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Epidemiology of the 2009 Pandemic Influenza A (H1N1)

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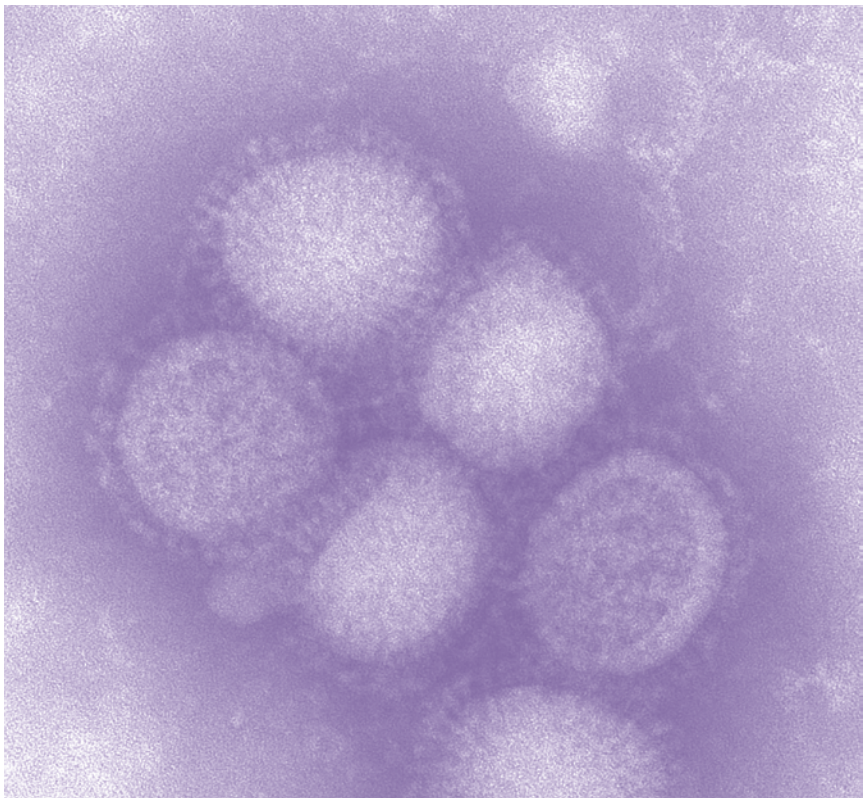
Introduction

The pandemic influenza A (H1N1) virus (pH1N1) spread quickly throughout the world following the April 2009 outbreak in Mexico, and it was the first major influenza pandemic since 1969. In order to effectively prepare for and respond to future pandemics, it is crucial to fully understand the characteristics of the 2009 outbreak. The objective of this review is to focus on the salient epidemiological features of the 2009 pandemic, the known risk factors for severe disease during infection, and specific vulnerable populations.



Timeline of Spread from Mexico

The earliest events in the 2009 H1N1 pandemic can be traced back to La Gloria, Veracruz, Mexico, where an unusual number of influenza-like illness (ILI) cases were reported as early as March 5, 2009 (1). By April 12, the World Health Organization (WHO) requested that the Mexican government verify the suspected outbreak of acute respiratory infections (ARIs) (2). It has been estimated that 28.5% of the population in La Gloria was affected by the outbreak between March 5 and April 10. Shortly thereafter, the Mexico Ministry of Health received 47 reports of severe pneumonia cases, including 12 reported deaths, in Mexico City and San Luis Potosi. The government responded by increasing national surveillance for ARIs and pneumonia on April 17, and by collaborating with the WHO Global Outbreak and Alert Response Network, and the Pan American Health Organization.

Samples collected from ARI cases during the surveillance period were sent to the National Microbiology Lab (NML) of the Public Health Agency of Canada and the Influenza Division of the United States Centers for Disease Control and Prevention (CDC) on April 21, 2009. Four days earlier, the CDC had concluded that the respiratory illnesses of 2 unrelated children in California were due to a novel swine-origin H1N1 Influenza

A virus (3, 4), with onsets of illness occurring between March 28 and 30. Surveillance was subsequently enhanced in California on April 21 (3). By April 24, the presence of genetically similar pH1N1 viruses in 12 of 18 samples from Mexico was confirmed by both the NML and CDC, suggesting sustained human-to-human transmission of the virus (1, 2).

On April 24, 2009, the WHO announced that the U.S. had reported 7 cases of confirmed pH1N1 (5 in California and 2 in Texas), in addition to the cases that had been reported in Mexico. The transmission of an animal virus to humans, the presence of multiple community outbreaks and the young age of the majority of case reports led the WHO to classify the spread of the virus as being of high concern (1). On April 25, following the spread of pH1N1 to 5 U.S. states and 19 out of 32 Mexican states, the WHO Director-General declared a "public health emergency of international concern". Canada first reported 6 confirmed pH1N1 cases on April 26 and, along with Spain, was one of the first countries outside of the U.S. and Mexico to confirm the presence of the virus. One of the earliest outbreak events in Canada occurred at a Nova Scotia private school on April 23 among a group of students who had travelled to Mexico during spring break (5). Samples were collected from 5 students, and 4 specimens were confirmed to be pH1N1 cases by the NML on April 24. Ultimately, 99 cases were associated with the school outbreak, 43 of which were laboratory confirmed as pH1N1.

After April 25, the pandemic evolved quickly and the number of countries reporting confirmed pH1N1 cases rose rapidly. Although it was assumed that air travel was responsible for the rapid spread of the virus, several studies confirmed and quantified the within-flight risk of pH1N1 transmission. Interestingly, the spread of pH1N1 correlated strongly with the volume of passengers typically arriving in a given country from Mexico during early summer, suggesting the benefits of using flight volume data to predict countries most at risk of

Key Points

- Case studies and computer modeling data suggest that while transmission events in first class cabins are relatively rare, transmission is more likely to occur in economy class during long-haul flights.
- R_0 of greater than 1 implies that the infection will continue to spread in the absence of control measures.
- Most studies agree that pH1N1 exhibited modest transmissibility, suggesting that swift implementation of antiviral treatment/prophylaxis and social distancing measures could have a high degree of success in limiting the spread of the pandemic.
- Case fatality rates (CFRs) are extremely difficult to accurately estimate due to the high levels of case underreporting, lack of complete pH1N1 laboratory confirmation and the occurence of subclinical cases.
- An estimate of the case-intensive care ratio (CIR) at 0.16% to 1.44% suggested that populations without access to sufficient intensive care services would experience a much higher CFR rate than the general populations of Canada and the U.S.
- There is no evidence to suggest a protective effect among contacts from the seasonal influenza vaccine, but antiviral prophylaxis did significantly reduce the risk of transmission in household contacts.
- The median age of patients who succumbed to pH1N1 was 51, reflecting the increased risk of dealth in older adults, despite their lower risk of infection.
- Between 25% and 50% of patients with severe pH1N1 disease also exhibited underlying health conditions.
- Severe obesity and morbid obesity (defined as BMI>35 and BMI>40, respectively) posed a 5- to 10-fold higher risk for severe or fatal infection.
- Pregnant women who took antivirals within 2 days of symptom onset were highly unlikely to develop severe illness.
- The increased fraction of the Aboriginal community presenting with severe pH1N1 disease was not unique for this pandemic and was also seen in the 1918 H1N1 Spanish influenza pandemic, to which mortality in Aboriginal communities in North America (3%-9%) was significantly higher than among non-Aboriginal communities.

importation of infectious diseases such as influenza (6). Case studies and computer modeling data suggest that while transmission events in first class cabins are relatively rare, transmission is more likely to occur in economy class during long haul flights (7). Based on secondary attack rates identified on a flight to New Zealand, pH1N1 flight transmission risk is estimated at 1.9% (8).

By April 30, 11 countries, including New Zealand, Israel, the United Kingdom, Austria, Germany, the Netherlands and Switzerland, reported confirmed pH1N1 cases (1). The virus quickly spread to other European countries, as well as to Hong Kong and Korea by May 2. As local testing capacities increased, Mexico reported a total of 397 cases and 16 deaths, while Canada reported 51 cases. The number of infections increased quickly in Canada during early May, totalling 165 confirmed reports by May 6. A total of 23 countries reported at least 1 pH1N1 case by this time. CDC analysis of the initial cases reported outside the U.S. and Mexico for which travel history was recorded (n=178) found that 82% of people infected had recently visited Mexico, and of those who did not, 52% had been in contact with someone who had (9).

The first death in Canada was reported on May 9, by which time 29 countries had reported a total of 3,440 cases, with 2 deaths in the U.S. and 45 in Mexico (1). By May 18, the virus had spread to 40 countries, with 8,829 confirmed cases, and the highest burden of newly reported cases occurring in Mexico and Japan. Confirmed cases in Canada continued to rise quickly, with 921 cases reported by May 27, and a total of 13,398 cases reported in 48 countries worldwide. By June 11, the date on which the WHO declared a worldwide pandemic, 74 countries had reported 28,774 cases with 144 deaths. Canada confirmed 2,446 cases and 4 deaths. At the end of August 2009, the WHO reported decreasing influenza activity, particularly in North America (1). The most recent situation update, released on Aug 6, 2010, reported the presence of pH1N1 in more than 214 countries, and at least 18,449 reported deaths. The pandemic was not officially declared to be over by the WHO until Aug. 10, 2010, although the number of new infections decreased in most countries prior to that date (10). At the time of writing, most influenza transmission is occurring in South Asia, although Ghana continues to report transmission of pH1N1, accounting for approximately 27% of the circulating influenza viruses. Overall, the WHO reports low levels of circulating influenza around the globe.

R_0 estimates for pH1N1 2009 are relatively consistent, and range from 1.3 to 1.8.

Epidemiological Characteristics of pH1N1

Reproductive Number

The basic reproductive number (R_0) represents the average number of new infections generated by a single acute case in a susceptible population, and can be crucial in informing public health intervention policies during an outbreak. R_0 values of less than 1 suggest that an infection will fail to sustain transmission within a population, whereas R_0 of greater than 1 implies that the infection will continue to spread in the absence of control measures. It has been estimated that the previous H2N2 and H3N2 pandemics exhibited R_0 values of 1.5-1.8 (moderate transmissibility), while the 1918 H1N1 pandemic transmission was high, with R_0 of 1.8-2.4 (11). R_0 estimates for pH1N1 2009 are relatively consistent, and range from 1.3 to 1.8. Analysis of 3,152 laboratory-confirmed cases in Ontario, Canada suggested a reproductive number of 1.31 (12), consistent with other estimates from Mexico (13), the U.S. (14, 15, 16) and the United Kingdom (17). Outside of North America and Europe, R_0 estimates were slightly higher, with values of 1.78-2.07 in Thailand (18). Some studies suggest that school-based outbreaks , responsible for high levels of infection among children, exhibit much higher transmission rates and R_0 values of 1.7 up to 3.3 (14, 19). Generally, however, most studies agree that pH1N1 exhibited modest transmissibility, suggesting that swift implementation of antiviral treatment/prophylaxis and social distancing measures could have a high degree of success in limiting the spread of the pandemic.

Incubation Period, Latent Period and Serial Interval

The mean incubation period of pH1N1 was approximately 4 days, with an average duration of symptoms of 7 days (12). The latent period (i.e. the time from infection to infectiousness) is estimated to be 2.6 days, and the duration of infectiousness is 2.5 days to 3.4 days, which may be slightly longer than, but not dramatically different

from, the duration typically observed with seasonal influenza, (13, 17, 19, 20). Multiple studies suggest that infectiousness likely begins shortly before symptoms occur (17, 21). The serial interval, which represents the length of time between onset of infectiousness in one case and the subsequent onset of infectiousness in a person infected by that case, is approximately 3 days to 4.5 days, and is similar to at least one estimate of currently circulating H3N2 (with a serial interval of 3.4 days) (5, 12, 13, 21, 22, 23).

Case-Fatality Rates

Case-fatality rates (CFRs) are extremely difficult to accurately estimate due to the high levels of case underreporting, lack of complete pH1N1 laboratory confirmation and the occurrence of subclinical cases. As a result, estimates from different studies and regions vary widely. A Canadian study reported CFR of 0.3%, with a 4.5% risk of hospital admission among reported cases in Ontario (12). Although children were disproportionately susceptible to infection, adults over the age of 65 were overrepresented among fatalities in this report. In the U.S., using multiple approaches to estimate the true number of cases based on reported cases, the CFR was estimated to be between 0.007% and 0.048% and was again consistently highest among older age groups. An estimate of the case-intensive care ratio (CIR) at 0.16% to 1.44% suggested that populations without access to sufficient intensive care services would experience a much higher CFR than the general populations of Canada and the U.S. (24). Outside of North America, estimated CFR were slightly higher, including rates of 0.58% in Thailand (18). However, some higher rates reported from countries outside North America may be related to lower rates of testing. CFR estimates of the Mexican epidemic ranged from 0.08% to 0.4%, with most confidence in values between 0.15% and 0.25% (14).

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Secondary Attack Rate

Studies of household transmission in the U.S. report a secondary attack rate (SAR) of 11.3% to 14% among household contacts of infected schoolchildren, with the highest SAR among contacts 0-4 years old (19, 21, 22). These estimates are close to the low end of the SAR exhibited by seasonal influenza, again suggesting relatively low transmission of pH1N1 (19, 21). Transmission between schoolchildren was generally more efficient than household transmission, with SARs of 17% to 21% (5, 19). In the U.S., approximately 30% to 40% of reported transmission occurred in households and 20% in schools (11). Overall, contacts under 18 years of age are almost 2 times more susceptible to infection than adults of 18-50 years of age, while those over 50 years are less susceptible, suggesting that the high burden of hospitalization among the <40 age group was not due solely to case-ascertainment bias (21, 24). The increased susceptibility of children to influenza was observed primarily in pH1N1 cases, and not in matched cases of seasonal influenza infections (23). There is no evidence to suggest a protective effect among contacts from the seasonal influenza vaccine, but antiviral prophylaxis did significantly reduce the risk of transmission in household contacts (5, 17, 22,).

Seroprevalence

Confirmed cases represent a minority of all those who have been infected by the virus (25). The number of detected cases largely reflects the proportion of symptomatic individuals who presented for medical care and were tested for the infection. Such cases are, therefore, likely to be influenced by regional differences in the ease of accessing medical care, awareness of the pandemic and differences in physicians' practices, laboratory testing guidelines and other systemic factors. Obtaining accurate estimates of the cumulative incidence of asymptomatic cases, likely at least as common as the symptomatic cases (26), can only be achieved using serological surveys aimed at detecting evidence for prior infection with the pH1N1 virus. Several studies addressed this by assessing pre-pandemic seroprevalence, representing cross-reactive antibody responses potentially due to exposure to strains with shared epitopes, with all reporting higher seroprevalence among older adults (27, 28, 29, 30, 31). Four per cent of individuals who were born after 1980 had pre-existing cross-reactive antibody titres of 40 or more against 2009 H1N1, while 34% of individuals born before 1950 had titres of 80 or more. Vaccination with seasonal trivalent inactivated influenza vaccines induced little if any cross-reactive antibody responses (28).

Seroprevalence also varies between regions within the same country (27, 32, 33). Miller *et al* studied prevalence of antibodies in samples

predating the pandemic and detected antibodies cross-reacting against 2009 H1N1 in 1.8% of children aged 0-4 years, and up to 31.3% in adults aged 80 years or older. The seroprevalence in September 2009, after the first wave of the pandemic, estimated that around 1 in every 3 children was infected, a figure that was 10 times higher than estimated from clinical surveillance (34). Similarly, Ross *et al* reported seroprevalence of 21% in the Pittsburgh area, and extrapolated that at least 63 million persons world-wide became infected in 2009 (30). Skowronski *et al* (35) recently reported the rates of seroprotection (defined as hemagglutination inhibition titres of >40) to be less than 10% before the onset of the 2009 pandemic with an increase to 46%. They described a U-shaped age distribution of seroprotection rates among those less than 20 years old and those 80 years and older, with a prevalence rate of 70%. Seroprotection was 44% among those aged 20-49 and 30% among those 50-79 years. The lowest protection rate was observed among people aged 70-79 years (21%) and highest among those 90 years and older (88%) (35).

Correlates of Severe Disease

Among 1,479 confirmed hospitalized cases in Canada between April 26 and September 26, 2009, 16% were admitted to an intensive care unit (ICU) and survived, while 5% of the hospitalized cases died; this is consistent with data from the U.S. and Mexico (14, 36). Unsurprisingly, many patients who were admitted to hospital and ICU with severe pH1N1 disease exhibited risk factors already known to be associated with severe seasonal influenza infection. Characterization of severe cases and fatalities in Canada and the U.S. has, however, identified a number of correlates of severe pH1N1 disease.

Age-related risk of hospitalization and death

The H1N1 pandemic was especially notable due to the comparatively high rates of morbidity among healthy, young adults, which are not typically observed with seasonal influenza (14). Several studies of confirmed pH1N1 cases in Canada and the U.S. report the median age of infections to be 23-27 years old (36, 37). Young children under the age of 5 had a higher incidence of infection and hospitalization without severe outcome compared to other age groups, but were not at high risk for mortality (36, 37). Adults aged 20-64 were significantly more likely to be admitted to the ICU than other age groups, while overall, those over the age of 45 were more likely to die (36, 37, 38, 39). The median age of mortalities in Canada was 51, reflecting the increased risk of death in older adults, despite their lower risk of infection (36).

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Comorbidities and Underlying Conditions

In all studies, between 25% and 50% of patients with severe pH1N1 disease also exhibited underlying health conditions. In Canada, 30% to 48% of infections presented in persons with comorbidities; diabetes, heart disease and immunosuppression were associated with the highest risk of severe infection, while lung diseases and obesity were among the most common underlying conditions (36, 38, 40). Lung diseases identified as underlying conditions and risk factors included asthma and chronic obstructive pulmonary disease (COPD); COPD was associated with a likelihood ratio of 2.1 for severe disease and poor outcome (41, 42). In children, asthma was identified as a significant risk factor for pH1N1 infection compared to seasonal influenza (37).

Studies outside of Canada reported higher rates of comorbidities, which were present in 72% to 90% of adult cases (37, 39). HIV was reported as a risk factor for fatal disease in a study from South Africa. Among the 91 fatal cases in South Africa, only 32 had HIV test results, of which 17 tested positive. Additionally, many of the 32 cases were also pregnant, hence the precise role of HIV as a risk factor remains to be determined (43). In many studies, in contrast to previous studies of both pandemic and seasonal influenza, obesity, defined as BMI>30, was uniquely identified and was frequently cited as a comorbidity and risk factor for severe infection (44). Kumar *et al* (38) reported obesity among a third of the individuals admitted to ICU. Due to multiple confounding factors it is unclear whether the effect is due to obesity-associated health conditions or immune-related mechanisms (14, 37, 38, 39). Severe obesity and morbid obesity (defined as BMI>35 and BMI>40, respectively) posed a 5- to 10-fold higher risk for severe or fatal infection (37, 38, 44, 45, 46).

Vulnerable Populations – Pregnant Women:

Pregnant women, regardless of

the stage of their pregnancy, were significantly more likely to be hospitalized due to confirmed pH1N1 infection than non-pregnant women. In the absence of other underlying conditions, pregnant women accounted for up to 30% of female cases aged 20-39 years old (38, 39, 47). Pregnant women or women in the immediate postpartum period were also overrepresented among fatalities, and severe maternal pH1N1 illness was commonly associated with severe infant outcomes among mothers who delivered while sick (47, 48). Despite the undisputed higher incidence of disease in this population, at least one study found no evidence for increased risk of severe disease during pregnancy in Canadian patients (36). It is important to consider that higher rates of hospitalization among pregnant women may partially reflect a tendency to admit pregnant women with less severe illness. Importantly, however, the time to receive oseltamivir was significantly associated with the severity of illness during pregnancy; pregnant women who took antivirals within 2 days of symptom onset were highly unlikely to develop severe illness (48, 49, 50).

Vulnerable Populations – Indigenous Peoples

The increased fraction of the Aboriginal community presenting with severe pH1N1 disease was not unique for this pandemic and was also seen in the 1918 H1N1 Spanish influenza pandemic, during which mortality in Aboriginal communities in North America (3% to 9%) was significantly higher than among non-Aboriginal communities (51, 52).

Studies from North America and Australia document an over-representation of infected individuals belonging to indigenous populations. Aboriginal and Torres Strait Islanders account for 2.5% of the Australian population, but made up 9.7% of patients admitted to Australian ICUs with confirmed pH1N1. Maori represent 13.6% of the New Zealand population, but accounted for 25% of ICU admissions in the ANZIC study (46). Kumar *et al* (38) also reported 25.6% of the individuals admitted to ICUs in Canada were First Nations, Inuit and Metis peoples. This rate is an over-representation compared to the 4.4% of self-reported Aboriginal status according to the 2001 census (Statistics Canada) and 13.5% in Manitoba, where First Nations, Inuit and Metis accounted for nearly a third of the patients included in the study (38). Similarly, 2 U.S. states (Arizona and New Mexico) observed a disproportionate number of deaths related to pH1N1 among American Indian/Alaska Natives. These observations led to the initiation of an investigation, which subsequently resulted in an additional 12 state health departments confirming higher rates of mortality among these populations. The results indicated that pH1N1 mortality rates among American Indian/Alaska Natives were 4 times higher than persons in all other ethnic populations combined (53).

These studies do not examine the causal factors for a higher influenza mortality rate among Aboriginal populations as compared to the general population. Various reasons may account for the observed differences. These may include higher prevalence of underlying chronic illness, such as diabetes, and higher rates of obesity, as well as socioeconomic factors, such as less access to care, delayed seeking of care, higher rates of poverty and more people living in a household. Furthermore, ethnicity data collection was variable in the studies and a proportion of individuals did not have their ethnicity documented.

Summary

The emergence of a novel influenza A/H1N1 virus in 2009 led to rapid global spread of the disease and resulted in the first pandemic of the 21st century. Concerted efforts in North American countries enabled rapid identification and availability of testing for the pandemic strain. The amount of information that was gathered to determine all aspects of the virus' virology, pathogenesis, epidemiology and clinical course of the illness is unprecedented. The 2009 pH1N1 pandemic was characterized by high rates of morbidity among young adults with high rates of hospital admission. Fortunately, the overall burden of disease caused by pH1N1 was not as high as initially predicted, likely due in part to the implementation of public health control measures and constant surveillance. Pregnant and early postpartum women were more prone to severe disease. Well documented risk factors for severe or fatal influenza, such as advanced age, chronic lung disease and immunosuppression, were more common among individuals admitted to ICUs due to pH1N1, and obesity was identified as a risk factor that was not previously associated with severe influenza disease. Indigenous populations were over-represented among individuals who reported with severe respiratory illness; however, the mechanisms underlying this predisposition remain to be elucidated. These data will help inform future pandemic preparedness plans, as they will shed light on which interventions would likely be most effective in reducing morbidity and mortality in vulnerable populations.

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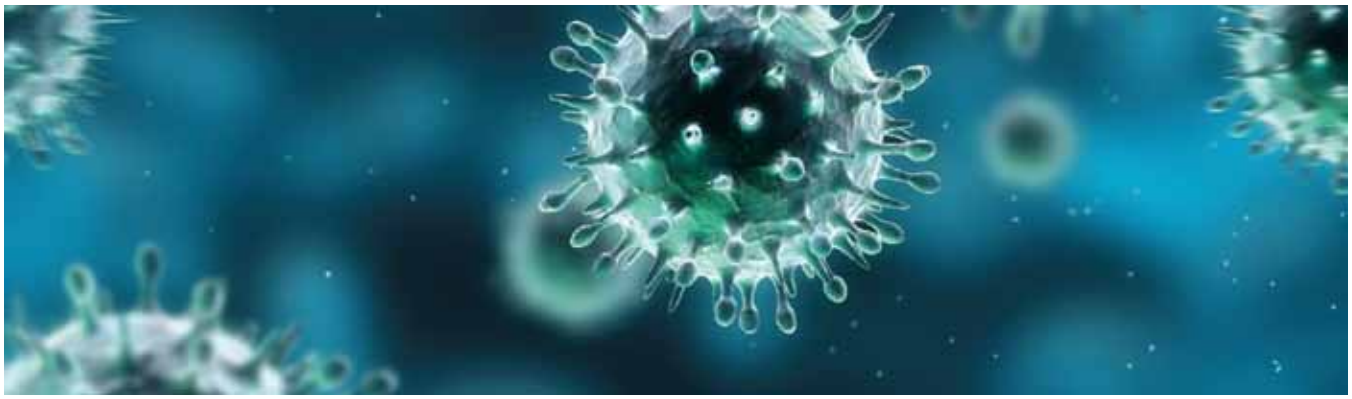

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