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SWINE-ORIGIN INFLUENZA A (H1N1) VIRUS: AS PANDEMIC INFECTION

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ABSTRACT

Flu viruses have mainly affected humans, birds and pigs worldwide. Influenza A viruses is highly infectious respiratory pathogens that can infect many species. The swine flu H1N1 reassorted subtype caused the first global pandemic in last 40 years, resulting in substantial illness, hospitalizations of millions of peoples and thousands of deaths throughout the world. There is no direct evidence that the reassortment events culminating in the 1918, 1957 or 1968 pandemic influenza viruses originated from pigs. Genetic reassortment among avian, human and/or swine influenza virus gene segments has occurred in pigs and some novel reassortant swine viruses have been transmitted to humans. The WHO declared the H1N1 pandemic on June 11, 2009, after more than 70 countries reported 30000 cases of H1N1 infection. Pandemic (H1N1) influenza most commonly causes a self-limited illness; however, significant morbidity and mortality were reported in the young, the obese and in pregnant women. The CDC recommends real time PCR as the method of choice for diagnosing H1N1. The U.S. Centers for Disease Control and Prevention recommends the use of Oseltamivir (Tamiflu) or Zanamivir (Relenza) for the treatment. The drugs of choice for treatment and prophylaxis of pandemic (H1N1) influenza are the neuraminidase inhibitors, Oseltamivir and Zanamivir. In this review, a brief overview on swine flu is presented highlighting the characteristics of the causative virus, the disease and its public health consequences, advances made in its diagnosis, vaccine and control to be adapted in the wake of an outbreak.

KEYWORDS: H1N1 influenza, Virology, swine influenza in humans, diagnosis, vaccine.

INTRODUCTION

Influenza (“flu”) is a contagious disease that spreads around the World every winter, usually between October and May. Viruses are the cause of several deadly diseases such as yellow fever, dengue, hepatitis or seasonal Influenza. The etiologic agent of the latter, the Influenza virus, can cause mild to severe illnesses depending on the Influenza type and strain.[1] A pandemic occurs when a new viral strain appears, against which the human population has no immunity, resulting in epidemics worldwide with high mortality and morbidity.[2] The influenza A virus has been responsible for three global pandemics in the last century: the Spanish Flu in 1918, Asian Flu in 1957 and the Hong Kong Flu in 1968.[3] Influenza virus outbreaks occur with regularity, but the severity of outbreaks differs. A prime example is the recent emergence of swine-origin influenza viruses A/H1N1 (S-OIVs) that have transmitted to and spread among humans, resulting in outbreaks [4]. Swine influenza is a common contagious respiratory disease of pigs caused by influenza A viruses.[5] The outbreak of the novel A H1N1 virus (swine flu) was declared a global pandemic by the World Health Organization (WHO) from 11 June 2009 until 10 August 2010.[3] As of January 10, 2010, more than 208 countries have reported the laboratory confirmed cases of the novel influenza H1N1 2009 strains, including at least 13,554 deaths.[6] The 2009 outbreak of Influenza A virus subtype H1N1 is a pandemic of a new strain of influenza virus identified in April 2009, commonly referred to as ‘‘swine flu.” The pandemic has caused fatal infection and more than 80 deaths in over 40 countries from the first detected country Mexico to several other countries in north and South America, Europe, and Asia.[7] Influenza A of the H1N1 subtype, known as swine flu, was identified as a new strain in Mexico and is now considered the fastest moving pandemic in the history of the world.[8] The first cases of H1N1/2009 in Scotland were detected at the end of April 2009 in a couple returning from their honeymoon in Mexico.[9] Swine flu is a new emerging infectious disease that is the present discussed topic of medical scientists around the world. It becomes pandemic disease around the world at present.[10] Swine flu is a new emerging infectious disease. It is a new infection by new H1N1 in influenza virus that can be transmitted from human to human.[11] A novel influenza A (H1N1) pandemic occurred in early 2009 and caused severe morbidity and fatality. Many respiratory pathogens can present with “influenza-like” symptoms. Infections caused by other respiratory pathogens may present similarly to influenza infections, making it difficult to distinguish them clinically.[12]

EPIDEMIOLOGY

Swine flu is an infection caused by a virus. It's named for a virus that pigs can get. People do not normally get swine flu, but human infections can and do happen.[13] The new virus shares some characteristics of a pandemic strain, e.g. it can be transmitted from humans to humans, causes disease, people are not or only partially immune to the virus from previous infections and exposure results in productive infection.[4] The novel H1N1 strain which is responsible for the current outbreak of swine origin influenza was first recognized at the border between Mexico and United States in April 2009 and during a short span of two months became the first pandemic of the 21st century.[14] Prior to this the same triple reassorted virus has been isolated in swine as early as 1998 with sporadic infections in humans as well.[15, 16] The pandemic influenza A H1N1 2009 virus (A/2009/H1N1) finally arrived, causing the first pandemic influenza of the new millennium, which has affected over 214 countries and caused over 18,449 deaths.[17] It is estimated that the influenza pandemic that started with the 1918 Spanish flu killed 20 to 50 million people worldwide, followed by epidemics of Asian flu in 1957, Hong Kong flu in 1968 and Russian flu in 1977, each with random severe attacks on human populations.[2] The H1N1 form of swine flu is one of the descendants of the strain that caused the 1918 flu pandemic. As well as persisting in pigs, the descendants of the 1918 virus have also circulated in humans through the 20th century, contributing to the normal seasonal epidemics of influenza.[18] The first identification of an influenza virus as a cause of disease in pigs occurred about ten years later, in 1930. For the following 60 years, swine influenza strains were almost exclusively H1N1. Then, between 1997 and 2002, new strains of three different subtypes and five different genotypes emerged as causes of influenza among pigs in North America.[15] As on 13th August 2009 WHO has reported 1, 82,166 laboratories confirmed cases of influenza A/H1N1 and 1799 deaths from 178 countries. In 2015 the instances of Swine Flu substantially increased to five year highs with over 10000 cases reported and 774 deaths in India.

VIROLOGY

The types of influenza virus found in pigs are known as swine influenza generally called swine flu or swine-origin influenza virus (S-OIV).[19] Swine Influenza is a respiratory disease of pig caused by Type A influenza viruses that causes regular outbreak in pigs.[20] Influenza virus belongs to the genus Orthomyxovirus in the family Orthomyxoviridae which consists of influenza A, B and C viruses and has an envelope, single-stranded, negatively sensed RNA, eight separate segments and pleomorphic appearance with an average diameter of 120nm.[21]

The virus was found to be an H1N1 virus (Figure.1)[25] that was genetically and antigenically unrelated to human seasonal influenza viruses and genetically related to viruses circulating in swine.[4] The currently circulating strain of swine origin influenza virus of the H1N1 strain has undergone triple reassortment and contains genes from the avian, swine and human viruses.[22]

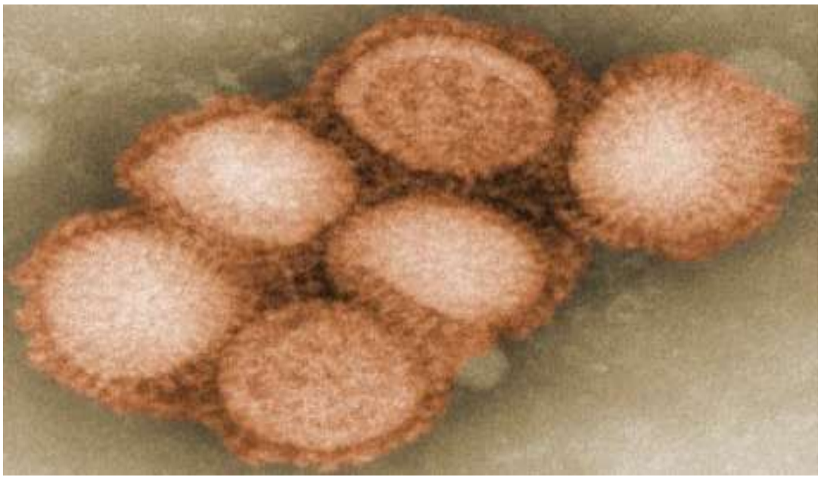

Figure.1: The pandemic H1N1 flu virus[25]

The reassortment is an important evolutionary mechanism which can result in antigenic shifts that modify host range, pathology, and transmission of the influenza A viruses. In this process, the influenza virus strain with epidemic and/or pandemic potential can be created. Cases of this kind were in 1957 (Asian flu), 1968 (Hong Kong flu) and recently in 2009 (Mexico).[23]

The influenza virus is an RNA virus divided into three types, A, B, and C, based on the antigenicity of the inner viral nuceloprotein and matrix proteins.[24] The H1N1 virus is Influenza A virus that belongs to the family of orthomyxoviruses, and has a segmented negative single-stranded RNA genome made of eight segments that each encodes 1-2 proteins necessary for virus attachment to host cells and spread of viral infection.[6] The novel Influenza-A subtype H1N1 is an apt example of how rapidly viruses evolve. All influenza viruses contain two surface antigens namely-hemagglutinin (H) and neuraminidase (N) and the viral strains are assigned an HxNx nomenclature based on which forms of these two proteins are present. There are 16 H and 9 N subtypes known in birds, of which only H-1, 2 and 3, and N-1 and 2 are commonly found in humans.[26] Haemagglutinin is an antigenic glycoprotein which causes erythrocytes to clump together. It is responsible for the binding of the virus to the cell that is being infected. Neuraminidases (also called sialidase) are glycoside hydrolase enzymes. They assist in the mobility of new virus particles through infected cells and in the budding from the host cells.[3]

The principal hosts of these influenza viruses are birds; influenza virus A causes infections to humans, swine and birds.[27] H1N1 was first reported in 1918 which caused enormous mortality.[28] Avian influenza viruses replicate less efficiently in humans and in other primates. In 1918, the influenza epidemic also swept through all 12 administrative districts of Taiwan in less than a month.[29] The viral structure differs from strain-to-strain due to rapid genetic mutation in the genome and newly identified strain H1N1 responsible for swine flu in humans is the latest add-on to the list.[30] H1N1, H1N2 and H3N2 subtype swine influenza viruses have occasionally infected humans before but such zoonotic transmission events did not lead to sustained human-to-human transmission in the manner this swine-origin influenza virus has done.[31]

TRANSMISSION

People who work with poultry and swine, especially those with intense exposures, are at increased risk of zoonotic infection with influenza virus endemic in these animals, and constitute a population of human hosts in which zoonosis and reassortment can co-occur.[32] The transmission is by droplet infection and fomites. Pigs are thought to have an important role in inter-species transmission of influenza, because they have receptors to both avian and human influenza virus strains (Figure.2).[34] Consequently, they have been considered a possible "mixing vessel" in which genetic material can be exchanged, with the potential to result in novel progeny viruses to which humans are immunologically naive and highly susceptible.[33]

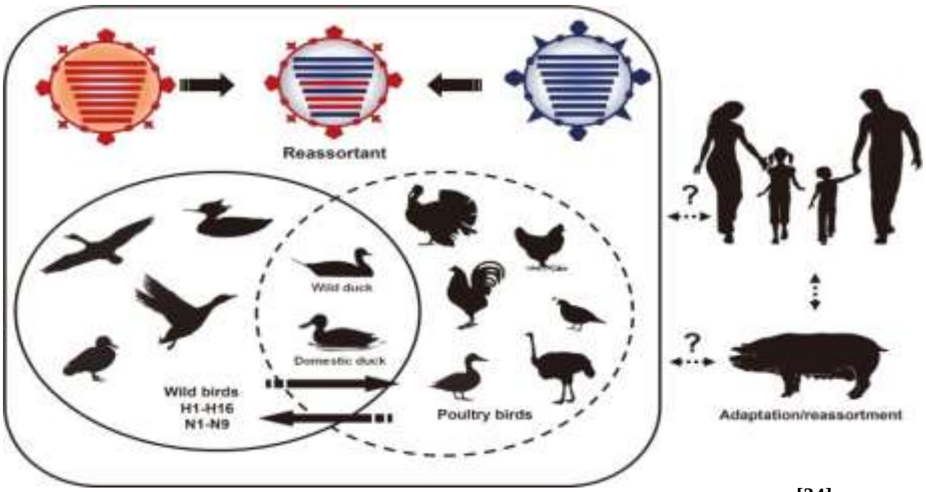

Figure.2: The Transmission of Influenza A Viruses [34]

The novel H1N1 influenza virus that emerged in humans in Mexico in early 2009 and transmitted efficiently in the human population with global spread has been declared a pandemic strain.[35] The virus has crossed the species barrier to humans, exhibits sustained human-to-human transmission and appears to retain the potential to transmit back to swine. Thus continued reassortment with swine viruses is a cause for concern. H1N1, H1N2, H3N2 subtype swine influenza viruses have occasionally infected humans before, but such zoonotic transmission events did not lead to sustained human-to-human transmission. Its transmission among humans appears to be higher than that observed with seasonal influenza.[4] Mostly children and young adults are infected and maintain transmission. Clinical disease generally appears mild; hospitalization occurred in patients with underlying lung or cardiac disease, diabetes or on immunosuppressive therapy.[36] Bidirectional transmission of influenza A viruses between swine and humans is facilitated by unique swine– human interfaces such as agricultural fairs, where swine from multiple sources commingle with human exhibitors and visitors.[37] Swine flu (H1N1) is a rapidly spreading influenza A virus transmitted between humans through coughing or sneezing or via contaminated hands or surfaces.[38]

CLINICAL FEATURES AND SYMPTOMS

Influenza-like illness is clinically defined by the abrupt onset of fever and respiratory symptoms, such as rhinorrhea, sore throat, and cough, often with myalgia or headache; therefore, the specificity of this clinical definition can be as low as 10% during non influenza seasons and as high as 80% during an outbreak period.[17] The typical symptoms of swine flu are a sudden fever of at least 38 ^{0}C and sudden cough with at least one other symptom of chills, lethargy, dehydration, headache, sorethroat, coryza, diarrhoea, vomiting, abdominal pain, myalgia or arthralgia (Figure.3).[40]

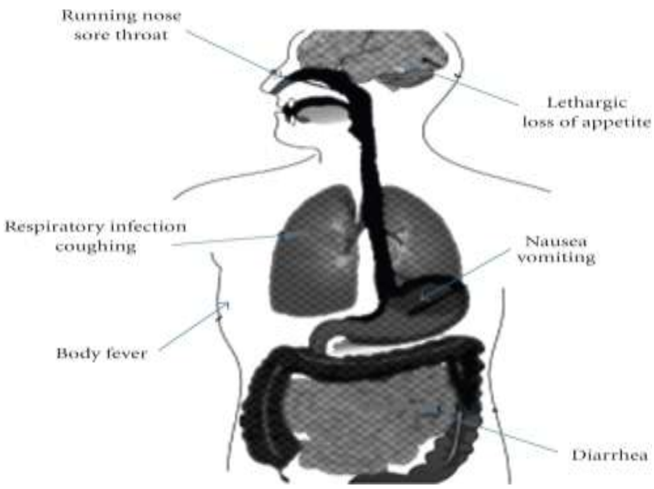

Figure.3: Symptoms of Swine flu due to novel H1N1 viral attack [40]

Gastro intestinal symptoms (vomiting and diarrhoea) have also been reported more often withH1N1 than with seasonal flu.[3, 41] Before 1918, influenza in humans was well known, but the disease had never been described in pigs. Similarities in the clinical presentations and pathologic features of influenza in humans and swine suggested that pandemic human influenza in 1918 was actually adapted to the pig, and the search for the causative agent began.[42] Such reassortment has created novel and important human pathogens, which vary in virulence and human transmissibility.[43]

DIAGNOSIS

The clinical features of influenza infection overlap with other respiratory infections; the diagnosis is often delayed due to low suspicion and the limited use of specific diagnostic tests [44].Routine investigations required for evaluation and management of a patient with symptoms as described above will be required. These may include hematological, biochemical, radiological and microbiological tests as necessary. A diagnosis of confirmed swine flu requires laboratory testing of a respiratory sample (a simple nose and throat swab). Tests used to detect influenza virus infections in humans can include RT-PCR, virus isolation and assays to detect influenza virus antigens.[45,46,47] Many recent swine influenza cases were diagnosed by genetic methods, particularly RT-PCR.[48]

Confirmation of Pandemic influenza A (H1N1) infection is through.

- Real time RT PCR or
- Isolation of the virus in culture or
- Four-fold rise in virus specific neutralizing antibodies.

Routine diagnostic tests used to detect human influenza viruses, including commercial rapid test kits, do not necessarily detect zoonotic viruses.[45, 46, 49] One indication that a novel, possibly zoonotic influenza, virus might be present is the detection of influenza A virus, but not the hemagglutinins in seasonal human influenza viruses.[45] Zoonotic influenza virus infections are occasionally diagnosed retrospectively by serology,[50,51] but serological diagnosis can be complicated by cross-reactivity with human influenza viruses. A further difficulty is that the HA and NA of some swine influenza viruses (the main targets of antibody responses) originally came from human influenza viruses, to which people may have already been exposed. Testing for novel influenza viruses is generally performed by state, regional or national public health laboratories.[45, 47] The diagnosis of influenza A H1N1 swine flu was performed by RT-PCR testing of nasopharyngeal-swab specimens collected on admission to hospital, according to published guidelines from U.S. Centers of Disease Control and Prevention (CDC protocol of real-time RTPCR for influenza A (H1N1).[52,54] The oral or nasal fluid collection and RNA virus preserving filter paper card is commercially available. This method allows a specific diagnosis of novel influenza (H1N1) as opposed to seasonal influenza. Near patient point of care tests are in development. Rapid case identification is essential for prompt patient management and public health actions. This study developed real-time and conventional reverse transcription-polymerase chain reaction (rRT-PCR and cRT-PCR) assays for pandemicH1N1 detection, and compared their sensitivities with protocols developed by WHO reference centres.[17, 55] The most accurate laboratory tests, such as real-time reverse transcriptase polymerase chain reaction (rRT-PCR) are only available in certain laboratories, and these tests can take several days to obtain results.The CDC Realtime RTPCR (rRTPCR) Protocol for Detection and Characterization of Swine Influenza includes a panel of oligonucleotide primers and duallabeled hydrolysis (Taqman ®) probes to be used in real-time RT-PCR assays for the in vitro qualitative detection and characterization of swine influenza viruses in respiratory specimens and viral cultures. The Influenza A primer and probe set is designed for universal detection of type A influenza viruses.[56] The Swine Influenza A primer and probe set is designed to specifically detect all swine influenza A viruses. The Swine H1 primer and probe set is designed to specifically detect swine H1 influenza. This assay is utilized for testing influenza A positive respiratory specimens (unsubtypable) taken from suspect swine influenza A infected patients.[53, 57]

PREVENTION

Prevention of swine influenza has three components: prevention in swine, prevention of transmission to humans, and prevention of its spread among humans.[58] Obviously, the most effective way to prevent any infectious disease pandemic is to invest in the improvement of social conditions. Tuberculosis is an excellent example. Data currently provided by the Global Influenza Surveillance Network are insufficient; they are not population based and therefore do not provide reliable data on disease severity, nor on case fatality.[59] Influenza vaccination is the primary method for preventing influenza and its severe complications. Flu can make some people much sicker than others. These people include young children, older, pregnant women and immunocompromised patients. Prevention and control measures for swine influenza are based on our understanding of seasonal human influenza and consideration of potential modes of transmission. Vaccination is associated with reductions in influenza related respiratory illness and physician visits among all age groups, hospitalization and death among persons at high risk, otitis media among children, and work absenteeism among adults.[39]

VACCINATION

Influenza transmission depends on multiple factors, including swine age, immunity, vaccination status and the presence of maternal antibodies. Vaccination is commonly used as a control measure for influenza in swine farms.[60] Vaccination has been shown to reduce influenza A virus transmission in pigs in experimental settings but the effects of vaccination at the farm level remain unclear.[61] In the aftermath of the 2009 pandemic, several studies were conducted to see who received influenza vaccines. These studies show that whites are much more likely to be vaccinated for seasonal influenza and for the H1N1 strain than African Americans.[62] Influenza viruses continuously undergo antigenic changes with gradual accumulation of mutations in hemagglutinin (HA) that is a major determinant in subtype specificity. The identification of conserved epitopes within specific HA subtypes give an important clue for developing new vaccines and diagnostics.[63]

The goal of immunization with the influenza vaccine is to generate antibodies to HA, because HA-specific antibodies neutralize the virus and provide protection against infection by circulating influenza virus. In contrast, the neuraminidase (NA) antigen of influenza is the target for the NA-inhibitor antivirals Oseltamivir and zanamivir, which played a vital role in managing 2009 H1N1 infections, preventing morbidity and mortality.[64]

The genetics of the virus are so novel that humans are unlikely to have much immunity to it, scientists say. The current seasonal flu vaccine, which targets a different H1N1 strain, also isn’t likely to offer any protection. During the H1N1 pandemic, rapid and accurate diagnosis for proper triage and empiric treatment with Oseltamivir were important.[65] Oseltamivir is known to shorten the duration of seasonal influenza by about 36 h in healthy children and to reduce the incidence of complications.[66] Although the current status of Oseltamivir in the treatment of H1N1 viral infection is controversial, the majority of studies have found it useful.[67] Surveillance is not just academic; it is key to getting early warnings of events that call for swift adaptations of control strategies. Swine flu is currently sensitive to the antiviral drug Oseltamivir (Tamiflu), for example, but seasonal H1N1 is resistant. Was the new virus to acquire resistance that would render redundant the Tamiflu stockpiled by many nationals part of their pandemic plans.[68] Antiviral drugs effective against H1N1 virus include Oseltamivir and Zamanavir and with good supportive care.[69]

Newly emerging Oseltamivir resistant influenza A H1N1 strains in 2007/2008 were any different from other circulating influenza strains in terms of patient characteristics, clinical picture or epidemiology. Following initial seeding in Luxembourg at the start of the season, Oseltamivir-resistant strains appear to have spread at a similar rate as Oseltamivir sensitive strains, i.e. antiviral drug resistance did not seem to affect fitness.[70] The drug Oseltamivir is to be administered orally within 48 hours of falling sick for best results. Delay in diagnosis and lack of availability of drug in public sector can contribute to the adverse outcome.[71] A single 15-µg dose of 2009 H1N1 vaccine was immunogenic in adults, with mild to moderate vaccine associated reactions. The side-effect profile of the H1N1 vaccine, particularly the frequency and severity of solicited and unsolicited adverse events, is consistent with our previous experience with seasonal influenza vaccines in adults.[72]

TREATMENT

If a person becomes sick with swine flu, antiviral drugs can make the illness milder and make the patient feel better faster. They may also prevent serious flu complications. For treatment, antiviral drugs work best if started soon after getting sick (within two days of symptoms). Beside antivirals, supportive care at home or in a hospital focuses on controlling fevers, relieving pain and maintaining fluid balance, as well as identifying and treating any secondary infections or other medical problems. The U.S. Centers for Disease Control and Prevention recommends the use of Oseltamivir (Tamiflu) or zanamivir (Relenza) for the treatment and/or prevention of infection with swine influenza viruses; However, the majority of people infected with the virus make a full recovery without requiring medical attention or antiviral drugs.[73] The virus isolated in the 2009 outbreak has been found resistant to Amantadine and Rimantadine.[74]

Treatment with Oseltamivir was associated with a reduction in days of fever, length of hospital stay, use of mechanical ventilation and mortality. Treatment was more effective if it was begun within the first 48 h after the onset of symptoms, but it was also useful if begun later. A safe and effective vaccine to prevent disease from this new influenza strain was available in developed countries soon after the pandemic began; thus, the rate of adverse effects was comparable to that of seasonal influenza vaccines.[75] The percentage of hospitalized patients receiving antiviral treatment prior to hospital admission and the time period between illness onset and AV receipt provides a reliable reflection of implementation of policy, providing a surrogate measure of policy efficacy. It can be inferred that the most effective policies would ensure that those at greatest risk of severe disease would have rapid access to antiviral medicines in the outpatient setting, prior to hospital admission.[73] An effective response to a pandemic requires at least 4 distinct elements. First, material resources, such as vaccines, antiviral drugs, and personal protective equipment are essential. Second, a commitment to planning, exercising, and refining plans is necessary. Third, a sufficiently large and robustly trained workforce is the basis of any response. Fourth, a commitment to improvement is crucial.[76]

DISCUSSION

Influenza viruses are able to infect humans, swine, and avian species, and swine have long been considered a potential source of new influenza viruses that can infect humans. H1N1 is an Influenza A virus. Influenza A viruses causes recurrent outbreaks at the local or global scale, with potentially severe consequences for human health and the global economy. Swine influenza virus infections in humans have been reported in the United States, Canada, Europe and Asia. There are no unique clinical features that distinguish swine influenza in humans from typical influenza. Although a number of the case patients have predisposing immune compromising conditions, healthy persons are also clearly at risk for illness and death from swine influenza. Sporadic cases of swine influenza in humans, combined with seroepidemiological studies demonstrating increased risk of swine influenza in occupationally exposed workers, highlight the crucial role that this group may play in the development of new strains of influenza virus. Persons who work with swine should be considered for sentinel influenza surveillance, and may be an important group to include in pandemic planning. Determination of infection with influenza virus is required, testing with r RTPCR or virus isolation should be performed. Additional evaluations of the accuracy of RIDTs (Rapid influenza diagnostic tests) in detecting novel influenza A (H1N1) virus should be conducted.

CONCLUSION

Swine flu refers to swine influenza or the viral infection caused by any of the several types of swine influenza virus. Only people who used to have direct contact with pigs were observed to get swine flu in the past. But, H1N1 virus is a new swine flu virus and it contains the genetic material of swine, bird and human influenza virus. Swine Flu is caused by influenza viruses, and is spread mainly by coughing, sneezing, and close contact. Flu can make some people much sicker than others. These people include young children, older, pregnant women and immunocompromised patients. Prevention and control measures for swine influenza are based on our understanding of seasonal human influenza and consideration of potential modes of transmission. As a result, the use of control strategies, especially vaccination, is critical for the control of influenza virus infections among domestic animals, to reduce their potential as sources for outbreaks among humans.

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