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Cases of Swine Influenza in Humans: A Review of the Literature

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Abstract

As the threat of a pandemic looms, improvement in our understanding of interspecies transmission of influenza is necessary. Using the search terms "swine," "influenza," and "human," we searched the PubMed database in April 2006 to identify publications describing symptomatic infections of humans with influenza viruses of swine origin. From these reports, we extracted data regarding demographic characteristics, epidemiological investigations, and laboratory results. We found 50 cases of apparent zoonotic swine influenza virus infection, 37 of which involved civilians and 13 of which involved military personnel, with a case-fatality rate of 14% (7 of 50 persons). Most civilian subjects (61%) reported exposure to swine. Although sporadic clinical cases of swine influenza occur in humans, the true incidence of zoonotic swine influenza virus infection is unknown. Because prior studies have shown that persons who work with swine are at increased risk of zoonotic influenza virus infection, it is prudent to include them in pandemic planning efforts.

Influenza as a disease of pigs was first recognized during the Spanish influenza pandemic of 1918–1919. Veterinarian J. S. Koen was the first to describe the illness, observing frequent outbreaks of influenza in families followed immediately by illness in their swine herds, and vice versa [1]. Influenza virus was first isolated from pigs in 1930 by Shope and Lewis [2], with the virus isolated from humans several years later [3]. The first isolation of a swine influenza virus from a human occurred in 1974 [4], confirming speculation that swine-origin influenza viruses could infect humans.

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 [5]. 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 [6,7]. As the threat of a pandemic due to highly pathogenic H5N1 avian influenza virus strains looms, a better understanding of inter-species transmission of influenza is necessary. We reviewed the literature to compile and summarize all reported cases of human infection with swine influenza virus.

METHODS

Search strategy

In April 2006, we searched the PubMed database, without any language restriction, using the search terms "swine," "influenza," and "human," to find reports describing cases of human

Potential conflicts of interest. All authors: no conflicts.

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infection thought to be caused by swine influenza virus strains. Additional articles were identified through the reference sections of the studies retrieved.

Selection of studies

The titles and abstracts of all identified studies were reviewed using the following inclusion criteria: there was mention of ≥ 1 case of influenza-like illness in humans and there was isolation of virus or serological evidence of swine influenza virus infection. Seroprevalence studies were not included.

Data analysis

Discrete data for analysis were extracted from included studies. When data were not available from the article, attempts were made to contact study authors and state health departments for missing information. Statistical analyses (counts and proportions) were made using spreadsheet software.

RESULTS

The initial PubMed search strategy retrieved 735 studies. Of these, 70 articles were selected for review because they mentioned cases of influenza-like illness in humans and included laboratory evidence of infection. The remaining 665 articles were not relevant to this review. Four additional studies were identified through the reference sections of the selected articles. One case was found as a part of an ongoing prospective study of zoonotic influenza in farmers at the University of Iowa's Center for Emerging Infectious Diseases (Iowa City) [8]. We identified 37 civilian [4,8–30] and 13 military cases [11,31–34] of human influenza associated with swine influenza virus strains, spanning the years 1958–2005. Five possible cases were not included because individual information was unavailable, and it was unclear whether they represented additional cases or duplicates [27]. Civilian and military cases are presented separately.

Civilian cases

Nineteen cases were reported in the United States [4,8,10–18,21,22,25–27], 6 in Czechoslovakia, [9] 4 in The Netherlands [20,23,24], 3 in Russia [19], 3 in Switzerland [20, 29], 1 in Canada [30], and 1 in Hong Kong [28] (table 1). Of the US cases, 6 occurred in Wisconsin [10,11,14,15,21,25], 3 in Minnesota [4,16,26], 2 in Virginia [11], 2 in Texas [17], 1 in Nevada [18], 1 in Missouri [13], 1 in Iowa [8], and 1 in Maryland [22]. One subject was evaluated at St. Jude Children's Research Hospital in Memphis, Tennessee, after referral for Hodgkin lymphoma, but the home state of the patient was not recorded [12]. Six cases occurred in the summer months [4,22,24,25,30], and 29 occurred between September and March [8– 15,17–21,23,26,28,29] (data were not available for 2 cases). There were 22 cases in male patients [4,8-15,17,19-23,27,29,30] and 13 in female patients [9,11,18,19,21,23-26,28] (data were not available for 2 patients). The median age of the patients was 24.5 years. Twenty-two (61%) of the case patients reported a recent exposure to pigs [4,8-12,14-17,19-22,24-26,29, 30], whereas 14 had no known swine exposure [9,11,13,18–20,23,28]. Of those with known exposure to swine, 2 were laboratory workers who acquired accidental infection while working with sick pigs under what were described as biosafety level 3 conditions [25]. Two others were employed in a research facility [9,22], 2 were visitors at a county fair [21] or livestock show [17], 1 was a livestock show swine barn attendant [17], and 1 worked at a meat-packing house [12]. Thirteen had occupational exposures to pigs through living or working on swine farms [4,8,10,11,14–16,19,20,24,26,29,30]. The nature of swine exposure for 1 patient was not available [16]. Of the 14 with no known exposure to swine, 5 were family members of case patient 1 and represented a cluster of person-to-person transmission [9]. Of the 9 remaining

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case patients without known exposure to swine, isolates confirmed the diagnosis for 7 [18–20,23,28].

Twenty of the subjects were described as healthy (table 2) [8–11,17,20,22–26,30]. Among those with underlying medical conditions, 1 had asthma [20], 2 had Hodgkin disease [4,12], 1 had acute lymphocytic leukemia in remission [18], 1 had a history of chronic bronchitis and splenectomy [11], 1 had thrombocytopenia [9], and 1 was pregnant [21]. Medical histories were unavailable for 10 case patients. All case patients were described as having pneumonia, upper respiratory infection, or acute respiratory disease.

Six (17%) of the infected persons died [4,18,19,21,22,26]. No information about outcome was available for 2 cases [16,27]. All of those who died had pneumonia: 4 had viral pneumonia with influenza the only pathogen isolated [18,21,22,26], whereas 1 had *Streptococcus viridans, Neisseria* species, and *Klebsiella* isolated in addition to influenza virus [4]. Case patient 19 also had extensive abdominal organ involvement, with mesenteric vessel thrombosis, small bowel gangrene, and peritonitis [19]. Case patient 32 had a hemophagocytic syndrome related to disrupted immune regulation [26]. Of the 6 who died, 1 had leukemia [18], 1 had Hodgkin disease [4], 1 was pregnant [21], and 2 were previously healthy [22,26]; information regarding underlying illness was unavailable for 1 patient [19].

H3N2 viruses were isolated in 4 cases [23,28,30]; the remainder involved H1N1 viruses [4, 8–22,24–27,29]. Human-avian reassortant swine viruses were isolated from 2 cases from The Netherlands [20,23,24], 2 in the United States [8,27], and 1 in Canada [30]. The first human case of infection with an H3N2 virus of swine origin was reported in The Netherlands in 1992 [23]. None of the cases of H3N2 virus infection were fatal. Eleven of the diagnoses of zoonotic swine influenza virus infection were based on serological studies [9–13], and 26 were confirmed by isolation of virus [4,8,14,15,17–30]. Epidemiological investigation revealed probable human-to-human transmission in the cluster in Czechoslovakia, when 5 family members became ill after exposure to the index case [9]. It was also determined that probable human-to-human transmission occurred when several health care workers developed an influenza-like illness after caring for a pregnant woman who later died of swine influenza [21,35]. Possible human-to-human transmission occurred in 5 cases [10,17,18,23], and there was no evidence of human-to-human transmission in 16 cases [4,8,11–13,15,17,19,22,25,28, 29].

Fort Dix cases

An outbreak of swine influenza A due to an H1N1 virus resulted in 1 death and respiratory illness in 12 additional soldiers at Fort Dix, New Jersey, causing hospitalizations over a 22-day period in early 1976 [31]. No evidence of exposure to pigs was ever found. The average age of the patients was 18, and all were male subjects in previously good health. Five diagnoses were confirmed by isolation of the virus, and 8 were based on serological studies performed retrospectively. A subsequent epidemiological investigation revealed that up to 230 soldiers were infected with the virus [32].

DISCUSSION

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 had predisposing immunocompromising conditions, healthy persons are also clearly at risk for illness and death from swine influenza. The high proportion of fatalities in this case series likely reflects a strong case ascertainment bias. The majority of case patients reported contact with pigs, consistent

with seroepidemiological studies that have demonstrated increased rates of swine influenza virus infection in people with occupational swine exposure [36–38].

Bias resulting from heightened awareness and increased surveillance soon after the 1976 Fort Dix episode may have resulted in a transient increase in identification of cases that would otherwise have been attributed to human influenza. Of the 6 North American cases after 1982, 3 were identified because the cases were fatal in healthy young subjects and because a cause was actively pursued. Two cases occurred in laboratory workers with known exposure to swine influenza, so the index of suspicion was high. Therefore, it is likely that nonfatal cases of swine influenza continue to occur but are not identified. Furthermore, fatal cases may be missed when they occur in persons with predisposing conditions in whom death due to influenza would not be unusual.

Persons who work with swine may play an important role in the mixing of influenza virus strains, leading to reassortment and development of novel progeny strains with pandemic potential. People with exposure to pigs may be among the first to be infected in the event of a novel virus becoming epizootic in swine herds, and those who work with swine may serve as a bridge for transmission of the virus to their communities [39]. A policy of vaccinating swine workers annually with human influenza vaccine would decrease the risk of reassortment events.

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.

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 Table 1

 Demographic and exposure data for 37 patients with swine influenza virus infection.

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Dacso [17] Patriarca et al. [19] Chuvakova et al. [19] Chuvakova et al. [19] Chuvakova et al. [19] Chuvakova et al. [19] Mos et al. [20] McKimey et al. [20] McKimey et al. [21] Wentworth et al. [22] Rimmelzwaan et al. [22] Wentworth et al. [25] Wentworth et al. [25] Yes	nt				
Patriarca et al. [18]NoChuvakova et al. [19]NoChuvakova et al. [19]NoChuvakova et al. [19]NoChuvakova et al. [20]Node Jong et al. [20]Yesde Jong et al. [20]YesMentworth et al. [22]YesWentworth et al. [23]NoClaas et al. [23]NoRimmelzwaan et al. [25]YesWentworth et al. [25]YesKimura et al. [26]Yes	Livestock show visitor	6 M	February	1980	Texas
Chuvakova et al. [19] Yes Chuvakova et al. [19] No Chuvakova et al. [19] No de Jong et al. [20] Yes de Jong et al. [20] Yes McKinney et al. [21] Yes Wentworth et al. [22] Yes Claas et al. [23] No Claas et al. [23] No Claas et al. [23] Yes Wentworth et al. [25] Yes Wentworth et al. [25] Yes	No known swine exposure			1982	Nevada
Chuvakova et al. [19] No Chuvakova et al. [19] No de Jong et al. [20] Yes de Jong et al. [20] Yes de Jong et al. [20] No de Jong et al. [21] Yes McKimey et al. [22] Yes Claas et al. [23] No Claas et al. [23] No Rimmelzwaan et al. [24] Yes Wentworth et al. [25] Yes	Occupational exposure		November	1983	Russia
Chuvakova et al. [19] No de Jong et al. [20] Yes de Jong et al. [20] Yes de Jong et al. [20] Yes McKimey et al. [21] Yes Wentworth et al. [22] Yes Rimmelzwaan et al. [24] Yes Wentworth et al. [25] Yes Wentworth et al. [25] Yes	No known swine exposure		December	1983	Russia
de Jong et al. [20] de Jong et al. [20] de Jong et al. [20] McKimey et al. [20] Wentworth et al. [22] Claas et al. [22] Rimmelzwaan et al. [24] Wentworth et al. [25] Wentworth et al. [25] Yes	No known swine exposure			1983	Russia
de Jong et al. [20] de Jong et al. [20] McKimey et al. [21] Wentworth et al. [22] Claas et al. [22] Rimmelzwaan et al. [24] Wentworth et al. [25] Wentworth et al. [25] Yes	Occupational exposure		January	1986	Switzerland
de Jong et al. [20] McKinney et al. [21] Wentworth et al. [22] Claas et al. [22] Claas et al. [23] Rimmelzwaan et al. [24] Wentworth et al. [25] Wentworth et al. [25] Yes	No known swine exposure			1986	Switzerland
McKimey et al. [21] Yes Wentworth et al. [22] Yes Claas et al. [23] No Claas et al. [23] No Rimmelzwaan et al. [24] Yes Wentworth et al. [25] Yes Wentworth et al. [25] Yes	tional exposure			1986	Netherlands
Wentworth et al. [22] Yes Claas et al. [22] No Claas et al. [23] No Claas et al. [23] No Rimmelzwaan et al. [24] Yes Wentworth et al. [25] Yes Kimura et al. [26] Yes	untv fair)			1988	Wisconsin
Claas et al. [23] No Claas et al. [23] No Rimmelzwaan et al. [24] Yes Wentworth et al. [25] Yes Kimura et al. [25] Yes	Animal caretaker (swine	27 M		1991	Marvland
Claas et al. [23] No Claas et al. [23] No Rimmelzwaan et al. [24] Yes Wentworth et al. [25] Yes Wentworth et al. [25] Yes	.e)				•
Claas et al. [23] No Rimmelzwaan et al. [24] Yes Wentworth et al. [25] Yes Wentworth et al. [25] Yes	No known swine exposure		November	1992	Netherlands
Rimmelzwan et al. [24] Yes Wentworth et al. [25] Yes Wentworth et al. [25] Yes Kimura et al. [26] Yes	No known swine exposure			1993	Netherlands
Wentworth et al. [25] Yes Wentworth et al. [25] Yes Kimura et al. [26] Yes	n swine farm			1993	Netherlands
Wentworth et al. [25] Yes Kimura et al. [26] Yes	Laboratory workers exposed to	39 M		1994	Wisconsin
Wentworth et al. [25] Yes Kimura et al. [26] Yes	S				
Kimura et al. [26] Yes	Laboratory workers exposed to	31 F	August	1994	Wisconsin
Kimura et al. [26] Yes	S				
	Occupational exposure	37 F		1995	Minnesota
Cooper et al. [27] NA				1998	United States
Gregory et al. [28] No	No known swine exposure			1999	Hong Kong
Gregory et al. [29]	armer			2002	Switzerland
Gray et al. [8]	armer	50 M		2005	Iowa
[0	armer			2005	Canada

NOTE. CDC, Centers for Disease Control and Prevention; NA, not available.

^aPatient was aged 10 months.

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Laboratory an	Laboratory and clinical data for 37 patients with	Table 2 ents with swine influenza virus infection.	Table 2 nfection.			
Patient	Reference	Underlying illness	Vital status	Laboratory study	Subtype	Person-to- person transmission
_	Kluska et al. [9]	Healthy	Recovered	Serology	HINI	Probable
2	Kluska et al. [9]	Healthy	Recovered	Serology	HINI	Probable
ŝ	Kluska et al. [9]	Healthy	Recovered	Serology	HINI	Probable
4	Kluska et al. [9]	Thrombocytopenia	Recovered	Serology	HINI	Probable
5	Kluska et al. [9]	Healthy	Recovered	Serology	INIH	Probable
9	Kluska et al. [9]	Healthy	Recovered	Serology	HINI	Probable
L i	Smith [4]	Hodgkin disease	Died	Isolate	INIH	No evidence
8	O'Brien et al. [10]	Healthy	Recovered	Serology	HINI	Possible
6	Thompson et al. [11]	Healthy	Recovered	Serology	HINI	No evidence
10	Thompson et al. [11]	Splenectomy	Recovered	Serology	INIH	No evidence
11	Smith [12]	Hodgkin disease	Recovered	Serology	HINI	No evidence
12	CDC [13]	NA	Recovered	Serology	HINI	No evidence
13	CDC [14]	NA	Recovered	Isolate	HINI	NA
14	CDC [15]	NA	Recovered	Isolate	HINI	No evidence
15	Dowdle et al. [16]	NA	NA	NA	HINI	NA
16	Dacso et al. [17]	Healthy	Recovered	Isolate	HINI	Possible
17	Dacso et al. [17]	Healthy	Recovered	Isolate	HINI	No evidence
18	Patriarca et al. [18]	ALL in remission	Died	Isolate	HINI	Possible
19	Chuvakova et al. [19]	NA	Died	Isolate	HINI	No evidence
20	Chuvakova et al. [19]	NA	Recovered	Isolate	HINI	No evidence
21	Chuvakova et al. [19]	NA	Recovered	Isolate	HINI	No evidence
22	de Jong et al. [20]	Asthma	Recovered	Isolate	INIH	NA
23	de Jong et al. [20]	Healthy	Recovered	Isolate	HINI	NA
24	de Jong et al. [20]	Healthy	Recovered	Isolate	HINI	NA
25	McKinney et al. [21]	Pregnancy	Died	Isolate	HINI	Probable
26	Wentworth et al. [22]	Healthy	Died	Isolate	HINI	No evidence
27	Claas et al. [23]	Healthy	Recovered	Isolate	H3N2	Possible
28	Claas et al. [23]	Healthy	Recovered	Isolate	H3N2	Possible
29	Rimmelzwaan et al. [24]	Healthy	Recovered	Isolate	HINI	NA
30	Wentworth et al. [25]	Healthy	Recovered	Isolate	HINI	No evidence
31	Wentworth et al. [25]	Healthy	Recovered	Isolate	HINI	No evidence
32	Kimura et al. [26]	Healthy	Died	Isolate	HINI	NA
33	Cooper et al. [27]	NA	NA	Isolate	HINI	NA
34	Gregory et al. [28]	NA	Recovered	Isolate	H3N2	No evidence
35	Gregory et al. [29]	NA	Recovered	Isolate	HINI	No evidence
36	Grav et al. [8]	Healthy	Recovered	Isolate	HINI	No evidence
37	Olsen et al. [30]	Healthy	Recovered	Isolate	H3N2	NA
i		n				

NOTE. ALL, acute lymphocytic leukemia; CDC, Centers for Disease Control and Prevention; NA, not available.