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Yahya Al Asseri Date

Trends of H1N1 Cases, Tabuk Region, Kingdom of Saudi Arabia, 2009 – 2015

By

Author: Yahya Al Asseri
Degree to be awarded: MPH
Global Health

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Scott JN McNabb, PhD, MS
Committee Chair

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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Abstract

Background: In 2009 a new strain of influenza A (H1N1) emerged and spread globally, leading to the first influenza pandemic of the 21st century. The Kingdom of Saudi Arabia (KSA) had special responsibility because it stewards the annual mass gathering of the Hajj. Tabuk province is a port of pilgrims coming for Hajj; studying trends of H1N1 cases there could yield new and important information.

Methods: A cross-sectional retrospective analysis of all reported H1N1 cases in Tabuk province between 2009 and 2015 was undertaken to estimate the trends by incidence rates (IRs) and 95% confidence intervals (CIs) using Byars approximation. These data were part of the case-based regional surveillance shared by the Department of Infectious Diseases, Tabuk General Directorate of Health.

Results: A total of 471 cases of H1N1 were recorded during the period 2009 – 2015. The number of cases was greatest in 2009, when there were 317 cases and an IR of 39.9 cases/100,000 (95% CI = 35.7 – 44.5). The IR decreased over time and 242 males and 220 females were affected mortality rates of 2.5% and 2.7%, respectively. Saudis composed the majority of cases: 403 cases with a total of 12 deaths (3% mortality rate). The mean age of cases was 28.6 years with a standard deviation (SD) of 18 years; the mean age of deaths was 40.7 years with an SD of 22 years. Fever was the most prominent symptoms with a range of occurrence from 94% to 100%, followed by cough with 60% to 86%. The epidemic curve showed November in 2009 and December in 2015 as months with greatest number of cases.

Discussion: H1N1 trends in Tabuk showed that the new virus was still circulating with a similar distribution from 2011 – 2015. However, surveillance for influence has not been evaluated since inception and to ensure effective public health practice, we recommend a formal evaluation be initiated.

Trends of H1N1 Cases, Tabuk Region, Kingdom of Saudi Arabia, 2009 – 2015

By

Yahya Al Asseri

MBBS, DFE
University of Dammam, King Saud University
2006, 2013

Thesis Committee Chair: **Scott JN McNabb, PhD, MS**

A thesis submitted to the Faculty of the
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Chapter 1 – Introduction

In 2009 a new strain of influenza A emerged (H1N1) and spread to many countries, leading to the first influenza pandemic of the 21st century. H1N1 spread quickly. First isolated in Mexico in April 2009, by the end of May it was found in over 43 countries. That year, 12,515 people were infected and 91 deaths were recorded[1,2]. Health organizations around the world, including the WHO and CDC, devoted much attention to the sweeping new strain of virus, which could be transmitted from human to human. The H1N1 virus's relatively high mortality rate among suspected and confirmed cases and rapid spread over multiple countries led the WHO and CDC to declare the situation a public health emergency of international concern (PHEIC)[2,3].

The Kingdom of Saudi Arabia (KSA) was one country that reported new virus cases in early 2009. For many reasons, KSA was one of the most important players in the context of controlling the new pandemic. The most important factor was the Hajj ritual, the largest mass gathering worldwide. Making this pilgrimage is a pillar of Islam that every Muslim must perform at least once in his or her lifetime. Every year, 2-3 million Muslims travel through many different countries on their way to Makkah city during the month of Thul-hejja, the twelfth month of the lunar calendar. Due to this yearly event, the risk of the spread of this type of infection within and outside of KSA was very high.

Implementation, control, and prevention measures require significant effort to plan and execute. When the new virus was first reported, the WHO and CDC worked in cooperation with the Saudi Ministry of Health (MoH) under the supervision of highest-level authorities of the government. The MoH was established by a royal decree in 1951 and administers a large-scale health system serving the needs of all of KSA's residents. The

Directorate-General of Parasitic and Infectious Diseases (DPID), which falls under the preventive medicine department, is one of the most important branches of the MoH. The DPID has three main objectives: the eradication or removal of severe communicable diseases, the prevention and control of infectious and parasitic diseases, and the prevention of communicable disease-related complications [4]. Since the global pandemic of H1N1 in 2009, the DPID has been running and maintaining the nationwide surveillance program for influenza (A) based on reports faxed from all the 13 of KSA administrative regions.

The first laboratory-confirmed case of H1N1 in KSA was reported June 3, 2009[5,6]. In concert with the global control and prevention efforts initiated by international organizations such as the WHO and CDC, the KSA MoH worked at full capacity on the scene. The awareness alarm was struck at the highest levels of authority of the country. That same month, the MoH convened a consultation meeting with its counterparts in other global public health organizations to pool and exchange the public health knowledge and experience necessary to cope with two threats: Hajj season and the H1N1 pandemic[7]. As a result, a nationwide plan was launched by the MoH and disseminated to all 13 regions. The aim of the plan was to mitigate the impact of the new pandemic on people and health care facilities[8]. Primarily, the MoH worked to identify cases and treat them, to isolate patients who were confirmed, and to identify the contacts of confirmed cases. Later, when the vaccine became available, vaccination campaigns were launched and strongly promoted by legal regulations and the media.

Initially, the case definition included every patient complaining of fever, cough, and sore throat with significant chest x-ray showing any signs of pneumonia or lower

respiratory tract infection in general. Later, in 2010, the case definition was limited to include only those with the above symptoms who were also in need of hospital admission.

Implementation of the MoH's plan began, and the influenza surveillance system was strengthened to achieve the MOH's objectives. Surveillance system data had to be analyzed to evaluate the situation and the plan. Being aware of the incidence of mortality and morbidity arising from H1N1 in KSA was of high importance.

KSA is located at the most southwest part of Asia, with a population of 30,770,375[9,10] distributed among 13 regions (also called provinces). Each region has an administrative capital and multiple governorates. Tabuk is one of the most important provinces in KSA. Located in the most northwest part of KSA, it has a population of 791,535 and is considered an important entry point for many people coming from different countries, especially during Hajj season[11]. More than 50,000 pilgrims cross Tabuk towards Makkah to perform Hajj rituals each year. Tabuk region has eight cities, which include 12 hospitals and 74 primary health care centers, operating under the direction of the General Directorate of Health Affairs, the MoH representative in the region. Departments and branches among general directorate of health affairs in Tabuk city are a mirror of the central organization of the MoH in Riyadh, the kingdom's capital and the MoH headquarters. The Department of Public Health in Tabuk city operates under the direction of the DPID in Riyadh. All legislation and recommendations regarding infectious disease control and prevention are made at the headquarters and then disseminated to the 13 regional health directorates throughout the kingdom.

As an important part of KSA and a major gateway for many travelers, Tabuk region has unique characteristics. Because of this, the region warrants special attention in order to

evaluate the impact of the global pandemic on its community. The objective of this study is to evaluate the trends of mortality and morbidity that resulted from 2009 H1N1 global outbreak and the years following, up to 2015, in Tabuk region. To achieve this objective, we will analyze the demographic and treatment data of those who had H1N1 during this period, including age, nationality, and sex; their signs and symptoms; hospitalization history; treatment history; and outcome (recovered or died).

A comparison will be made between the trends of cases during the global outbreak, from 2009 – 2010, and during the post-pandemic period, from 2011 – 2015. This comparison will provide a good picture of the effect of the change in case definition and strategies of control and prevention occurring in these two stages. Since the trends of H1N1 cases in Tabuk region have not been studied before, this analysis will be useful for providing insight into many aspects of the situation. In addition, this analysis will serve as a reference source for comparing Tabuk to other parts of the kingdom and to national data.

Chapter 2 – Literature Review

The 2009 H1N1 virus pandemic was considered the first influenza pandemic of the 21st century. Because H1N1 is a type of influenza, the history of influenza in general will be reviewed. This study will examine the trends of H1N1 cases in part of the Kingdom of Saudi Arabia, so the epidemiology and worldwide impact of the 2009 H1N1 pandemic is considered key to understanding the nature of the new virus and how it differs from other influenzas, especially seasonal variations. We will identify highly important variables to ascertain how the disease is affecting the population and communities by reviewing demographic data in the published literature (especially age and sex of those affected), signs and symptoms of H1N1, hospitalization history, methods confirming the diagnosis, treatment and patient management, vaccination effectiveness, mortality rates, and measures taken to control and prevent it. We aim to reach a better understanding of H1N1 in Tabuk city in comparison to other parts of KSA and other places in the world. In addition, we will discuss H1N1 as it relates to the Hajj, the largest global mass gathering, when 2-3 million pilgrims from all over the world gather yearly in very small area over a short time period.

Background on Influenza

Influenza, or the flu, is a common virus that has affected humans throughout history. The signs and symptoms that commonly characterize it range from mild to severe, such as fever, cough, sore throat, lethargy, headache, and runny nose. Influenza viruses are RNA viruses of three types: A, B and C. Influenza virus A in particular has been divided into many subtypes depending on its hemagglutinin (HA) neuraminidase (NA) proteins contained in its genes (e.g., the H1N1 subtype that causes what was formerly called swine

flu)[12]. One of the characteristics that makes influenza A unique (and distinct from types B and C) is that it can live and proliferate in many types of animals such as birds, pigs, horses, and waterfowl[13,14].

Usually influenza viruses infect people by entering their bodies through the nose and mouth air passages, where they adhere to the mucous membrane and then invade body tissues when circulating through the blood stream. The coughing and sneezing of an infected person is the primary means of the virus's spread between humans. Most often, the virus has an incubation period of 2-7 days, after which the disease's and signs and symptoms appear. People are usually sick for a week and rarely require hospital admission unless there are complications.

Influenza viruses can be detected by different tests, e.g. rapid tests, where samples of mucous membrane are taken from sputum, throat, nose or pharynx by swab, and by a more accurate test called polymerase chain reaction. Proper hand washing using antiseptic soap and wearing a surgical mask both are very effective methods for prevention of infection transmission[15]. Further in the way of infection control and prevention, the WHO recommends yearly influenza vaccinations, though they protect against only three or four subtypes of influenza viruses[16].

Worldwide Influenza Outbreaks

Flu spreads all over the world in annual local outbreaks, which lead to 3 to 5 million cases of severe illness, and about 250,000 to 500,000 deaths globally. In the northern and southern parts of the globe, outbreaks occur mainly in the winter, while in the areas close to the equator, epidemics can occur at any time of year. Deaths from the flu occur mostly among children, the elderly, and those suffering from complications or chronic health

problems that affect their immunity[16]. Pandemics, which are larger outbreaks involving more than one country, can occur for influenza, but are much less frequent than local outbreaks. A total of 1000,000 deaths resulted from three huge pandemics that took place during the 20th century: the Spanish flu in 1918, the Asian flu in 1958, and the Hong Kong avian flu in 1968 [17]. In June 2009, the first pandemic of the 21st century occurred involving a new strain of influenza A, H1N1[18]. It was characterized by high ability of spread and appeared in many countries in few months. That's what was made the worldwide fear to be in its highest level.

The 2009 pandemic were the second caused by H1N1 (the first was the Spanish flu of 1918). The 2009 H1N1 pandemic involved a new strain of the virus with a unique triple combination of gene mutations containing segments from human, swine and avian influenza A viruses[19]. In the 1918 H1N1 pandemic, scientists believed that the virus also affected swine, and since that time, influenza A virus has been continually isolated from pigs[20]. In 1930, the first influenza A virus was isolated from diseased pigs in United States[21]. Influenza A viruses that have been continuously isolated from infected pigs are called classical H1N1 viruses. Until the 1980s, classical H1N1 viruses were believed to be constantly stable antigenically throughout their continuous circulation in pigs over many different countries in the Americas, Europe, and Asia[22]. This was attributed to the scarcity of pandemics since 1918 (apart from some local outbreaks such as the Fort Dix outbreak in 1976)[23]. However, the pathogenicity of the 2009 H1N1 virus was comparable to that of the H5N1 avian influenza virus, which can produce appreciable pathology in the lungs of mice, ferrets and non-human mammals[24].

H1N1 Pandemic of 2009

There was great concern upon the emergence of the new H1N1 virus and a fear that this pandemic could rival the ones of the last century, with deaths totaling in the millions[19,25,26]. The 2009 H1N1 pandemic started as a local outbreak of flu-like illness in February 2009 in two Mexican cities. By April 2009, two independent cases were identified to have contracted the new H1N1 strain in California. By the end of April that year, after addressing the fact of human-to-human transmission and international spread, the WHO raised the pandemic alert from Phase 3 to Phase 4, and then to phase 5.

In June 2009, at least two continents were reported to be included in this pandemic, which drove the WHO to raise the alert to its highest level, phase 6[19,27]. By December 2009, the total number of laboratory-confirmed cases of H1N1 was 622,000, with approximately 12,220 deaths reported from more than 208 countries and overseas territories with at least one reported case from each of them.

Tracking the real number of cases was in fact difficult during the pandemic's surge, and according to some, the actual number of cases was underestimated. A reason behind the underestimation may be the change in strategy by the WHO, where aimed to judge the time, that directed the efforts of reporting countries towards concentrating more on investigating severe cases and extreme events rather than counting case reports[19].

Impact of 2009 Outbreak

With limited accurate data and frequent changes in reporting system strategies (along with assumed underestimation), proper judgment of the impact and potential of the 2009 pandemic was very difficult. Nevertheless, it was still important to make estimates and assess the situation to inform appropriate health responses. Fraser, et al., in their 2009 study, made an early assessment of transmissibility and severity of the new disease by

analyzing early data on the Mexican outbreak. They estimated based on confirmed and suspected deaths reported up to that time that about 23,000 (ranging from 6,000 to 32,000) individuals had been infected in Mexico by late April 2009, and at the same time they estimated the case fatality ratio (CFR) to be of 0.4% (ranging from 0.3 to 1.8%). They also found the outbreak CFR in local communities such as in La Gloria and Veracruz to have an upper bound of 0.6% (95% CI).

The study also stated that the clinical severity was less than that documented during the 1918 H1N1 pandemic and could be highly comparable to the pandemic that occured in 1957 due to avian influenza, although substantial doubt about data accuracy remains notable[1]. Furthermore, based on serology estimation, the 2009 H1N1 influenza A looked to have had a higher general attack rate than seasonal influenza[28].

2009 H1N1 Pandemic Epidemiology

By studying the epidemiology of the 2009 pandemic, the main age-groups was highly infected were school-aged children and young adults which is also differ from seasonal highest age of infection. On the other hand, although, the older people age-group seemed to been protective, but was of the highest case-fatality rate. Thus, the older people categorized to be in lower risk group of getting the infection, but once they got infected they will be in the highest risk of death[29,30].

Approximately, cosistent results were found in KSA. In one study conducted at Riyadh city about the characteristics of 2009 pandemic influenza A (H1N1) infection upon patients presented to King Khalid univesity hospital, the researcher found that the mean age of 117 cases of laboratory-confirmed cases was 19.6 years with standard deviation of 16.7 years[31]. Another study conducted to describe the fist one hundered H1N1 cases during

the 2009 pandemic in KSA revealed that the ages of reported cases ranging between 1 to 56 years and highest percentage of cases was in the age group of 20 to 30 years followed by the age group of 1 to 10 years[32]. Sex distribution of the 2009 H1N1 cases showed almost close precentage of infection between men and women where some study founded that to be 55- 60% among men and 40- 45% among women[19,31,32].

H1N1 Case Definition and Surveillance

Like other influenza ilness, people who got infected by H1N1 were ranged from being asymptomatic to be complained extreme fatal illness which may be caused by excerbation by one or more of the underlying (e.g., diabeties or heart disease) or being complicated by serioud lower respiatory tract infection with muti-organ failure.

2009 H1N1 case definition by CDC was stated to be (any case of Influenza-Like-Illness (ILI) with fever of >37.8°C (>100°F) plus cough and/or sore throat in the absence of a known cause other than influenza. CDC also, was categorized the case definition as: confirmed, probable and susbected. Confirmed case: was defined to by any indivisual with acute respiratory illness and has a confirmed lab resulte of having 2009 H1N1 virus through either: Real time reverse-transcription polymerase (rRT-PCR), or viral culture. Probable case came to be defined as: any indivisual with (ILI) who is positive to influenza A, but negative for H1 and H3 by rRT-PCR. The suspected case definition was to be related to epidemiological links (such as a history of cntact with confirmed or probable case within last 7 days) rather than being having signs or symptoms of ILI and didn't fit any definition of either the confirmed or pobable case[33].

Including chest radiography work in form of chest x-ray in the case definiton may reflect less important. One study showed that out of 179 patients with a high suspicion of

H1N1 infection who had an initial chest radiograph, there is 65 men (56%) had a normal chest radiograph, while 35 (55.6%) had an abnormal chest X-ray, and about 51 women (44%) had a normal chest X-ray, while 20 (44%) had abnormal chest X-rays[34].

Generally, many resources indicated that most of cases were presenting with typical mild (ILI) singns and symptoms which is usually self limiting in few days[35]. Fever were the most frequent symptom followed by cough then sore throat, headache, lethargy and nausea. Vomiting and diarrhea occur usually in less frequent. In united states, from April 15 through May 5, 2009, a total of 642 confirmed cases identified in about 41 states and showed that the most common presenting symptom was fever constituting of (94%) of total examined patients followed by cough (92%) then sore throat (66%). Vomiting and diarrhea identified to be occurred in 25% for each one of the two symptoms[36].

From the previously mentioned study,[31], almost same results were found about presenting signs and symptoms in Saudi Arabia. This study showed that fever was the most frequent symptoms, where it was reported in 99 patients out of 117 forming (85.3%), followed by cough with (81%), runny nose (33.6%) and sore throat (21.3%). Very localized study, conducted in one tertiary hospital in Saudi Arabia, alos, founded very close results, where fever occurred in 72.6%, followed by cough 69.2%[37]. Younger children were mostly presenting with atypical ILI signs and symptoms, and thus they were less frequent to present with fever and cough.

H1N1 Hospital Treatment

Only up to 10% of total individual who get the illness (2009 H1N1) were in need to be admitted to the hospital for further management. In United States and Canada there were about 2- 5% of confirmed cases admitted to the hospital and about 6% in Mexico[38-40].

7- 10% of all hospitalized patients were pregnant women and most of them in their second or thired trimester of pregnancy. Furthermore, 10- 25% of all hospitalized patients were required to be admitted to intensive care unit and up to 9% were died. Younger children (<5 years) verfiyed to have highest hospitalization rate followed by age-group 5-14 years with relative risk [RR]=3.3 and 3.2, respectively, compared to the general population[30,41].

H1N1 Diagnosis

The real-time reverse transcriptase polymerase chain reaction (rRT-PCR) test, which used very widely during the 2009 pandemic, considered the gold standard diagnostic test. Sensitivity and specificity of the rRT-PCR test was favoring it over the other tests. Many literatures showed that the rRT-PCR test has high sensitivity, rapidity, producibility and specificity to detect H1N1 as rapid as outbreaks situation need[42-44]. Many other tests available and can be used for H1N1 detection. For example, rapid influenza diagnostic tests that depend on detection of viruses antigen have an excellent specificity that could reach more than 95% but at the same time they are very variable in sensitivity which usually ranging between 10-70%. Isolation of H1N1 by tissue culture consider one of the important diagnostic test which must be done fo patient fitting the case definition, but it is usually not enough to be done alone for two reasons, first, it takes longer time for the result, so it could make the clinical management late, and the negative result doesn't excluded the infection[19,45]. Samples for testing (respiratoy specimen) usually being taken from air passages (mouth, nose and pharynx). Preffered specimens may be the nasopharyngeal swab combined by oropharyngeal swab for many experts. Lower respiratory specimen highly recommended specifically in patients who developed pnuemonia.

H1N1 Case Management

Case management of patients infected with 2009 H1N1 virus could by highly varied. While the simple supportive care including well nurishing (hyderation and proper food) and using antipyretics like (acetaminophen or ibuprofen) could be useful for majority f 2009 H1N1 patients, still some needs antiviral management. Antiviral therapy, particularily neuraminidase inhibitors, including oseltamivir (Tamiflu) and zanamivir (Relenza), considered the drugs of choice for 2009 H1N1 infection, which at the same time showed very low percentage of resistance to them.

By December 2009, there were more than ten thousands cases examined in regarding anitviral treatment and only 136 resulted to be resistant to oseltamivir (Tamiflu)[19]. Antiviral preffered to started within 48 hours of illness first symptoms appeared, where that was linked to the best outcome. But still using them even later being recommended[19,46,47]. Furthermore, early using of antiviral therapy (neuraminidase inhibitors) signficantly founded to have preventive effect of death in patients develped complications particularly pnuemonia[48]. Antiviral therapy should be started empirically as soon as possible for any patient need hospitaliation and fitting the case definition, any patient with sever progressive complicated illness and those whom at high risk (e.g. very young children and prgnant women)[33,49].

Control and Prevention Strategies

As in rgard of ther types of infuenza, building a strategies for control and prevention of 2009 H1N1 became the top priority for the global public health during the pandemic. Achievable control and prevention strategies can be categorized to include antiviral therapy, vaccination of population and could be include also the non-pharmaceutical

measures such as case isolation, household quarantine, school or workplace closure and travel restrictions[50,51]. School closure, although hasn't a big effect on overall attack rate, was found to reduce peak of attack rate by 40% during the peak of pandemic. However, travel restriction was also found to has important rule in control and prevention of spread of the infection if applied 99% where the spread culd be delaied more than 3 weeks.

Applying more than one measure at the same time found to have higher effect on the attack rate. For example, Given prophylaxis to the household contacts, treating at least 50% of population with proper drugs and reactive school closure found to reduce the clinical attack rate by 40-50%. Even if it is logistically challenging, the spreading prophylaxis very widely believed to reduce attack rates by over 75%. Furthermore, well coverage by vaccine, even if its efficacy is low, also believed to reduce the attack rate very dramatically[50].

On level of indivisuals, presonal protective behaviours and attitude (e.g. hand hygiene, wearing a face mask, cough etiquette, social distancing, and contact avoidance) were associated minimally with ILI. At the same time health education were found to be strong promotinal methods for those presonal protective measurs[52].

Vaccines

In fact, the effective vaccine ranking the 1st important strategy to control and prevent spread of influenza infection. Thus, during 2009 pandemic, FDA and the European Medicine Agency (EMEA) have been approved two vaccines to be used in controlling and preventing the spread of the disease. Both vaccines showed very safe use through priliminary data[53].

Five categories of persons were recognized by the Advisory Committee on Immunization Practice (ACIP) to have the priority in vaccinations efforts where they are at

high risk of getting complications due to influenza infection including: pregnant women, household contact and caregivers for people less than 6 months, health care and emergency departement workers, indivisuals in age of 6 months throuh 24 years and indivisuals of age 24-64 years with underlying medical risk factors that could be complicated by influenza infection[54]. By November 2009, around 80 million doses of the vaccine had been distributed all over the world and about 65 million people have been vaccinated as estimated by the WHO.

Despite of the fact that the 2009 vaccine matched the safeist profile among seasonal influenza vaccines that have been in use since 60 years, less than 10 casse of suspected Guillain-Barré syndrome reported among people who have been vaccinated[19,54,55]. Beside the fear of serious side effects of the 2009 vaccine, the believe that the 2009 infection is not that serious disease raised as cause of refusal f the vaccine. In Saudi Arabia, a cohort study that attempted to measure the acceptance level among participants about the 2009 vaccine showed less than half of them dinied vaccination because the believe that the disease is nt much serious. Also, it showed that the refusal percentage were higher among health care workers[56].

H1N1 and Hajj Season

Despite of high risk in regarding Hajj season, represented by pooling of many factors such as crowdedness, presence of high susceptable people and different health education level and personal attitude, behaviour and practice among pilgrims, the infection by 2009 H1N1 virus counted less than seasonal influenza and other respiratory illnesses among 2009 pilgrims[57-59]. In order to make highest preparedeness twoard control and prevention of 2009 pandemic especially during Hajj season, KSA represented by MoH worked in its

highest cpacity in parallel with global health agencies and held a serious of consulation meeting with them. A set of recommendations and plans were established. Ensurance of optimum health care providing to pilgrims and minimal transmissions of the disease to their homes was the main goal of the preparedeness plan. That is require frequently revision and evaluation of that plan to secure the future mass gathering and make it able to use in othe setting[7].

Chapter 3 – Manuscript

Abstract

Background: In 2009 a new strain of influenza A (H1N1) emerged and spread globally, leading to the first influenza pandemic of the 21st century. The Kingdom of Saudi Arabia (KSA) had special responsibility because it stewards the annual mass gathering of the Hajj. Tabuk province is a port of pilgrims coming for Hajj; studying trends of H1N1 cases there could yield new and important information.
Methods: A cross-sectional retrospective analysis of all reported H1N1 cases in Tabuk province between 2009 and 2015 was undertaken to estimate the trends by incidence rates (IRs) and 95% confidence intervals (CIs) using Byars approximation. These data were part of the case-based regional surveillance shared by the Department of Infectious Diseases, Tabuk General Directorate of Health.
Results: A total of 471 cases of H1N1 were recorded during the period 2009 – 2015. The number of cases was greatest in 2009, when there were 317 cases and an IR of 39.9 cases/100,000 (95% CI = 35.7 – 44.5). The IR decreased over time and 242 males and 220 females were affected mortality rates of 2.5% and 2.7%, respectively. Saudis composed the majority of cases: 403 cases with a total of 12 deaths (3% mortality rate). The mean age of cases was 28.6 years with a standard deviation (SD) of 18 years; the mean age of deaths was 40.7 years with an SD of 22 years. Fever was the most prominent symptoms with a range of occurrence from 94% to 100%, followed by cough with 60% to 86%. The epidemic curve showed November in 2009 and December in 2015 as months with greatest number of cases.
Discussion: H1N1 trends in Tabuk showed that the new virus was still circulating with a similar distribution from 2011 – 2015. However, surveillance for influence has not been evaluated since inception and to ensure effective public health practice, we recommend a formal evaluation be initiated.

Introduction

In 2009, a new strain of influenza A emerged to spread globally, leading to the first influenza pandemic of the 21st century. The new virus, called H1N1, caused worldwide panic and pushed the WHO to declare the first public health emergency of international concern (PHEIC).

The Kingdom of Saudi Arabia (KSA) was one of the countries that reported new H1N1 cases in early 2009. For many reasons, KSA was one of the most important players in the context of controlling the new pandemic alongside other global health agencies. A critical factor was the Hajj season, the largest mass gathering in the world. Due to this yearly event, the risk of the spread of H1N1 within and outside of KSA was very high. For this reason, the WHO and CDC worked in cooperation with the KSA Ministry of Health (MoH) under the supervision of highest-level authorities of the government.

Tabuk province is one of the most important of KSA's regions. Located in the northwest corner of KSA, it has a population of 791,535 and is considered an important entry point for many people coming from different countries, especially during Hajj. More than 50,000 pilgrims cross Tabuk towards Makkah to perform Hajj each year. Because of this, the region warrants special attention for evaluating the impact of the global pandemic on its community. This study compares Tabuk with other KSA provinces to make recommendations to improve policy.

Methods

Data Source

An H1N1 dataset (part of the regional surveillance system) was shared by the Department of Infectious Diseases, Tabuk General Directorate of Health, KSA. Data collection is case-based, ongoing, and reported to the General Directorate of Parasitic & Infectious Diseases at the KSA MoH headquarters in Riyadh.

Study Variables

The initial dataset was received as an SPSS file containing years 2009 – 2010 and an Excel file for subsequent years. The SPSS file had data points encoded as text values, while the Excel file was numerically encoded. The two datasets were recoded into numerical values for alignment of common variables. The dataset contained demographics, age, gender, nationality, admission date, discharge/death date, outcome, treatment, signs and symptoms, hospitalization and symptom profile variables. Eight symptom variables were originally encoded with numerical values and were concatenated into a single variable that represent a symptom profile (e.g., 1 for fever, 2 for cough). Missing data on signs/symptoms was interpreted as not presenting with those signs/symptoms; outcome data was not available for 9 subjects in 2009.

Statistical analyses

A cross-sectional retrospective analysis of all reported H1N1 cases in Tabuk province between 2009 and 2015 was conducted to estimate the incidence rates (IRs) and 95% confidence intervals (CIs) using Byars Approximation[60]. We stratified the IRs by

nationality and gender. IRs were calculated using the number of cases per year over the total population per 100,000 individuals.

We used the Chi-square test to determine the statistical difference between the IRs of males and females and Saudi and Non-Saudi nationals. We used Fisher's exact t-test to determine the statistical association between outcome and demographic characteristics. Corresponding p-values were reported.

The source of population data was the General Authority for Statistics for KSA, which released their mid-annual population estimates from 2010 – 2025 using a model estimate from the population distribution in the provinces and regions according to the 2010 annual census. The population dataset contained estimates for the total population per province and by nationality per province. This dataset was used to estimate the IR for the total population and by nationality. By gender, population data were only available in the 2010 census. In order to estimate the population data for other years, we first estimated the growth factor in each province per year based on the population data as reported by the Central Department of Statistics and Information (CDSI) from 2007 – 2012. We also estimated gender by proportion of the population for each province. Assuming the same growth factor for both men and women, and maintaining the average proportion in the population from 2007 – 2012, we estimated the size of the population by gender in other years. The overlap between the CDSI population data per province from 2010 – 2012 matched the General Authority of Statistics data from 2010 – 2012.

A p-value of less than 0.05 was considered statistically significant. Descriptive and analytic statistics were generated using SAS™ 9.4 (SAS Institute, Cary, NC) and IRs and CIs were calculated using Microsoft Excel™ 2016 (Microsoft, Seattle, WA).

Results

The number of H1N1 cases in Tabuk province was highly variable over the study period. Of 317 reported cases in 2009, 308 listed outcomes. There were 8 total deaths [2.6%] that year. The number of cases decreased dramatically in the following years. There were 21 cases with 2 deaths (9.5%) in 2010; 3 cases with no deaths 2011; no reported cases in 2012; 7 cases with 1 death (14.3%) in 2013; and no reported cases in 2014. In 2015, the number of cases increased again, reaching 123, with only 1 death (0.8%).

By gender, 242 males had the H1N1 virus from 2009 – 2015, with mortality rate of 2.5%, and 220 females had H1N1, with a mortality rate of 2.7%. Saudis composed the majority of those having H1N1: 403 cases with a total of 12 deaths (3% mortality rate), while 59 cases were non-Saudi, with zero deaths. The mean age of cases was 28.6 years with a standard deviation (SD) of 18 years; the mean age of deaths was 40.7 years with an SD of 22 years (Table 1).

Table 1. *Demographic Characteristics of Confirmed H1N1 Cases and Deaths, Tabuk Province, Kingdom of Saudi Arabia, 2009 – 2015*

Characteristic	# Cases	# Deaths (%)	P-value
Year			
2009	**308**	**8 (2.6)**	
2010	**21**	**2 (9.5)**	**0.0570**
2011	**3**	**0 (0)**	
2013	**7**	**1 (14.3)**	
2015	**123**	**1 (0.8)**	
Gender			
Male	**242**	**6 (2.5)**	**0.8671**
Female	**220**	**6 (2.7)**	
Nationality			
Saudi	**403**	**12 (3)**	**0.3784**

Non-Saudi	**59**	**0 (0)**
Age		
Mean	**28.6**	**40.7**
SD	**18.0**	**22.0**

A total of 471 cases of H1N1 were recorded during the period from 2009 – 2015. The number of cases was highest in 2009, when there were 317 cases and an incidence rate (IR) of 39.9 cases/100,000 (95% CI = 35.7 – 44.5). The IR decreased over the following years. In 2010, the IR was 2.6 cases/100,000 (95% CI = 1.7 – 3.9); in 2011, the IR was 0.4 cases/100,000 (95% CI = 0.1 – 1.0); in 2013, the IR was 0.8 cases/100.000 (95% CI = 0.7 – 1.6). In 2015, the IR increased again, reaching 13.6 cases/100,000 (95% CI = 11.3 – 16.1) (Table 2). No cases were reported in 2012 and 2014.

Table 2. *Confirmed Cases of H1N1 and Incidence Rates, by Year, Tabuk Province, Kingdom of Saudi Arabia, 2009 – 2015*

Year	#	IR°	95% CI*
2009	**317**	**39.9**	**35.7 – 44.5**
2010	**21**	**2.6**	**1.7 – 3.9**
2011	**3**	**0.4**	**0.1 – 1.0**
2013	**7**	**0.8**	**0.7 – 1.6**
2015	**123**	**13.6**	**11.3 – 16.1**
Total	**471**		

A statistically significant association was found between the IR of each year of study and the nationality of H1N1 cases in Tabuk province in 2009, the year of global pandemic. That year, 286 Saudis were confirmed to have H1N1, with an IR of 43.5 cases/100,000 (95% CI = 38.7 - 48.8) while 31 non-Saudi had H1N1, with an IR of 22.5 cases/100,000 (95% CI = 15.6 - 31.6) (p=0.0001637). In subsequent years, the association was not significant; there were predominantly higher numbers of cases and higher IRs among Saudi nationals than among non-Saudis (Table 3).

Table 3. *Confirmed Cases of H1N1 and Incidence Rates, by Year and Nationality, Tabuk province, Kingdom of Saudi Arabia, 2009 – 2015*

Year	Saudi			Non-Saudi			P-value
	#	IR°	95% CI*	#	IR°	95% CI*	
2009	286	43.5	38.7 – 48.8	31	22.5	15.6 – 31.6	0.0004
2010	19	2.8	1.8 – 4.3	2	1.5	0.3 – 4.8	0.4169
2011	3	0.4	0.1 – 1.2	0	0	0 – 0.4	0.5754
2013	6	0.8	0.4 – 1.7	1	0.7	0.1 – 3.1	0.9140
2015	97	12.9	10.6 – 15.8	26	16.2	10.8 – 23.3	0.3221
Total	409			59			

The association of gender and the number of confirmed cases of each year was not significant. There were a higher number of cases among males than females through the study period. In 2009, the IR among males (37.7 cases/100,000; 95% CI = 32.3 - 43.9) was higher than among females (31.1 cases/100,000; 95% CI = 26.5 - 36.3) (Table 4). In subsequent years of the study, the IRs among females were higher than among males (Table 4).

Table 4. *Confirmed Cases of H1N1 and Incidence Rates, by Year and Sex, Tabuk Province, Kingdom of Saudi Arabia, 2009 – 2015*

Year	Male			Female			P-value
	#	IR°	95% CI*	#	IR°	95% CI*	
2009	163	37.7	32.3 – 43.9	154	31.1	26.5 – 36.3	0.08442
2010	11	2.5	1.3 – 4.3	10	2.8	1.4 – 4.9	0.8258
2011	3	0.7	0.2 – 1.8	0	0	0 – 0.7	0.1688
2013	3	0.6	0.2 – 1.7	4	1.1	0.4 – 2.5	0.5367
2015	66	13.3	10.4 – 16.8	57	14.2	10.8 – 18.2	0.7333
Total	244			224			

Our analysis of the signs and symptoms of H1N1 among patients showed that fever ranked first, with 94% to 100% of all patients developing it. Second was cough, with 60 - 86% of patients developing it. Shortness of breath (SOB) ranked the third most common

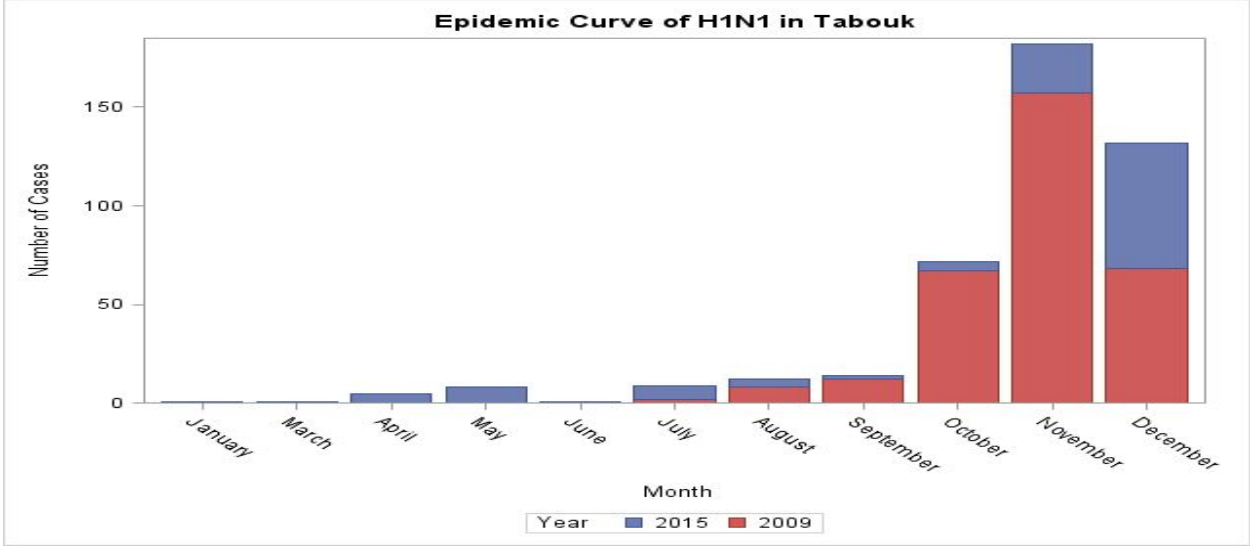
symptom in 2010 (57% of patients), 2013 (72% of patients), and 2015 (15% of patients). Sore throat was the third most common symptom in 2009 (75% of patients) and 2011 (34% of patients). The fourth and fifth most common symptoms were distributed among runny nose, headache, muscle pain, sore throat and SOB (as shown in Table 5).

Table 5. *Top Five Signs/ Symptoms of Confirmed Cases of H1N1, Tabuk Province, Kingdom of Saudi Arabia, 2009 – 2015*

	2009	2010	2011	2013	2015
1	Fever (94%)	Fever (96%)	Fever (100%)	Fever (100%)	Fever (97%)
2	Cough (78%)	Cough (85%)	Cough (67%)	Cough (86%)	Cough (60%)
3	Sore Throat (75%)	SOB* (57%)	Sore Throat (34%)	SOB* (72%)	SOB* (15%)
4	Runny Nose (70%)	Headache (34%)	Muscle Pain (34%)	Sore Throat (43%)	Muscle Pain (10%)
5	SOB* (42%)	Sore Throat (30%)	Runny Nose (34%)	Muscle Pain (30%)	Sore Throat (7%)

Epidemic curve showed that during 2009 the cases were reported from July through December with a peak in November. While in 2015 the cases were almost reported throughout the year with a peak in December. In both, 2009 and 2015, the majority of cases were in November and December (Figure 1).

Figure 1: *Epidemic Curve of H1N1 Cases, 2009 – 2015, Tabuk Province, Kingdom of Saudi Arabia, 2009 – 2015*



Discussion

This study explored the trends of H1N1 cases in Tabuk province, KSA, from the outbreak of the global pandemic in 2009, through the post-pandemic period, to the end of 2015. This study's results were consistent with others reported in studies worldwide. The IR was at its highest in 2009, when there were 317 cases and an IR of 39.9 cases/100,000 (95% CI = 35.7 – 44.5). The very high IR reflects the new virus's characteristic rapid transmission and spread. This was especially clear at the beginning of the global outbreak; 622,000 confirmed cases were reported from 208 countries within only a few months in 2009[19].

Other factors could play a role in the high 2009 IR. Geographically, Tabuk is an important crossroads of pilgrim activity during Hajj seasons. In addition, the case definition at this time was broader than it is now, and back then, there was less acceptance of vaccination among the population and fewer people were vaccinated.

Each year from 2010 – 2014, the number of cases was very low compared to 2009. This could be attributed to a few factors, the main on being the MoH changes in its strategy and protocols. The H1N1 case definition was narrowed. Vaccinations became mandatory. In late 2009, Tamiflu began to be used, and by early 2010, its use was pushed, which may explain the steep drop in number of cases and subsequently IR. The MoH also launched media campaigns in cooperation with other related government sectors, and these contributed to an increase in people's knowledge and awareness of the importance of vaccine use to prevent acquiring and spreading H1N1. These campaigns also significantly lowered people's fears of the vaccine's adverse effects.

Another factor contributing to lower reported cases from 2010 to 2014 may be under-reporting or the low quality of reporting. In early 2015, electronic reporting of H1N1 cases was instituted through the nationwide Health Electronic Surveillance Network (HESN), an electronic, web-based system developed to facilitate the collection, analysis, and transfer of data. HESN helped eliminate reporting delays and errors resulting from manual entry and thus elevated the quality and accuracy of H1N1 case reporting. This could explain the increase in cases in 2015. Furthermore, due to MERS-Cov intensive case detection surveillance, MoH requested to obtain an extra sample for H1N1 from each suspected MERS-Cov patient. Other reasons like vaccine coverage and effectiveness could be also a factors.

Despite non-significant p-values for associations between mortality rates in each year, paired with nationality and gender, these results are consistent with demographic findings in other studies conducted in Saudi Arabia and worldwide on the H1N1 2009 pandemic [19,31,32,37].

In this study, the mean age of cases was 28.6 years with an SD of 18 years. This result was similar to that in a study describing the first 100 cases of H1N1 in KSA, which found the highest number of cases to be in the 20-30 year old age group[32]. In this study, the mean age of patients at death was 40.7 years old with an SD of 22 years. This result gave a good inference for low mortality rate; the disease mostly affected a younger age group, but the highest number of deaths occurred among those who were middle-aged.

In this study, most patients who had H1N1 presented with fever, which is ranked the most common symptom (affecting 94-100% of H1N1 patients through the study period). Cough was the second most common symptom. This is similar to other studies'

findings. In a different study, fever affected 94% of patients, and cough 92%[36]. Similar results were found in the study conducted in KSA on the characteristics H1N1 in patients presenting to a university hospital in Riyadh in 2009: 85.3% of patients presented with fever and 81% presented with cough[6]. Sore throat and shortness of breath ranked third among symptoms in different years, and this was also consistent with other studies. Runny nose, muscle pain, headache, and upper gastrointestinal symptoms (e.g., vomiting and diarrhea) were scattered over cases and are all considered familiar upper respiratory tract infection symptoms[61].

Although this study's results were highly consistent with worldwide H1N1 trends, there were limitations that could have affected them. Cases and their distribution factors could have been underestimated as a result of under-reporting, low quality reports, previous reporting methods (e.g., by fax), and improper case definition could have interfered with the statistical significance of associations within the results such as mortality rates per year, male to female ratio, and nationality distribution. The fact that numerous important variables were omitted from the surveillance system itself is another study limitation. The inclusion of the following variables should be considered: vaccination status, hospitalization periods, intensive care unit (ICU) admission. Knowing vaccination status of patients during data collection will be very helpful inferring whether the vaccine actually contributed to the sharp decrease in the number of cases in the years following the pandemic or not. There was no additional information available about the severity of the disease and resulting complications. Adding more measurable variables to the data collection such as hospitalization length of stay, ICU admission, and type of complication (if any) would be a way to address this limitation.

Throughout the epidemic curve we can noticed the close similarity of the new virus activity to worldwide results. The winter season is considered the preferred time for virus activity and as a result the occurrence of the outbreaks especially in the northern and southern parts of the globe[16].

Chapter 4 – Conclusion and Recommendations

The H1N1 trends in Tabuk from 2011 – 2015 showed that the new virus is still circulating in the community. The distribution and nature of the disease reflected in our analysis was consistent with reported worldwide disease characteristics. The surveillance system in Tabuk province and at the central level of the KSA MoH would benefit from improvement. The need to strengthen the ongoing surveillance system could be the first step to controlling and preventing H1N1. The following are recommendations that can be used to improve KSA MoH efforts.

1- Set up a clear, strong, and strict strategic plan to gather as wide a number of cases as possible. This can be achieved by revising the case definition to include highly suspected cases in the laboratory work up of H1N1 confirmation.

2- Emphasize the role of electronic surveillance (HESN) in improving case detection and eliminating the errors of previous reporting methods (which could have resulted in an underestimation of cases), and underline the importance of a strict commitment to using it.

3- Enforce implementation of MoH protocols and strategies of control and prevention for health care workers, health facilities, and administrative departments.

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