deaths per million (range 1.2 to 14.8). It is unclear whether these removed countries reported so few deaths due to surveillance issues or insufficient pandemic activity, though unfortunately the countries that are reporting the lowest rates are among the less developed of those reporting mortality.

Given these patterns it was assumed that a country might expect about 6.1 reported deaths per million in the first year of pandemic activity. However, there will be some inflation in countries with more limited access to healthcare and different co-morbidities/risk factors other than those generally observed in the Western world. Also further deaths might also arise in future seasons that could be attributed to the current pandemic strain. One might assume that a further 10% of a population could be infected in later years (compared to the 15% attack rate observed so far),[99] especially in countries with more limited immunity levels. Thus future mortality might reach 10 deaths per million for a typical comparator country.

To consider the effect of access to healthcare directly, the number of cases requiring intensive care arising from pandemic (H1N1) 2009 were considered. Eleven countries report the cumulative number of cases in ITU and cumulative number of deaths to ECDC.[100] These data must be treated with care due to known lags between hospitalisation and death during an ongoing epidemic, the fact that not all deaths arise within ITU and variation in hospital admission policies in different member states. Excluding Luxembourg and Malta where more deaths than ITU admissions have occurred, 1,816 ITU admission are reported so far with 465 corresponding deaths. This suggests that crudely one might expect around 4 (2-10) times as many deaths in countries where access to ITU is more limited, depending on how many of those deaths reported occurred following a stay in ITU. Extending this analysis to include all hospital admissions provides an inflationary factor of around 23 (5-58) times.

[98] European Centre for Disease Control, Daily Update: 2009 influenza A (H1N1) pandemic, 18 December 2009.
[99] Miller, et al, Tracking the incidence of pandemic influenza A/H1N1v infection in England: a serological evaluation, in press.
[100] European Centre for Disease Control, Daily Update: 2009 influenza A (H1N1) pandemic, 18 December 2009.

Evidence exists to suggest that aboriginal populations are at higher risk of severe outcome upon contracting pandemic (H1N1) 2009 than other groups, in some countries. This may be due to multiple related issues such as access to healthcare, prior immunity, and general deprivation correlated with co-morbidity prevalence and so 'double counting' of inflationary factors may occur from simple analysis. However, recent studies have shown that aboriginal populations are 4-7 times as likely to die as other populations within the country in question.[101] Whilst access to healthcare in some of these populations may be similar to that experienced in rural African communities the prevalent co-morbidities may be very different but it is challenging to quantify these from the data on timescales currently available, though it might be of value for later investigation.

An analysis has correlated GDP (a proxy for access to healthcare and likely risk factors related to deprivation) to excess mortality in 1918[102]. When fitted to a regression model almost half of the variation in mortality at a national level may be explained by GDP per capita. The authors found a thirty-fold variation in excess death rates observed in 1918-20 period between sub-national regions. A possible range of factors contributed to this variation. At a national level excess mortality varied from 0.2% in Denmark and 4.4% in India. Considering the 27 countries quoted, the average excess mortality found was 1.07% and so the calculated excess mortality for India is 4.4 fold higher. The study forecast 29% of worldwide mortality arising from a 1918 type pandemic to occur in sub-Saharan Africa.

The estimated 2007 GDP per capita averaged for the country classifications is shown in Table 8, with the impact of extending the regression analysis methodology to the context of the current pandemic. Table 9 shows the effects of this analysis on inflating mortality rates applied to the risk group estimates in Table 7. Plotting the *reported* mortality per million against GDP shows fewer deaths in countries with low GDP (i.e. a different trend to that expected from prior analysis[103]). However, this is not a fair test due to the fact that countries have not experienced the totality of their pandemic activity and the surveillance network in poorer countries will be limited. Whilst caution must be exercised with the evidence base available during the current pandemic for negative correlation of mortality with GDP, GDP incorporates factors not explicitly included in the above estimates of LEDC mortality reviewed so far and future work will be required to try to understand this effect.

Consideration of excess mortality arising from another pandemic, the intensive care burden of the current pandemic and mortality in aboriginal populations has provided a possible four-fold increase in observed mortality for each element. The three methods of estimating inflationary effects due to

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[101] Centers for Disease Control and Prevention, Morbidity and Mortality Weekly Report, Deaths related to 2009. Pandemic Influenza A(H1N1) among American Indian/Alaska Natives, 11/12/09.
[102] Murray, et al. Estimation of potential global pandemic influenza mortality on the basis of vital registry data from the 1918-20 pandemic: a quantitative analysis. Lancet, 2006. 368, 2211-2216.
[103] Murray, et al. Estimation of potential global pandemic influenza mortality on the basis of vital registry data from the 1918-20 pandemic: a quantitative analysis. Lancet, 2006. 368, 2211-2216.

access to healthcare and deprivation in LEDCs will contain overlaps. The authors of the 1918 analysis point out that the apparent variation in excess mortality covers a large number of confounding issues,[104] however modern healthcare systems may reduce the mortality observed in countries with good healthcare systems for the current pandemic (extra to the apparent severity of the strain itself). Aboriginal populations in developed countries offer some proxy for LEDCs though the lack of similar risk factors within the populations limits the translation of inflationary multipliers. Given the current lack of observed mortality in LEDCs either many deaths have gone unnoticed (and may do until estimates of excess mortality rates are available) or the pandemic has not yet reached these countries in sufficient numbers. These estimates may be refined as more countries complete their initial year of pandemic activity, but it is unlikely that many countries in the Northern Hemisphere will have this in time to be of use to this work. Given the timescales and the current scarcity of evidence sources the percentages quoted in Table 6 are used and, as an upper bound, inflated by a factor of four to accommodate a possible lack of access to modern healthcare systems. These values may then be multiplied by the mortality ratio for a typical country and scaled by the age specific mortality proportions identified above (as in Table 9) and compared to the targets in the Millennium Development Goals.

Summary of potential impacts indicated by modelling

- Hierarchical cluster analysis allowed us to construct six categories of countries with common factors (age, pregnancy and disease prevalence); four of these matched sub-Saharan African countries (Table 1 and Figure 1).
- Analysis of age specific mortality ignoring risk factors that may inflate overall mortality indicate that 15-22% of deaths may occur in the under 5 age group, 20-25% in 5 to 15 age group and 26-31% in women of childbearing age in the four country classifications of major interest (Table 4).
- Analysis of South African and UK mortality data suggest a relative risk of dying of pandemic (H1N1) 2009 of around 10 if a co-morbidity was present compared to not, and around 40 if that co-morbidity was TB.
- Countries with high levels of HIV prevalence and high birth rates might see up to 20% more deaths due to the presence of these factors alone (Table 6).
- The number of currently reported deaths suggest that a national level mortality ratio might be 6.1 per million in the first year of pandemic activity in a typical comparator country.
- Variations in the 1918 pandemic mortality, access to healthcare and evidence from aboriginal populations separately suggest a four-fold inflation in mortality ratios for LEDC countries. Regression analysis of 1918 mortality data by per capita GDP may be translated to the current pandemic to suggest an inflation in deaths for the classification of countries (Table 8).

[104] Murray, et al. Estimation of potential global pandemic influenza mortality on the basis of vital registry data from the 1918-20 pandemic: a quantitative analysis. Lancet, 2006. 368, 2211-2216.

- For LEDCs reasonable planning limits the extra mortality that might occur due to the current pandemic, within groups associated with relevant MDGs would be:
    - Given the expected mortality ratio of 900 pregnant women per 100000 live births, an increase of 3-6% (i.e. 30-60 additional deaths per 100000)
    - Given the expected mortality ratio of 14500 children under five per 100000 live births, an increase of about 0.1% (i.e. 8-17 additional deaths per 100000).
    - Given the expected mortality ratio of 48 TB deaths 100000 general population, an increase of 1-2% (i.e. 0.6-0.9 additional deaths per 100000).
- This analysis has been limited by the existing evidence base relating to mortality associated with the current pandemic. Future work may refine these estimates as more data becomes available (deaths by age and risk factor, and also more specific prevalence levels of risk factors in the communities) and help to understand the sensitivity of the results to assumptions made throughout this analysis, though this may be too late to inform the UNIP requirements.

Comparison to Millennium Development Goals

This analysis was intended to assess the impact of the current pandemic (H1N1) 2009 on the Millennium Development Goals. In particular to what extent goal four (reduction of childhood mortality) and goal five (improvement in maternal health) might be affected by the excess mortality arising from the pandemic.

In 2007, the update on the attainment of the Millennium Development Goals reported that maternal deaths in sub-Saharan Africa was 900 per 100,000 live births, a reduction from 920 in 1990.[105] Sub-Saharan Africa consists of countries encapsulated in classes 1 through 4 in the demographic classification. From Table 9 it is seen that between 30 and 60 extra deaths per 100,000 live births might arise from the current influenza pandemic. From the derived pregnancy data from live birth information these values are immediately comparable, and so suggest an excess mortality much less than the currently expected total (that is an increase of 3-6% excess on top of that currently expected in the absence of the pandemic).

If it is assumed that child mortality was a constant stable process, the figure reported in the update to the Millennium Development Goals of 145 deaths before the age of 5 per 1,000 live births is equivalent to 14.5% or 14,500 per 100,000 under the age of 5 dying each year.[106] From Table 9 it is seen that between 8 and 17 extra deaths per 100,000 might arise due to the current influenza pandemic, an increase of less than 0.1%.

If it were practical to vaccinate pregnant women and young children in sub-Saharan Africa and the countries had not already suffered significant

[105] United Nations. The Millennium Development Goals Report 2009 - Statistical Annex, 2009.
[106] United Nations. The Millennium Development Goals Report 2009 - Statistical Annex, 2009.

outbreaks (and thus experienced a sizable proportion of the mortality expected for their risk group) then simplistically a large proportion (equal to the protective efficacy of the vaccine) of these deaths might be averted. Other interventions such as early treatment with antivirals or the provision of better access to healthcare, etc. would also clearly present opportunities to save some proportion of maternal and child deaths.

Conclusion

The urgent need for international bodies to act cannot be understated; significant steps must be taken to ensure that the coming influenza season in sub-Saharan Africa is faced with the knowledge gained from the earlier stages of the pandemic experienced in developed countries so that the lessons learnt can be put to good use in these low income countries. The first wave of pandemic (H1N1) 2009 is over in South Africa, yet the country is preparing for the next wave which is due in the coming months. Whilst a considerable amount of data on the first wave in South Africa has been gathered, there is inadequate information available from other sub-Saharan African countries and few opportunities to obtain further data due to the limited capabilities and capacity for laboratory diagnosis and surveillance.

While Sub-Saharan Africa faces multiple challenges, the overall aim of this paper was to assess the potential impact of pandemic (H1N1) 2009 on the health outcomes relevant to the Millennium Development Goals. The focus was on childhood and maternal mortality in the least resourced countries of sub-Saharan Africa whilst taking into account co-morbidities such as HIV/AIDS and TB in addition to the overall poorer health outcomes seen in populations throughout this region. In developed countries, pregnancy has been found to be a significant risk factor for complications and death due to the pandemic strain of influenza currently circulating. For developing countries, this will result in a higher maternal mortality rate during the pandemic period. It is possible that the impact of the pandemic could increase the maternal mortality rate, during the pandemic, to a level not seen for 15 to 20 years. Pandemic (H1N1) 2009 has had the greatest impact on children in developed countries and it is likely that this will remain the case in the developing world. People of all ages with HIV/AIDS and TB will also be at greater risk should they be infected with pandemic influenza.

The recommendations proposed by the authors stress the importance of urgently addressing the need to share information between countries. As the next influenza season begins, studies to monitor the impact of the disease on these populations must be proactively developed and ready for immediate implementation. Access to vaccine, antivirals and antibiotics for those who most need them should be enhanced. Special vaccination programmes can be difficult to implement. Consideration could therefore be given to developing opportunistic vaccination programmes as a means of complimenting special campaigns for the risk groups we have identified; i.e. offer vaccination whenever they attend healthcare delivery points as part of their routine care.

The only way we can build for the future is to ensure that steps are taken to build the necessary surveillance infrastructures in these countries. Reliable surveillance systems are crucial to provide a better understanding of current and future health threats due to influenza as well as other emerging diseases.

The first influenza pandemic of the 21st century is well underway. Although the impact has been relatively moderate in many developed countries, there is much we do not know about the potential for a disproportionate impact on populations in the least developed countries. There is a window of opportunity to implement measures to reduce the impact: the time to act is now.

Table 1: Characteristics of each cluster identified in the country classification procedure

Simple Label	Broad Descriptor	Children[107]	Adults[108]	Elderly[109]	Pregnant[110]	HIV[111]	TB[112]
Comparator	Europe, North America, Australia	16.3%	68.6%	15.1%	3.3%	0.3%	0.0%
Cluster 1	South West & Central Africa	46.2%	51.3%	2.5%	15.3%	2.6%	0.4%
Cluster 2	South East Africa	45.3%	51.5%	3.2%	13.3%	13.2%	0.4%
Cluster 3	Central African Belt	39.1%	57.4%	3.5%	9.9%	1.8%	0.3%
Cluster 4	Southern Africa	36.1%	59.9%	4.1%	7.7%	20.3%	0.7%
Cluster 5	North Africa & South East Asia	29.0%	65.1%	5.9%	5.6%	0.5%	0.1%
Cluster 6	Central Asia	23.6%	69.8%	6.6%	4.4%	0.6%	0.1%
Not required	Qatar and UAE	17.5%	81.4%	1.0%	5.3%	0.1%	0.1%

Table 2: Age-structured mortality data

	Argentina			United Kingdom			Combined		
	Deaths[113]	Population	Mortality Ratio per million	Deaths[114]	Population	Mortality Ratio per million	Deaths	Population	Mortality Ratio per million
0-4	46	3,384,721	13.6	16	3,779,161	4.2	62	7,163,882	8.7
5-14	63	6,742,762	9.4	24	7,012,318	3.4	87	13,755,080	6.4
15-24	51	6,692,351	7.7	26	8,244,497	3.2	77	14,936,848	5.2
25-49	196	13,606,410	14.4	71	21,479,236	3.3	267	35,085,646	7.6
50-64	122	5,581,449	21.8	49	11,180,714	4.4	171	16,762,163	10.2
65+	58	4,271,213	13.6	32	10,097,766	3.2	90	14,368,979	6.3
Overall	537	40,278,905	13.3	218	61,793,692	3.5	755	102,072,597	7.4
Females 15-49	128	7,236,596	17.7	48	13,962,062	3.5	177	21,198,658	8.3

[107] United Nations, Department of Economic and Social Affairs, Population Division. World Population Prospects: The 2008 Revision.
[108] United Nations, Department of Economic and Social Affairs, Population Division. World Population Prospects: The 2008 Revision.
[109] United Nations, Department of Economic and Social Affairs, Population Division. World Population Prospects: The 2008 Revision.
[110] United Nations, Department of Economic and Social Affairs, Population Division. World Population Prospects: The 2008 Revision.
[111] UNAIDS. Report on the global AIDS epidemic, 2008.
[112] World Health Organization. Global TB control: epidemiology, strategy, financing. WHO report 2009.
[113] Ministerio de Salud de la Nación, Influenza Pandémica (H1N1) 2009. República Argentina: Informe Semana Epidemiológica Nº 46.
[114] Donaldson LJ, et al, Mortality from pandemic A/H1N1 2009 influenza in England: public health surveillance study, in Press.

Table 3: Age-structured mortality given expected population level cross-protection levels

Age group	Proportion of population with prior immunity[115]	Argentina		United Kingdom		Combined	
		Mortality ratio per million for total population	Mortality ratio per million for inferred susceptible population	Mortality ratio per million for total population	Mortality ratio per million for inferred susceptible population	Mortality ratio per million for total population	Mortality ratio per million for inferred susceptible population
0-4	2%	13.6	13.8	4.2	4.3	8.7	8.8
5-14	4%	9.4	9.8	3.4	3.6	6.4	6.6
15-24	18%	7.7	9.3	3.2	3.8	5.2	6.3
25-49	10%	14.4	16.0	3.3	3.7	7.6	8.4
50-64	14%	21.8	25.4	4.4	5.1	10.2	11.9
65+	23%	13.6	17.7	3.2	4.1	6.3	8.2
Overall	15%	13.3	15.6	3.5	4.1	7.4	8.6

Table 4: Proportion of total mortality occurring in each age group for hypothetical countries

Simple Label	Broad Descriptor	0-4	5-14	15-24	25-49	50-64	65+	Female 15-49
Comparator	Europe, North America, Australia	6.1%	9.1%	8.9%	38.8%	25.2%	11.9%	22.8%
Cluster 1	South West & Central Africa	22.1%	24.5%	13.9%	29.1%	8.3%	2.1%	22.4%
Cluster 2	South East Africa	20.6%	25.0%	14.1%	28.8%	8.9%	2.6%	22.5%
Cluster 3	Central African Belt	17.1%	21.9%	14.4%	33.4%	10.3%	2.9%	24.4%
Cluster 4	South Africa	14.9%	21.0%	16.2%	33.2%	11.2%	3.4%	25.9%
Cluster 5	North Africa & South East Asia	11.4%	16.7%	13.2%	39.1%	14.8%	4.8%	25.7%
Cluster 6	Central Asia	9.1%	13.4%	12.3%	42.6%	17.3%	5.3%	26.3%
Not required	Qatar and UAE	6.9%	9.4%	9.9%	63.3%	9.6%	0.8%	16.8%

Table 5: South African co-morbidity data

Factor	Frequency of factor / Number of cases with data available	%
HIV infected	18 / 36 tested	50
Pregnant or puerperium	25 / 88	28
No co-morbidities identified	19 / 81	23
Diabetes	11 / 76	14
Obese	16 / 77	21
Cardiac disease†	8 / 75	11
Active tuberculosis (TB)	7 / 75	9

†Cardiac disease includes: previous stents, mitral stenosis, cardiomyopathy, congestive cardiac failure, previous valvular replacement, recent myocardial infarction, and previous cardiac bypass surgery; excludes hypertension.

Among pregnant woman, 95% (18/19) were within the third trimester of pregnancy and two women were puerperal (within 42 days post-delivery). The prevalence of HIV among pregnant and puerperal patients tested (10/14, 71%) was elevated and 19% (4/21) had documented active pulmonary TB.

[115] Miller et al. Tracking the incidence of pandemic influenza A/H1N1 infection in England: a serological evaluation. In press.

Table 6: Proportion of total mortality by risk group

Simple label	Pregnant	HIV	TB	Other risk factors (see text)	None	Relative Overall Mortality Rate
Comparator	2.5%	0.5%	0.4%	73.8%	22.8%	1.000
Cluster 1	9.9%	3.9%	4.9%	60.5%	20.8%	1.063
Cluster 2	7.8%	19.1%	4.1%	51.1%	17.9%	1.171
Cluster 3	7.8%	3.6%	4.5%	59.8%	24.4%	0.953
Cluster 4	5.0%	31.6%	6.5%	40.2%	16.7%	1.227
Cluster 5	5.2%	1.2%	1.7%	64.4%	27.6%	0.870
Cluster 6	4.4%	1.3%	1.1%	64.6%	28.6%	0.849
Not Required	4.2%	0.9%	0.9%	57.1%	36.9%	0.703

Table 7: Proportion of total mortality in selected age and risk groups

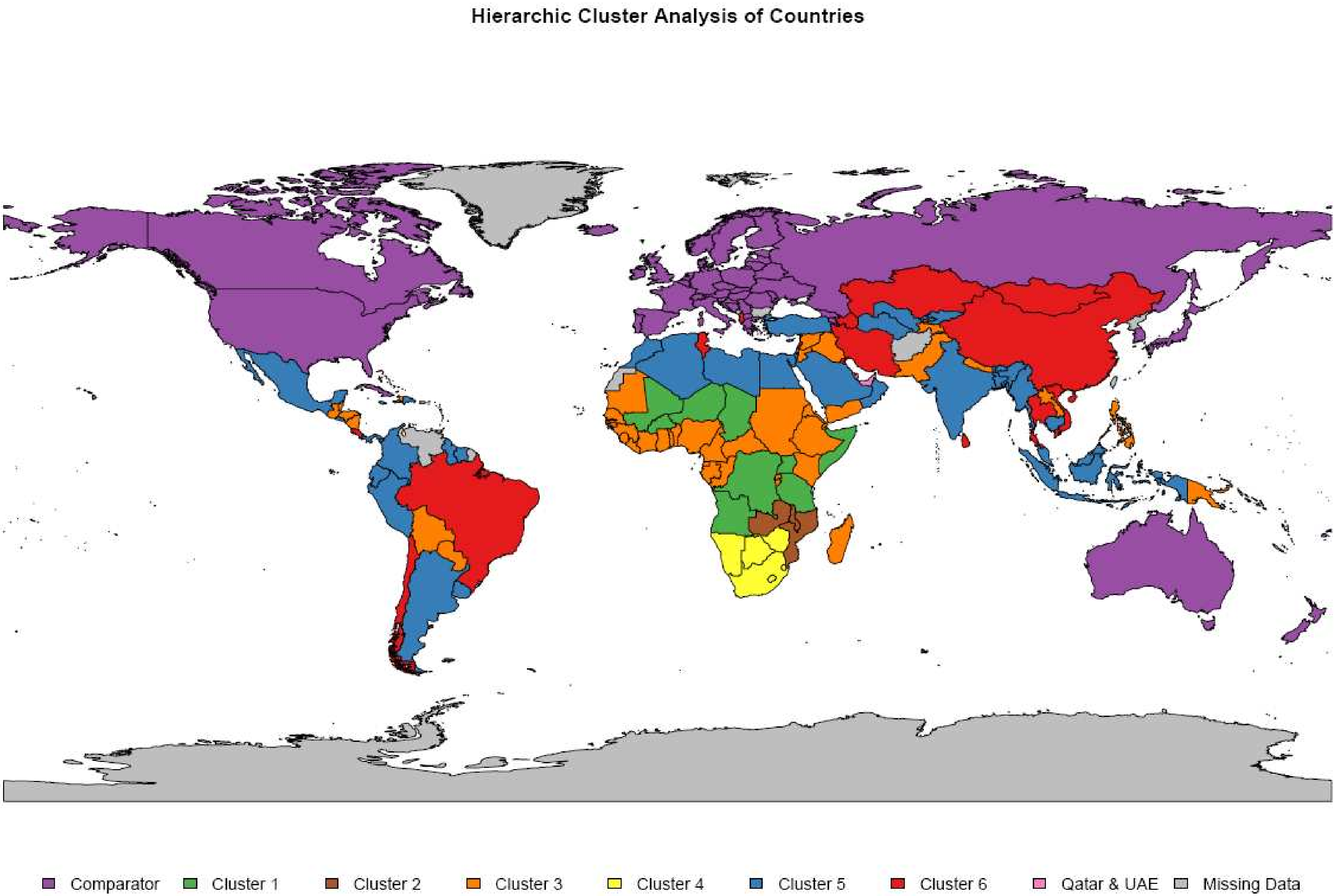
	Summary					
Simple Label	**0-4**	**5-14**	**Pregnant**	**F15-49**	**HIV**	**TB**
Comparator	5.4%	10.1%	2.5%	27.0%	0.5%	0.4%
Cluster 1	16.1%	22.2%	9.9%	32.9%	3.9%	4.9%
Cluster 2	13.2%	20.0%	7.8%	35.4%	19.1%	4.1%
Cluster 3	13.0%	20.5%	7.8%	33.2%	3.6%	4.5%
Cluster 4	8.3%	14.4%	5.0%	39.0%	31.6%	6.5%
Cluster 5	9.5%	17.2%	5.2%	31.8%	1.2%	1.7%
Cluster 6	7.8%	14.0%	4.4%	32.1%	1.3%	1.1%
Not Required	6.2%	10.1%	4.2%	22.3%	0.9%	0.9%

Table 8: Summary information of 2007 GDP and conversion of GDP to reflect possible inflation in mortality for the classifications identified above

	2007 GDP relative to USA (=100)			Murray-like multiplier on deaths relative to median comparator country:			Reasonable worst case mortality rate per million (assuming 10 per million in median comparator country)
Simple Label	min	med	max	for median country in class	for poorest country in class	for poorest country in class with poor access to intensive care	
Comparator	8.3	60.2	193.7	1.0	2.1	8.6	85.7
Cluster 1	1.1	2.9	12.0	3.2	4.7	18.8	187.6
Cluster 2	3.1	5.0	5.1	2.6	3.1	12.6	125.7
Cluster 3	0.9	5.2	38.8	2.6	5.0	20.1	201.2
Cluster 4	5.3	16.0	24.8	1.7	2.5	10.2	101.6
Cluster 5	4.8	16.7	55.7	1.6	2.6	10.5	105.4
Cluster 6	8.1	23.4	104.7	1.4	2.2	8.6	86.3
Not relevant	125.6	177.6	229.6	0.7	0.8	3.0	30.1

Table 9: Reasonable worst case mortality rates per 100,000 population for selected age and risk groups

Simple Label	0-4	5-14	F15-49	Pregnant	HIV	TB
Comparator	8.6	8.0	9.4	26.1	26.1	104.6
Cluster 1	17.4	16.0	28.8	56.6	56.6	226.3
Cluster 2	11.3	10.4	22.8	37.9	37.9	151.7
Cluster 3	17.4	15.8	25.5	60.6	60.6	242.3
Cluster 4	8.3	7.6	18.6	30.6	30.6	122.6
Cluster 5	9.0	8.2	10.9	31.8	31.8	127.3
Cluster 6	7.2	6.6	8.5	26.2	26.2	104.6
Not Required	2.1	1.9	2.6	9.1	9.1	36.5


Hierarchic Cluster Analysis of Countries
Comparator
Cluster 1
Cluster 2
Cluster 3
Cluster 4
Cluster 5
Cluster 6
Qatar & UAE
Missing Data

Appendix A

Proportions of total pandemic (H1N1) 2009 deaths attributable to co-morbidities by age group

	All Causes						
	0-4	**5-14**	**15-24**	**25-49**	**50-64**	**65+**	**F15-49**
Comparator	5.4%	10.1%	12.6%	37.4%	20.3%	14.1%	27.0%
Cluster 1	16.1%	22.2%	21.2%	31.8%	6.3%	2.3%	32.9%
Cluster 2	13.2%	20.0%	20.6%	36.7%	6.7%	2.9%	35.4%
Cluster 3	13.0%	20.5%	20.6%	34.6%	8.1%	3.2%	33.2%
Cluster 4	8.3%	14.4%	20.4%	44.5%	8.6%	3.8%	39.0%
Cluster 5	9.5%	17.2%	18.7%	37.6%	11.7%	5.4%	31.8%
Cluster 6	7.8%	14.0%	17.3%	40.8%	13.9%	6.1%	32.1%
Not Required	6.2%	10.1%	13.6%	61.1%	8.1%	1.0%	22.3%

	HIV						
	0-4	**5-14**	**15-24**	**25-49**	**50-64**	**65+**	**F15-49**
Comparator	0.0%	0.0%	0.1%	0.3%	0.1%	0.0%	0.2%
Cluster 1	0.2%	0.2%	0.6%	2.7%	0.2%	0.1%	2.0%
Cluster 2	0.6%	1.0%	3.2%	12.2%	1.4%	0.7%	9.5%
Cluster 3	0.1%	0.2%	0.6%	2.3%	0.2%	0.1%	1.9%
Cluster 4	0.6%	1.2%	5.1%	20.7%	2.6%	1.3%	15.8%
Cluster 5	0.0%	0.0%	0.3%	0.7%	0.1%	0.1%	0.4%
Cluster 6	0.0%	0.0%	0.3%	0.8%	0.1%	0.0%	0.4%
Not Required	0.0%	0.0%	0.2%	0.7%	0.0%	0.0%	0.0%

	TB						
	0-4	**5-14**	**15-24**	**25-49**	**50-64**	**65+**	**F15-49**
Comparator	0.0%	0.0%	0.0%	0.2%	0.1%	0.1%	0.1%
Cluster 1	0.1%	0.1%	1.0%	2.8%	0.7%	0.2%	1.6%
Cluster 2	0.0%	0.1%	0.7%	2.7%	0.4%	0.1%	1.6%
Cluster 3	0.0%	0.1%	0.9%	2.4%	0.7%	0.3%	1.4%
Cluster 4	0.1%	0.1%	1.1%	4.1%	0.8%	0.2%	2.5%
Cluster 5	0.0%	0.0%	0.3%	0.8%	0.3%	0.1%	0.4%
Cluster 6	0.0%	0.0%	0.2%	0.5%	0.3%	0.2%	0.2%
Not Required	0.0%	0.0%	0.3%	0.5%	0.1%	0.0%	0.1%

	Pregnancy						
	0-4	**5-14**	**15-24**	**25-49**	**50-64**	**65+**	**F15-49**
Comparator	0.0%	0.0%	0.6%	1.9%	0.0%	0.0%	2.5%
Cluster 1	0.0%	0.0%	4.7%	5.2%	0.0%	0.0%	9.9%
Cluster 2	0.0%	0.0%	3.8%	4.0%	0.0%	0.0%	7.8%
Cluster 3	0.0%	0.0%	3.1%	4.7%	0.0%	0.0%	7.8%
Cluster 4	0.0%	0.0%	2.2%	2.8%	0.0%	0.0%	5.0%
Cluster 5	0.0%	0.0%	1.9%	3.3%	0.0%	0.0%	5.2%
Cluster 6	0.0%	0.0%	1.5%	2.9%	0.0%	0.0%	4.4%
Not Required	0.0%	0.0%	0.8%	3.4%	0.0%	0.0%	4.2%

	Other 0-4	5-14	15-24	25-49	50-64	65+	F15-49
Comparator	4.0%	8.0%	9.8%	26.6%	14.2%	11.1%	18.1%
Cluster 1	11.2%	16.7%	12.0%	15.5%	3.6%	1.5%	13.8%
Cluster 2	8.8%	14.4%	10.2%	12.9%	3.3%	1.6%	11.7%
Cluster 3	8.6%	14.8%	12.3%	17.6%	4.5%	2.1%	14.9%
Cluster 4	5.0%	9.5%	9.2%	11.7%	3.2%	1.6%	10.5%
Cluster 5	6.2%	12.4%	12.3%	22.6%	7.0%	3.8%	17.2%
Cluster 6	5.1%	10.1%	11.7%	25.1%	8.4%	4.2%	17.9%
Not Required	3.5%	6.5%	8.5%	33.8%	4.2%	0.6%	10.4%

	None 0-4	5-14	15-24	25-49	50-64	65+	F15-49
Comparator	1.4%	2.1%	2.1%	8.4%	6.0%	2.9%	6.2%
Cluster 1	4.7%	5.2%	3.0%	5.7%	1.8%	0.5%	5.6%
Cluster 2	3.7%	4.5%	2.6%	4.8%	1.6%	0.5%	4.8%
Cluster 3	4.3%	5.4%	3.6%	7.7%	2.6%	0.7%	7.1%
Cluster 4	2.6%	3.6%	2.8%	5.3%	1.9%	0.6%	5.2%
Cluster 5	3.2%	4.7%	3.8%	10.2%	4.3%	1.4%	8.5%
Cluster 6	2.7%	3.9%	3.7%	11.6%	5.2%	1.6%	9.1%
Not Required	2.7%	3.6%	3.9%	22.6%	3.8%	0.3%	7.6%

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