DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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Influenza Risk Assessment Tool (IRAT) - Virus Report

Prepared by the CDC Influenza Division

Eurasian avian-like swine influenza A(H1N1) virus
Virus Strain: A/swine/Shandong/1207/2016; HA clade 1C.2.3; Genotype 4
Date of Evaluation: July 2020

Introduction

Human infections with influenza A viruses that commonly circulate in animals are rare and the risk of such infections to humans is generally low [1]. Sporadic human infections with animal influenza A viruses do occur, but typically in situations where individuals are exposed to infected animals through direct or indirect contact or to virus- contaminated environment. The Influenza Risk Assessment Tool (IRAT) [2] is used to examine multiple attributes of influenza A viruses that circulate in animals but have not gained the ability to spread by human-to-human transmission, and to assess the potential of these viruses to acquire this ability and the consequent potential public health impact.

Situation

Human infections with Eurasian avian-like swine influenza A(H1N1) viruses (EA SIV H1N1) have been reported occasionally in China [3]. Some infected persons reported direct or indirect exposure to swine. EA SIV H1N1 were first reported in Europe in 1979 [4] and first reported in China in 1993 [5]. Decades of viral evolution and spatial segregation have resulted in multiple clades of EA SIV H1N1 in European and Asian swine populations that are formally classified as clade 1C based on their H1 HA gene [6]. The nomenclature further delineates viruses found in China as belonging to clade 1C.2.3. Additionally, multiple genotypes have been identified in China as a result of reassortment with other SIVs including the 2009 pandemic A(H1N1)pdm09 virus that now circulates in global swine populations.

While many EA SIV H1N1 genotypes have now been described, a recent paper by Sun et al. described six genotypes (designated G1-G6) detected in China between 2011 and 2018 [3]. The paper identified one genotype, G4, that has been predominant in swine in China since 2016, and resulted in 3 known virologically confirmed human infections [3,7]. The G4 EA SIV H1N1 virus has been reported to show efficient infectivity and transmissibility in the ferret model, and in a study in China found that antibody titers against G4 viruses were more common in swine workers compared with the general population, suggesting that additional human infections have occurred [3]. Full genome sequences of the G4 viruses indicated the presence of EA SIV H1N1 HA and NA genes with a unique combination of internal genes including A(H1N1)pdm09 virus PB2, PB1, PA, NP and M genes and a triple reassortant NS gene.

Using the IRAT [2], the Centers for Disease Control and Prevention (CDC) assessed the pandemic potential of a representative strain of HA clade 1C.2.3, G4 genotype EA SIV H1N1 virus.

IRAT Evaluation

Influenza subject matter experts (SMEs) from CDC, Food and Drug Administration (FDA), Animal and Plant Health Inspection Service (APHIS), and Agricultural Research Service (ARS) were asked to evaluate the HA clade 1C.2.3, G4 genotype EA SIV H1N1 virus strain, A/swine/Shandong/1207/2016, using the ten risk elements defined in the IRAT. Each SME scored 1 to 3 elements based on their areas of expertise. The point estimate scores for each risk element were averaged, multiplied by predetermined weights, and summed to give an aggregate score for each of the two IRAT risk questions related to potential risk for emergence in humans and potential public health impact if the virus gained the ability to spread efficiently between humans [2].

With point scores ranging from 1 to 10, the average risk score for the potential emergence of swine influenza A/swine/Shandong/1207/2016 virus was 7.5. Emergence refers to the ability of the virus to achieve sustained human-to-human transmission (Table 1), and this score places the virus in the upper moderate risk category, which ranges from 4.0 to 7.9. The average risk score for the virus to potentially impact public health if it were to achieve sustained human-to-human transmission was 6.9 (Table 2). The impact refers to the severity and burden of disease, and this score was also in the upper moderate risk range. Overall, the virus is categorized in the upper moderate risk range. The scores for this virus for emergence was highest, and for public health impact was third highest, when compared to all other viruses scored on the IRAT to date.

Variability was not seen among SME point estimate scores in any of the risk element categories, in which the scores ranged from moderate to high risk, suggesting consistent interpretation of the available data.

Table 1: Estimated Risk of Emergence

Risk Element	**Weight (W)**	**Risk Score (RS)**	**W X RS**
Human Infections	0.2929	6.20	1.82
Transmission in Animal Models	0.1929	9.00	1.74
Receptor Binding	0.1429	8.25	1.18
Population Immunity	0.1096	8.33	0.91
Infections in Animals	0.0846	8.33	0.71
Genomic Analysis	0.0646	8.00	0.52
Antigenic Relatedness	0.0479	5.40	0.26
Global Distribution in Animals	0.0336	5.40	0.18
Disease Severity and Pathogenesis	0.0211	6.00	0.13
Antiviral Treatment Options	0.0100	6.67	0.07
TOTAL	**1.0001**		**7.50**

Table 2: Estimated Potential Public Health Impact Risk

Risk Element	Weight (W)	Risk Score (RS)	W X RS
Disease Severity and Pathogenesis	0.2929	6.00	1.76
Population Immunity	0.1929	8.33	1.61
Human Infections	0.1429	6.20	0.89
Antiviral Treatment Options	0.1096	6.67	0.73
Antigenic Relatedness	0.0846	5.40	0.46
Receptor Binding	0.0646	8.25	0.53
Genomic Analysis	0.0479	8.00	0.38
Transmission in Animal Models	0.0336	9.00	0.30
Global Distribution in Animals	0.0211	5.40	0.11
Infections in Animals	0.0100	8.33	0.08
TOTAL	**1.0001**		**6.85**

Individual Risk Element Summaries

Human Infections: Three sporadic, symptomatic virologically confirmed human infections in China have been reported, none with known epidemiologic links to swine exposure. There is serologic evidence of infection in occupationally exposed individuals and in the general population in limited areas in China, potentially supporting more widespread than sporadic infections. There are no reports of human-to-human transmission. Together these criteria meet the definition of moderate risk to humans for this element.

Transmission in Animal Models: In ferret studies, there was efficient direct transmission of virus through both contact and droplet spread. The M gene segment of the influenza A(H1N1)pdm09 virus, which is also in this EA SIV H1N1 virus, has been associated with indirect transmission through airborne spread in animal models. Together these data indicate high risk to humans for this element.

Receptor Binding: The A/swine/Shandong/1207/2016 and three other G4 viruses showed clear preference for binding to alpha-2,6 sialic acid receptors, characteristic of viruses that transmit human to human. Also, most G4 viruses contain amino acids characteristic of the principal receptor binding domain motifs which confer preference to human receptors. Together these data indicate high risk to humans for this element.

Population Immunity: Data suggest that the pre-existing population immunity to this virus is likely low (<10%). Also, serum antibodies in children immunized with a trivalent influenza vaccine reacted poorly against A/swine/Shandong/1207/2016 virus, with HAI titers <40. Together these data indicate high risk to humans for this element.

Infections in Animals: Endemicity of A/swine/Shandong/1207/2016 virus in China is established in domestic swine, a species in close contact with humans; sustained transmission is not known in other species. Together, this virus meets the criteria for high risk to humans for this element.

Genomic Analysis: The A/swine/Shandong/1207/2016 virus has genetic reassorted with human or other mammalian viruses, and molecular signatures of importance for human disease, indicating high risk to humans for this element.

Antigenic Relatedness: The virus was not antigenically related to seasonal human A(H1N1)pdm09 virus vaccines. The G4 and G5 viruses are antigenically closely related, suggesting the G5 pre-pandemic candidate vaccine virus (CVV) may provide adequate cross-reactivity with G4 viruses. Together indicating a moderate risk to humans for this element.

Global Distribution in Animals: Distribution of the virus is regional within China and within well-defined geographic or territorial boundaries that may be explained by movement of animals due to commerce. Controlling the distribution of the viruses in swine populations, and swine population density and management control efforts, do not effectively contain the virus. Together these data indicate a moderate risk to humans for this element. However, swine influenza is not a reportable disease internationally and varied surveillance and reporting systems limit clear knowledge of the extent of the geographic distribution of G4 genotype EA SIV H1N1 viruses.

Disease Severity and Pathogenesis: The G4 virus genotype caused disease in ferrets (up to 10% weight loss, 100% morbidity) and replicates in human lung cells. The human serology study indicated about 10% of swine workers may have been infected, but disease was not severe enough for individuals to seek medical attention, suggesting infection may be mild or subclinical in most individuals. Together these data indicate moderate risk to humans for this element.

Antivirals and Treatment Options: The virus has markers suggesting it is resistance to adamantanes; however, there are no known substitutions associated with reduced susceptibility to neuraminidase inhibitors nor known markers of reduced susceptibility to baloxavir. These data indicate moderate risk to humans for this element.

Comparison to other Viruses Scored with IRAT

The scores for the emergence risk and potential public health impact risk for the A/swine/Shandong/1207/2016 virus were plotted along with a selection of 10 other influenza viruses scored using the IRAT (Figure). The A/swine/Shandong/1207/2016 virus falls in the upper moderate risk range for both risk of emergence and potential impact. The score for the risk of emergence is the highest of all viruses evaluated to date with the IRAT and for public health impact is the third highest virus evaluated.

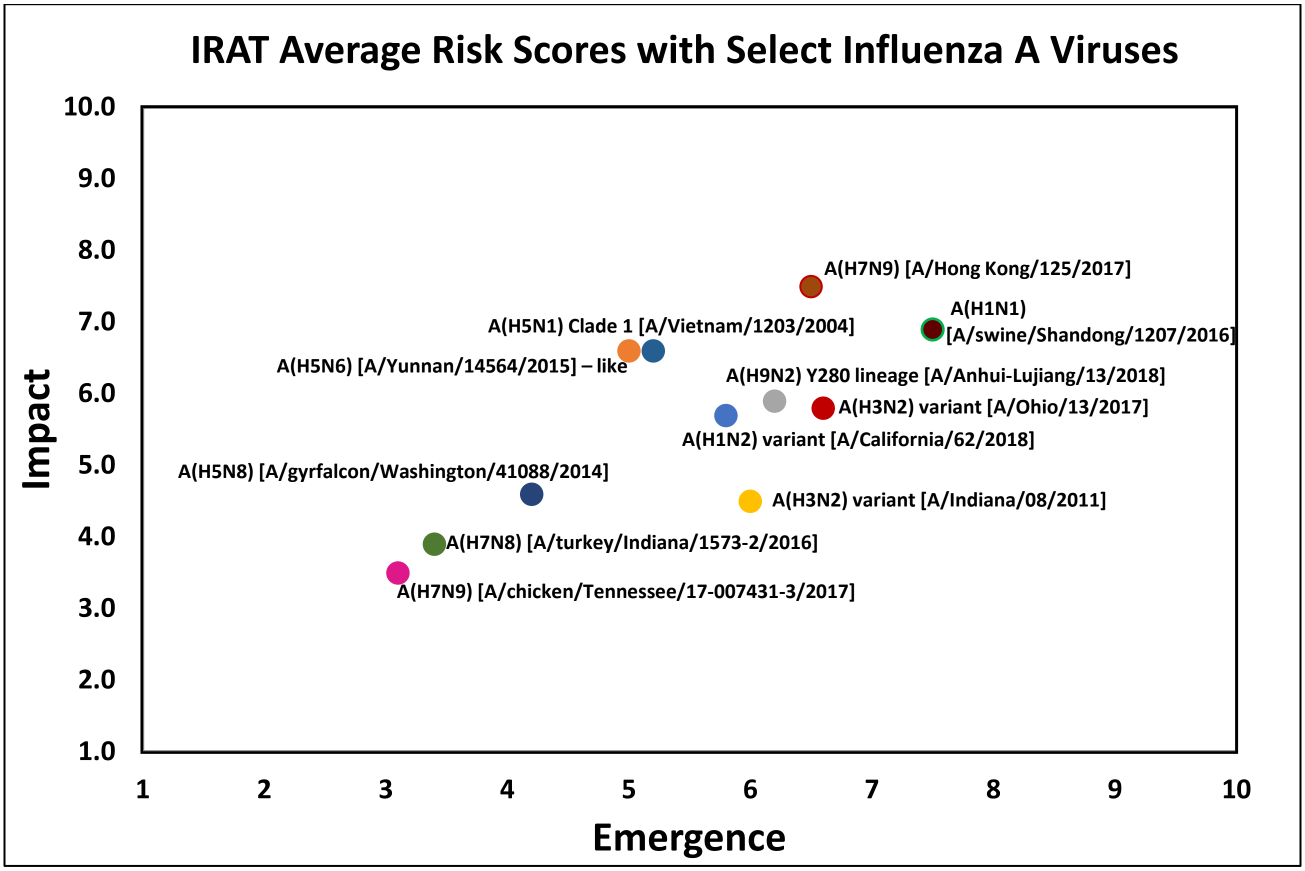

Figure: Average IRAT scores for A/swine/Shandong/1207/2016 plotted by emergence score and impact score. Additional select viruses scored using IRAT are displayed for comparison.

Note: IRAT results were generated using information and data known to influenza subject matter experts at the time of the evaluation. Subsequent findings may raise or lower the overall risk scores associated with the virus.

References

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