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Special Article

Swine- Origin Influenza A (H1N1) Pandemic Revisited

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Since the beginning of January 2008 sporadic cases of infections in humans caused by influenza A (H1N1) virus- resistant to available anti-influenza drugs have been reported worldwide [1,2]. The World Health Organization (WHO) in its report published on 18 March 2009 indicated that during weeks 1-4 (28 December 08-24 January 09), the level of overall influenza activity in the world increased. During this period, 1291 of 1362 A (H1N1) cases from 30 countries showed resistance to the antiviral drug osaltamivir. [3]. In Canada, United States of America, Japan, Republic of Korea, Hong Kong, France, Germany, Ireland, Sweden and United Kingdom the prevalence of oseltamivir resistance was reported to be more than 95% [3]. On 24 April WHO released the first alert indicating the occurrence of confirmed human cases of swine influenza (H1N1) in Mexico and the United States [4]. Subsequently the Centre for Disease Control and Prevention (CDC), in the United States confirmed that these human influenza cases were caused by a new strain of influenza A virus subtype (H1N1) [5].

With confirmation of sustained community level outbreaks in more countries- WHO Director-General, Margaret Chan, on 11 June 2009, decided to raise the alert level of influenza pandemic to Phase 6, the maximum level, signaling that the first pandemic of the twenty-first century was underway [6]. It was however stressed that the rise in pandemic alert level, was mainly attributed to the global spread of the virus, not its severity which can be mild, moderate, or severe. Influenza A viruses are medically important respiratory pathogens that cause both seasonal, endemic infections, and periodic, unpredictable pandemics [7]. The pandemic potential of Influenza A viruses have been ascribed to their host –range diversity, their genetic and antigenic diversity, and their ability to transform by constant genetic reassortment or spontaneous mutation [8].This can result in the emergence of novel progeny subtypes capable of both infecting and leading to sustained person-to- person transmission - to which there is little or no population immunity [7,8].

Since 1700, there have been approximately a dozen influenza A virus pandemics; the past 100 years has witnessed three pandemics in 1918, 1957, and 1968 (Table1) [9,10].The most famous and lethal outbreak of 1918, the so called "Spanish flu ", is dubbed as " the greatest medical holocaust in recorded history" and killed up to 50 million people worldwide [11]. As of 26 June 2009, the new influenza H1N1 virus has infected 55,867 people, and 238 deaths have been reported from 108 countries [12]. The United States has nearly half of the worlds swine influenza cases with nearly 21449 reported to CDC [12].

A plethora of names was coined to describe the virus and outbreak ; "Swine flu", "Pig flu"," Mexican flu"," Mexican virus" , "H1N1 flu", "New flu", "North American influenza", and "Novel influenza A (H1N1)" to name a few [10]. "Swine flu names are evolving faster than the swine flu itself," says Martin Ensernick, the noted science reporter on the chaos over the nomenclature [13]. The WHO announced that they would refer to the new influenza virus as" Influenza A (H1N1)" or "Influenza A (H1N1) virus, human" as opposed to "swine flu" also to clear the misconception that eating pork products carried a risk of infection [14].

Influenza viruses are enveloped negative-stranded RNA viruses with segmented genomes containing seven to eight gene segments and belong to the orthomyxoviridae family [15]. Distinguished by their internal and external proteins they are divided into three types (A, B and C). The three viruses differ in host range and pathogenicity [7]. Influenza B and C viruses are principally human

pathogens. However, influenza A viruses infect a variety of warm-blooded animals, primarily aquatic birds and sometimes other animal hosts, including swine, horses, cats, dogs and humans [16]. The type A viruses are the most virulent human pathogens among the three influenza types - cause the most severe of disease, and are often implicated in annual epidemics and occasional pandemics [7]. The influenza A viruses are classified into subtypes on the basis of antigenic characterization of the hemagglutinin (HA) and neuraminidase (NA) surface glycoproteins that project from the virion. Sixteen HA and three NA subtypes are recognized in nature, but only four 4HAs (H1, H2, H3, and H5) and 2NAs (N1 and N2) have been recorded thus far in epidemic and pandemic influenza A viruses [17].

Table 1: Influenza pandemics of the 20th and 21st century

Name of Pandemic	Year	Interval (yr)	Deaths	Subtype involved
Spanish flu	1918	18	40-80 million	H1N1
Asian flu	1957	39	I –1.5 million	H2N2
Hong Kong flu	1968	11	0.75-1 million	H3N2
Influenza A(H1N1)	2009	41	238*	H1N1

* As of 26 June 2009

There have been a lot of controversies and theories regarding the origins of the 2009 outbreak of new influenza A (H1N1). Did the virus have a natural origin? "A novel assembly of gene segments- by genetic exchange or spontaneous mutation"? Or, was it the product of a bio-experimental lab? "It might have been created using eggs to grow viruses and make new vaccines, and could have been accidentally leaked to the general public" says Australian researcher and antiviral drug "Tamiflu" developer Adrain Gibbs [18]. However, emerging scientific data support the hypothesis of a "natural genesis" with domestic pigs in North America playing a central role in the generation and maintenance of this virus. Protein homology analysis of more than 400 protein sequences including polymerase proteins PB2, PB1, and PA, HA, matrix 1(MP1), nonstructural 1(NS1) encoded by the new influenza A (H1N1) virus as well as other homologous proteins from influenza viruses from past flu seasons revealed that this virus has a swine lineage [19].

Phylogenetic analysis confirms the genetic distinctness, that seems to be characteristic in pig-human interspecies transmission of influenza A [19]. Cluster analysis of nucleotide sequences of the present-and viruses previously identified in humans, birds and swine indicate that the 2009 pandemic influenza A (H1N1) virus is a genetic reassortment of at least two swine viruses from North America and Eurasia [20]. The viruses are antigenically distinct from seasonal human A (H1N1), and possess previously unrecognized molecular determinants that could be responsible for the rapid human -to-human transmission [21]. Using evolutionary analysis to estimate the timescale of the origins, Smith and his research team from The University of Hong Kong, report that - exchange of genetic material of swine lineages may have occurred several years before human emergence. Their results published in "Nature" suggest initial transmission to humans occurred several months before recognition of the outbreak, and that the multiple genetic ancestry of this influenza A (H1N1) is not indicative of an artificial origin [22].

The biology of influenza A viruses is very complicated and pigs are thought to have a major role in inter-species transmission and generation of novel influenza strains [23,24]. Cells surface receptors of pig respiratory tract have oligosaccharides with sialic acid linked α2, 3 or α 2, 6 to the penultimate galactose, which have a broad specificity for influenza viruses [25].The former are preferred by most avian influenza viruses and latter by human viruses. These receptors make the pigs susceptible for infection with both avian and human viruses-which is an important determinant of host range restriction, and also providing an environment for the adaptation of avian HAs (HA anchors the virus to receptors) to acquire human α 2, 6 specificity [23,25]. Co-

infection combined with co-habitation of swine and poultry on small family farms worldwide has led to the "mixing vessel theory"- which suggests pigs may act as a mixing vessel for the reassortment of avian, swine and human viruses and generation of new "hybrid" pandemic viruses [23]. However, this threat posed by pigs seems to have been overlooked by policy makers and the scientific community- with their focus mainly on the prevention and control on avian A (H5N1) influenza [19].

Diagnostic tests for rapid detection and differentiation are urgently needed for early detection in suspected patients, prompt patient management, containing the disease, its surveillance, and allowing better pandemic preparedness. A limited number of standardized laboratory tests exist for the diagnosis of H1N1 infection. The WHO defines a probable clinical case as one that is confirmed by 1. Specific reverse transcription – time polymerase chain reaction (RT-PCR) assays, 2. Isolation of the novel H1N1 influenza virus, or 3. Detection of a fourfold rise of neutralization antibodies to this virus [26]. Detection of viral RNA by RT-PCR appears to be highly sensitive and can discriminate the novel H1N1 from other swine and H1 subtype viruses; this is the rapid test of choice for suspected influenza A(H1N1) illness [27]. Conventional 1-step RT-RCR assay and 1-step quantitative real- time RT-PCR assay to detect the present virus rapidly have been recently developed [27,28].

Prevention is better than cure. Vaccines are widely considered to be the first defense for providing advance protection against an influenza pandemic [29]. However, the effectiveness of influenza vaccines is arguable. The genes of the influenza viruses have high mutation rates and mutations that change amino acids in the antigenic portions of surface glycoproteins help to evade preexisting immunity." It would take years to produce an effective swine flu vaccine to meet global demands" says Greg Poland, head of the vaccine research program at the Mayo Clinic [30]. Neuraminadase inhibitors (oseltamivir and zanamivir), and M2 inhibitors (amantadine and rimantadine) are the currently available antiviral drugs to halt the spread of the virus in the body [31,32]. Development of new antiviral drugs is of paramount importance since currently circulating influenza virus strains have shown high frequencies of resistance to M2 inhibitors and variable frequency of resistance to oseltamivir among A (H1N1) strains [33]. The enzymatic properties and crystal structures of oseltamivir-resistant influenza virus neuraminidase mutants has recently been elucidated-which may hasten the development of more effective antiviral drugs [34]. New antiviral agents including polymerase inhibitors (I-705) and an attachment inhibitor (DAS181) are also currently being developed [33].

Influenza A viruses represent a major health threat in both endemic and pandemic forms. "The virus writes the rules and this one, like all influenza viruses, can change the rules, without rhyme or reason, at any time," says. Margaret Chan, Director-General of WHO [6]. The management of the present influenza pandemic needs a rational and pragmatic approach-based on the expert advice and recommendations of influenza experts, virologists and public health officials. Lessons must be learnt from the previous epidemics and pandemics. The H1N1 pandemic of 1918 killed millions. Humanity as a whole needs to fight back now to avert a similar catastrophe.

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