Influenza at the animal–human interface: a review of the literature for virological evidence of human infection with swine or avian influenza viruses other than A(H5N1)

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Factors that trigger human infection with animal influenza virus progressing into a pandemic are poorly understood. Within a project developing an evidence-based risk assessment framework for influenza viruses in animals, we conducted a review of the literature for evidence of human infection with animal influenza viruses by diagnostic methods used. The review covering Medline, Embase, SciSearch and CabAbstracts yielded 6,955 articles, of which we retained 89; for influenza A(H5N1) and A(H7N9), the official case counts of t   he World Health Organization were used. An additional 30 studies were included by scanning the reference lists. Here, we present the findings for confirmed infections with virological evidence. We found reports of 1,419 naturally infected human cases, of which 648 were associated with avian influenza virus (AIV) A(H5N1), 375 with other AIV subtypes, and 396 with swine influenza virus (SIV). Human cases naturally infected with AIV spanned haemagglutinin subtypes H5, H6, H7, H9 and H10. SIV cases were associated with endemic SIV of H1 and H3 subtype descending from North American and Eurasian SIV lineages and various reassortants thereof. Direct exposure to birds or swine was the most likely source of infection for the cases with available information on exposure.

Introduction

Influenza virus type A, a member of the family *Orthomyxoviridae*, is an enveloped virus with a negative-sense, single-stranded RNA genome organised in eight gene segments, which encode at least eleven proteins. Antigenic and genetic diversity of two surface glycoproteins, haemagglutinin (HA) and neuraminidase (NA), is used to classify type A influenza viruses into subtypes; 18 HA and 11 NA subtypes are known to date [1-5]. Water- and shorebirds were identified as reservoirs harbouring all subtypes, except A(H17N10) and A(H18N11) of which RNA was recently detected in bats from Guatemala and Peru, respectively [2,3]. Reservoir animals typically do not display symptoms. In contrast, the diversity of influenza viruses in mammalian hosts is limited to specific subtypes. Human-adapted seasonal influenza viruses since the beginning of the 20th century have had HA subtypes H1, H2 and H3, combined with NA subtypes N1 and N2.

The segmented nature of the genome facilitates the exchange of genetic material if a host is co-infected with two genetically different type A influenza viruses. This reassortment process, also known as antigenic shift if it involves the gene segment encoding the HA, can result in the generation of viruses with surface antigens against which the human population may not have pre-existing, protective antibodies. Additional flexibility is conferred by the accumulation of mutations during replication, potentially resulting in amino acid substitutions that can affect pre-existing immunity if the HA is involved (antigenic drift), host range, virulence, and other factors [6]. If this results in sustained

FIGURE 1

Search strategy for the literature review on animal influenza A virus infections in humans
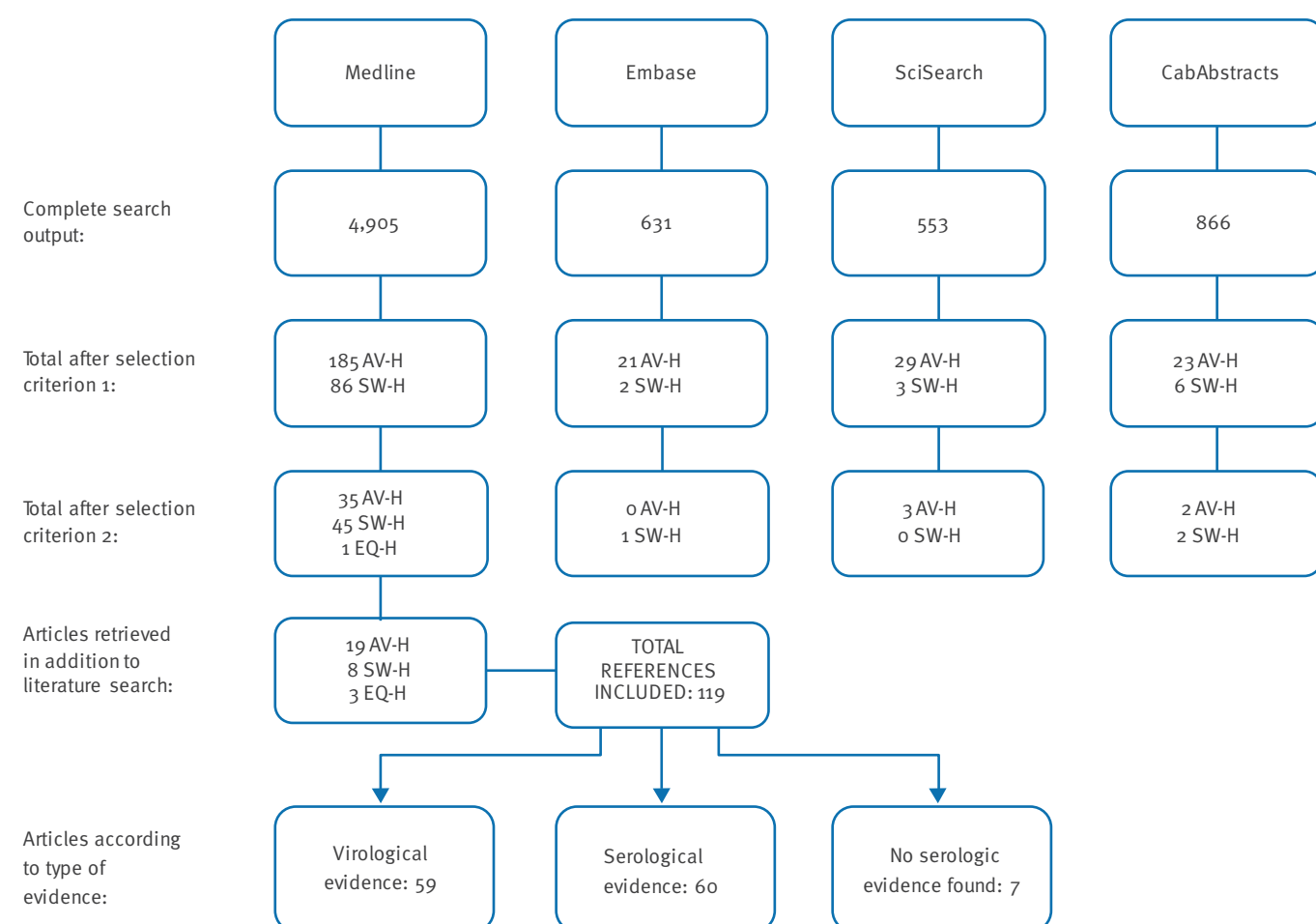
AV: avian; SW: swine; EQ: equine; H: human.

Selection step 1 extracted studies indicating information on human infection with animal influenza viruses in title and abstract. Selection step 2 excluded papers as specified in *Inclusion and exclusion criteria*. Seven articles described virological as well as serological evidence of infection. These references were counted once in the total count and listed twice in the row 'Articles according to type of evidence'. The virological evidence of human infection is presented in this paper. The indirect serological evidence will be described elsewhere.

human-to-human transmission of a virus against which a large proportion of the world's human population is immunologically naïve a pandemic can develop resulting in a large number of human cases occurring simultaneously worldwide [7,8]. Such novel introductions of reassorted viruses were at the root of four influenza pandemics in the last 100 years, and claimed the lives of millions of people, namely the 'Spanish flu' A(H1N1) in 1918, the 'Asian flu' A(H2N2) in 1957, the 'Hong Kong flu' A(H3N2) in 1968, and the recent pandemic caused by influenza A(H1N1)pdm09 in 2009 [9,10]. Influenza A(H1N1)pdm09 has replaced previous human seasonal A(H1N1) viruses [11] and, together with A(H3N2) and influenza B viruses, has been causing seasonal influenza epidemics in humans since 2009. With the emergence of the influenza A(H3N2) pandemic in 1968, influenza A(H2N2) viruses ceased to circulate in humans, but H2 subtypes are still present in birds

and were also recently isolated from diseased swine [12,13].

The factors that determine whether an animal influenza virus may acquire the ability to efficiently spread among humans are poorly understood [14]. Reassortment is not a necessary prerequisite for human infection, and there is clear documentation of direct transmission and human disease caused by animal influenza viruses, in particular avian (AIV) and swine (SIV) influenza viruses , such as AIV A(H5N1), A(H9N2) and various H7 subtypes, as well as European avian-like SIV A(H1N1) [15-22]. Early detection and in-depth investigation of such events may provide clues for (future) risk assessment of animal-to-human transmissions.

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TABLE 1A

Virological evidence of human infection with avian influenza A viruses, excluding high pathogenicity A(H5N1)

Year	(Tested)ᵃ/ confirmed cases	Subtype	Symptoms	Method	Patient information and nature of exposure	Location	Reference
1959	1/1	H7N7	Unknown	Culture in embryonated chicken eggs; subtyping with specific antisera	Source unknown; isolated from patient suffering from hepatitis	United States	Campbell et al. 1970 [52]
1977	1/1	H7N7	Keratoconjunctivits	Culture in embryonated chicken eggs	Laboratory technician accidentally infected with fowl plague	Melbourne, Australia	Taylor and Turner 1977 [53]
1979	1/1	H7N7	Conjunctivitis	Virus isolation	Source: experimentally infected harbour seal; Prior to that case, four additional possible cases who performed autopsies on infected harbour seals showed conjunctivitis but virus isolation was not performed	Massachusetts, United States	Webster et al. 1981 [54,60]
1991	11/2 14/3 15/6	H6N1 H4N8 H10N7	Ranging from respiratory and some constitutional symptoms to no symptoms	Culture in embryonated chicken eggs	Experimental infection	United States	Beare and Webster 1991 [75]
1996	1/1	LP H7N7	Conjunctivitis	Culture on rhesus monkey kidney cells	Source: straw contaminated with duck faeces	United Kingdom	Kurtz et al. 1996 [55]
1998	5/5	H9N2	Acute respiratory symptoms	Culture in embryonated chicken eggs, HI and NI assay	Poultry contact	Shantou (n=3), Shaoguan (n=2), China	Guo et al. 1999 [70]
1999	2/2	H9N2	Mild ILI	Cultured by WHO reference laboratory	4- and 1-year-old girl; one patient probably had contact with live poultry	Hong Kongᵇ	Peiris et al. 1999 [16]
1999	1/1	H9N2	Fever, cough, bronchitis	MDCK cell culture, HI and NI-assay	2-year-old female with probable poultry contact	Guangzhou, China	Guo et al. 2000 [71]
2003	453/89 (including one fatality)	HP H7N7	Conjunctivitis, ILI (fatality: fever, pneumonia, multi-organ failure, respiratory insufficiency)	Cell culture (used for the first 25 confirmed cases, afterwards RT-PCR used as screening method), typed and subtyped by HI assay (turkey RBC), RT-PCR	Poultry famer and family, cullers, veterinarians, medical personnel, others	Gelderland, North Brabant, Limburg, The Netherlands	Koopmans et al. 2004; Fouchier et al. 2004 [17,56]
2003	1/1	H9N2	Mild ILI	Culture in embryonated chicken eggs. HI and NI assay, sequencing	No history of contact with poultry	Hong Kongᵇ	Butt et al. 2005 [66]
2004	2/2	LP and HP H7N3	Conjunctivitis, mild ILI	RT-PCR, cell culture, sequencing	Occupational exposure to infected poultry (Veterinarian, general worker)	British Columbia, Canada	Tweed et al. 2004 [18]

Where more than one human case is stated, diagnostic tests were performed for all cases as stated in the Methods section, unless otherwise specified.

HI: haemagglutination inhibition; HP: highly pathogenic; ILI: influenza-like illness, LP: low pathogenic; MDCK: Madin Darby canine kidney; MN: microneutralisation; n.a.: not applicable; NI: neuraminidase inhibition; PCR: polymerase chain reaction; RBC: red blood cells; RT-PCR: reverse transcription polymerase chain reaction; rtRT-PCR: real-time reverse transcription polymerase chain reaction; WHO: World Health Organization.

ᵃ In most cases the number tested reflects only the confirmed cases reported in the reviewed paper where the authors did not report on the true number of suspected cases tested.

ᵇ Hong Kong Special Administrative Region (SAR), China.

TABLE 1B

Virological evidence of human infection with avian influenza A viruses, excluding high pathogenicity A(H5N1)

Year	(Tested)[a]/confirmed cases	Subtype	Symptoms	Method	Patient information and nature of exposure	Location	Reference
2004	2/2	H10N7	'Illness' (not further specified)	Virus isolation	Infants with indirect contact to poultry (father of one is poultry merchant)	Egypt	Pan American Health Organization, 2004 [76]
2006	1/1	LP H7N3	Conjunctivitis	PCR (no serological confirmation reported)	Source: infected poultry	United Kingdom	Nguyen-Van-Tam et al. 2006 [57]
2007	4/4	LP H7N2	Conjunctivitis, ILI	Confirmed influenza A[c]	Source: infected poultry	United Kingdom	Editorial team, 2007 [58]
2007	1/1	H9N2	Mild ILI	Information not available	Source: probably a bird market	Hong Kong[b]	United States Centers for Disease Control and Prevention 2008 [67]
2008, 2009	2/2[d]	H9N2	ILI, vomiting, dyspnoea	Rapid test, RT-PCR; MDCK cell culture; immunofluorescence assay; sequencing	Immunocompromised persons (with and without poultry contact)	Shenzhen and Hong Kong[b]	Cheng et al., 2011 [68]
2010	7/2	H10N7	Conjunctivitis, rhinorrhoea, sore throat	PCR, partial sequencing of haemagglutinin genes (no virus culture); no evidence of seroconversion	Abattoir workers exposed to infected poultry	New South Wales, Australia	Arzey et al. 2012 [20]
2011	1/1	H9N2[e]	Fever, headache, runny nose, cough, sneezing	Partial sequencing	51-month-old female exposed to slaughtered chickens	Bangladesh	International Centre for Diarrhoeal Disease Research, Bangladesh 2011 [69]
2012	2/2	HP H7N3	Conjunctivitis; no fever or respiratory symptoms	rtRT-PCR (n=2), culture in embryonated chicken eggs (n=1), sequencing (n=1)	32- and 52-year-old female/male poultry worker exposed to infected poultry	Jalisco, Mexico	United States Centers for Disease Control and Prevention 2012 [59]
2013	251/251 (including 56 fatalities)[f]	LP H7N9	Ranging from mild symptoms and recovery to severe respiratory symptoms and death	Virus isolation, PCR	Source: not specified	Shanghai, Beijing, Hong Kong[b], Anhui, Fujian, Jiangsu, Jiangxi, Guangdong, Guizhou, Henan, Hunan, Hebei, Shandong, Zheijang, provinces, China; two cases were imported to Taiwan from mainland China	European Centre for Disease Prevention and Control updated rapid risk assessment [23]

Where more than one human case is stated, diagnostic tests were performed for all cases as stated in the Methods section, unless otherwise specified.

HI: haemagglutination inhibition; HP: highly pathogenic; ILI: influenza-like illness, LP: low pathogenic; MDCK: Madin Darby canine kidney; MN: microneutralisation; n.a.: not applicable; NI: neuraminidase inhibition; PCR: polymerase chain reaction; RBC: red blood cells; RT-PCR: reverse transcription polymerase chain reaction; rtRT-PCR: real-time reverse transcription polymerase chain reaction; WHO: World Health Organization.

a   In most cases the number tested reflects only the confirmed cases reported in the reviewed paper where the authors did not report on the true number of suspected cases tested.
b   Hong Kong Special Administrative Region (SAR), China.
c   Authors assume that influenza A-positive test suggests influenza A(H7N2) infection because of close temporal-spatial links with influenza A(H7N2)-infected poultry and low seasonal influenza activity at that time.
d   One patient and her asymptomatic husband showed a titre of 80 in the microneutralisation assay, three and two weeks after onset of illness respectively.
e   Belongs to G1 lineage.
f   At the time of writing (31 January 2014) the number of cases was still on the increase.

Virological evidence of human infection with avian influenza A viruses, excluding high pathogenicity A(H5N1)

Year	(Tested)[a] / confirmed cases	Subtype	Symptoms	Method	Patient information and nature of exposure	Location	Reference
2013	1/1	H6N1	ILI, mild pneumonia	Virus isolation, full genome sequencing	20-year-old female; no exposure to poultry	Taiwan	Centers for Disease Control 2013 [79]
2013	1/1	H10N8	Severe pneumonia and death	Not specified	73-year-old immunocompromised female with underlying illness; exposed to live poultry	Jiangxi province, China	ProMED 2013 [77]
2013	1/1	H9N2	Chest infection, low fever, chills and cough	Not specified	86-year-old male with underlying illness; no recent poultry exposure	Shenzhen/Hong Kong[b]	ProMED 2013 [72]
2014	1/1	H9N2	Illness (not further specified); recovered	Not specified	7-year-old male with poultry exposure	Hunan, China	ProMED, 2014 [73]
2014	1/1	H10N8	Sore throat, dizziness, loss of strength, severe pneumonia[g]	Not specified	55-year-old female; visited agricultural market	Jiangxi, China	ProMED 2014 [78]
Total	784/386 (375 when experimentally infected human cases are subtracted)						29

Where more than one human case is stated, diagnostic tests were performed for all cases as stated in the Methods section, unless otherwise specified.

HI: haemagglutination inhibition; HP: highly pathogenic; ILI: influenza-like illness, LP: low pathogenic; MDCK: Madin Darby canine kidney; MN: microneutralisation; n.a.: not applicable; NI: neuraminidase inhibition; PCR: polymerase chain reaction; RBC: red blood cells; RT-PCR: reverse transcription polymerase chain reaction; rRT-PCR: real-time reverse transcription polymerase chain reaction; WHO: World Health Organization.

a   In most cases the number tested reflects only the confirmed cases reported in the reviewed paper where the authors did not report on the true number of suspected cases tested.

b   Hong Kong Special Administrative Region (SAR), China.

g   At the time of writing (31 January 2014) the patient was hospitalised and in critical condition.

Year	(Tested)[a]/ confirmed cases	Subtype	Symptoms	Method	Patient information and nature of exposure	Location	Reference
Not specified	7/3[b] 13/2	swH3N2[c] clH1N1	Mild: coryza	Virus isolation (not further specified)	Experimentally infected humans (intranasal, $10^{5.5}$ egg-infective doses)	Not specified (according to author affiliations: England)	Beare et al. 1972 [45]
1974	1/1 (fatal)	swH1N1[d]	Pneumonia	Culture on WI-38-, HeLa- and rhesus-monkey kidney-cells, inoculation of mice; HI assay (guinea pig RBC)	16-year-old Hodgkin's disease patient living on swine farm	Minnesota, United States	Smith et al. 1976 [42]
1976	20/5 (including 1 fatality)	swH1N1	Acute respiratory illness, pneumonia	Embryonated chicken egg culture, HA assay	Previously healthy soldiers without known exposure to swine	New Jersey, United States	Gaydos et al. 1977 [28]
1976	1/1	swH1N1[e]	Mild ILI	Virus isolation; HI assay	22-year-old swine worker exposed to ill, influenza-positive swine	Wisconsin, United States	United States Centers for Disease Control and Prevention 1976 [29]
1976	1/1	swH1N1[f]	ILI	Virus isolation; HI assay	13-year-old boy living on swine farm	Wisconsin, United States	United States Centers for Disease Control and Prevention 1976 [30]
1979/80	2/2	swH1N1[f]	ILI	Rhesus monkey kidney cell culture; embryonated chicken egg culture; HI assay	20-year-old fell ill after close contact with swine; 6-year-old visitor of livestock show without direct contact with swine	Texas, United States	Dacso et al. 1984 [31]
1982	1/1 (fatal)	swH1N1[f]	Pneumonia	Cynomolgus monkey kidney cells; embryonated chicken egg culture; RNA-oligonucleotide mapping	4-year-old female leukemia patient; no known exposure to swine	Nevada, United States	Patriarca et al. 1984 [32]
1983	3/3	swH1N1	Information not available	Isolation	65-year-old male with occupational exposure to swine; 10-year old female and 27-year-old male with unknown exposure to swine	Russia	Chuvakova et al. 1985 [27]
1986	a) 1/1 b) 2/2	swH1N1[g,h]	a) Pneumonia b) Mild ILI	a) Various cell cultures; embryonated chicken egg culture; HI and NI assay b) Various cell cultures; HI assay, complement fixation assay	a) 29-year-old farmer exposed to ill, influenza-infected pigs b) 50-year-old employee exposed to ill, influenza-infected pigs, and 3-year-old with no known contact with pigs	a) The Netherlands b) Switzerland	De Jong et al 1988 [33]

Where more than one human case is stated, diagnostic tests were performed for all cases as stated in the Methods section, unless otherwise specified.

BSL: biosafety level; cl: classical swine lineage; HA: haemagglutination; HeLa: Henriette Lacks cervical cancer cells; HI: haemagglutination inhibition; ILI: Influenza-like illness; MAb: monoclonal antibodies; MDCK: Madin Darby canine kidney; MN: microneutralisation; n.a.: not applicable; NI: neuraminidase inhibition; RBC: red blood cells; RT-PCR: reverse transcriptase polymerase chain reaction; rtRT-PCR: real-time reverse transcriptase polymerase chain reaction; sw: swine; SwL: swine-like; tr: triple reassortant; WI-38: human embryo lung fibroblast.

a   In most cases the number tested reflects only the confirmed cases reported in the reviewed paper where the authors did not report on the true number of suspected cases tested.

b   Number of humans from whom virus could be reisolated.

c   Swine/Taiwan/7310/70 related to A/Hong Kong/1/68.

d   Named A/Mayo Clinic/103/74, inhibited by antisera against A/swine/1976/31 and A/swine/Wisconsin/67.

e   A/New Jersey/8/76.

f   A/New Jersey/8/76-like influenza virus.

g   A/Netherlands/386/86, A/Geneva/5521/86, A/Geneva/5200/86.

h   Highest homology with European swine-influenza viruses.

TABLE 2B

Virological evidence of human infection with swine influenza A viruses

Year	(Tested)[a] / confirmed cases	Subtype	Symptoms	Method	Patient information and nature of exposure	Location	Reference
1988	1/1 (fatal)[i]	swLH1N1	Pneumonia	RNA fingerprinting; partial sequencing	32-year-old pregnant woman exposed to pigs at county fair showing ILI	Wisconsin, United States	McKinney et al. 1990 [34]
1991	1/1 (fatal)	swLH1N1[i]	Pneumonia	Rhesus monkey kidney cell culture; embryonated chicken egg culture; rtRT-PCR; oligonucleotide mapping; HI and NI assay; sequencing; experimental infection of swine	27-year-old animal caretaker exposed to swine showing respiratory symptoms	Maryland, United States	Wentworth et al. 1994 [35]
1992/93	2/2	swH3N2[k]	Mild respiratory symptoms	Virus isolation; HI assay; sequencing	1- and 2-year-old with no known exposure to swine	The Netherlands	Claas et al. 1994 [41]
1993	1/1	swH1N1[h]	Pneumonia	Tertiary monkey kidney cell culture; RT-PCR; immunofluorescence assay on MDCK cells; sequencing; HI assay	5-year-old living on swine farm (health status of swine not known)	The Netherlands	Rimmelzwaan et al. 2001 [36]
1994	2/2	swH1N1[l]	Mild ILI	Embryonated chicken egg culture; MDCK cell culture; HI- and NI-assay; sequencing; RT-PCR and other PCR-types; Eexperimental infection of swine	39- and 30-year-old BSL3 laboratory workers exposed to influenza-infected pigs	Wisconsin, United States	Wentworth et al. 1997 [37]
1995	1/1 (fatal)	swH1N1	Severe pneumonia	Virus isolation and subtyping	37-year-old healthy woman working on pig farm (health status of pigs unknown)	Minnesota, United States	Kimura et al. 1998 [38]
1999	1/1[m]	H3N2[n]	Mild ILI	MDCK cell culture; HI and NI assay; RT-PCR; sequencing	10-month-old girl (neither she nor her family had recent contact with pigs)	Hong Kong[o]	Gregory et al. 2001 [39]
2002	1/1	H1N1[p]	ILI	MDCK cell culture; HI assay (also serologically confirmed by HI)	50-year-old farmer (possibly from pigs showing respiratory symptoms)	Switzerland	Gregory et al. 2003 [21]
2004, 2005	1/1, 1/1	H1N2[q], H1N1[q]	Mild ILI	MDCK cell culture; HA assay (turkey RBC); HI assay'; rapid tests[s]; RT-PCR; sequencing	25- and 4-year-old male; neither had direct contact to pigs (incidental contact with backyard pigs could not be excluded)	Philippines Thailand	Komadina et al. 2007 [85]

Where more than one human case is stated, diagnostic tests were performed for all cases as stated in the Methods section, unless otherwise specified.

BSL: biosafety level; cl: classical swine lineage; HA: haemagglutination; HeLa: Henriette Lacks cervical cancer cells; HI: haemagglutination inhibition; ILI: Influenza-like illness; MAb: monoclonal antibodies; MDCK: Madin Darby canine kidney; MN: microneutralisation; n.a.: not applicable; NI: neuraminidase inhibition; RBC: red blood cells; RT-PCR: reverse transcriptase polymerase chain reaction; rtRT-PCR: real-time reverse transcriptase polymerase chain reaction; sw: swine; SwL: swine-like; tr: triple reassortant; WI-38: human embryo lung fibroblast.

[a] In most cases the number tested reflects only the confirmed cases reported in the reviewed paper where the authors did not report on the true number of suspected cases tested.

[h] Highest homology with European swine-influenza viruses.

[i] Patient's husband developed ILI symptoms one day before the patient (virus isolation not done)

[j] A/Maryland/12/91.

[k] Human-avian reassortants: A/Netherlands/5/93, A/Netherlands/35/93.

[l] Strain was similar to strain used in swine experiment and closely related to Sw/IN and A/WI/3523/88.

[m] Patient showed a titre of 160 by HI assay, the patient's mother a titre of 20, father, brother and grandparents titres of less than 10.

[n] Virus was closely related to viruses circulating in European pigs.

[o] Hong Kong Special Administrative Region (SAR), China.

[p] A/Switzerland/8808/02 (European avian-like lineage).

[q] Swine-like viruses: HA genetically similar to swine viruses circulating in swine in Asia at the time and to viruses that circulated in North America in the 1990s, whereas NA and internal genes were similar to European swine viruses.

[r] Both isolates tested negative against human strains.

[s] To determine whether isolates belong to influenza A or B.

TABLE 2C
Virological evidence of human infection with swine influenza A viruses

Year	(Tested)a/ confirmed cases	Subtype	Symptoms	Method	Patient information and nature of exposure	Location	Reference
2005	1/1	trH1N1[t]	Sore throat, runny/stuffed nose, cough, fever	Cell culture, RT-PCR, sequencing	50-year-old swine farm resident exposed to ill swine (not influenza confirmed)	Iowa, United States	Gray et al. 2007 [92]
2005	1/1[u]	trH1N1[v]	Acute mild respiratory illness; no fever	MDCK cell culture; RT-PCR; sequencing	Vaccinated one month before illness; assisted in butchering swine;	Wisconsin, United States	Newman et al. 2008 [89]
2005	1/1	trH3N2[w]	ILI	Culture on primary rhesus monkey kidney cells; sequencing	Previously healthy swine farmer exposed to influenza-positive pigs	Canada	Olsen et al. 2006 [40]
2006	1/1[x]	sw trH3N2[w]	ILI	HI assay (guinea pig RBC) RT-PCR, sequencing	7-month-old child living on communal farm; no direct exposure to animals, seropositive swine found on farm	Canada	Robinson et al. 2007 [96]
2007	1/1[y]	trH3N2[w]	Parotitis, nasal congestion; no fever, cough or pharyngitis	Virus isolation; HI assay (turkey RBC); sequencing	6-year-old boy living on swine farm (no illness in swine observed)	Canada	Bastien et al. 2009 [95]
2007	26/2[z]	swH1N1[aa]	ILI	Virus isolation; sequencing	People exposed to ill swine at county fair	Ohio, United States	Vincent et al. 2009 [87]; Yassine et al. 2009 [88]
2005–09	a) 10/10 b) 1/1	a) sw trH1N1[bb] b) trH1N2[cc]	Ranging from mild ILI to pneumonia	Rapid point of care test (n=8); Virus culture (n=7); rt RT-PCR (n=6); HI assay; complete genome pyrosequencing	Seven males (age: 16 months–36 years) our females (age: 4–48 years); exposure ranging from unknown contact, close proximity and direct contact with swine (some pigs were ill)	Wisconsin, Missouri, Iowa (n=3), Ohio (n=2), Illinois, Michigan, Minnesota and Texas, United State	Shinde et al. 2009 [93]

Where more than one human case is stated, diagnostic tests were performed for all cases as stated in the Methods section, unless otherwise specified.

BSL: biosafety level; cl: classical swine lineage; HA: haemagglutination; HeLa: Henriette Lacks cervical cancer cells; HI: haemagglutination inhibition; ILI: Influenza-like illness; MAb: monoclonal antibodies; MDCK: Madin Darby canine kidney; MN: microneutralisation; n.a.: not applicable; NI: neuraminidase inhibition; RBC: red blood cells; RT-PCR: reverse transcriptase polymerase chain reaction; rtRT-PCR: real-time reverse transcriptase polymerase chain reaction; sw: swine; SwL: swine-like; tr: triple reassortant; WI-38: human embryo lung fibroblast.

a In most cases the number tested reflects only the confirmed cases reported in the reviewed paper where the authors did not report on the true number of suspected cases tested.

t H1 HA, N1 NA, M, NP, NS genes descended from classical swine-, PB1 from human- and PA and PB2 from avian influenza virus lineages

u Patient showed a two-fold titre increase in MN assay (not in HI assay) and four family members and the patient's brother-in-law were seronegative by MN and HI assay.

v Predominant genotype of subtype H1N1 in North American pigs.

w Same genotype as human/classical swine/avian reassortant that emerged in 1998 in North America.

x Four of seven household members of the patient and four of 46 other residents of the farm showed serological evidence of infection.

y Household members were only serologically screened.

z Virus from at least two individuals was isolated and sequenced and turned out to be nearly identical to the swH1N1 isolated from the ill swine; not done for all human cases.

aa HA related to H1y cluster (H1N2-like) of contemporary H1-SIV, NA related to swine N1 phylogenetic cluster and internal genes were from triple-reassortant SIV lineage and group with cluster IV of A(H3N2) viruses.

bb H1N1: HA, NA, NP, NS, M (classical swine, North-American lineage), PB2, PA (avian, North American lineage), PB1 (human seasonal H3N2).

cc H1N2: HA (human seasonal H1N1), NP, M, NS (classical swine, North-American lineage), PB2, PA (avian, North-American lineage), PB1, NA (human seasonal H3N2).

TABLE 2D

Virological evidence of human infection with swine influenza A viruses

Year	(Tested)[a]/ confirmed cases	Subtype	Symptoms	Method	Patient information and nature of exposure	Location	Reference
2008	1/1[dd]	SwL trH1N1[ee]	ILI, vomiting, diarrhoea	Rapid test; culture; rRT-PCR; sequencing	19-year-old male exposed to healthy appearing pigs (no physical contact)	South Dakota, United States	Dawood et al. 2011 [90]
2008	1/1	swH1N1[ff]	ILI	MDCK cell culture; immunofluorescence using MAb; PCR; partial sequencing	50-year-old-female with direct contact to asymptomatic pigs	Spain	Adiego Sancho et al. 2009 [22]
2009	1/1[gg]	sw trH3N2	Fever, cough, sore throat	Rapid test; rtRT-PCR; sequencing	12-year-old boy (touched healthy appearing swine at a county fair, pigs were seropositive)	Kansas, United States	Cox et al. 2011 [97]
2009	3/3[hh]	sw trH1N1[ii]	ILI	MDCK cell culture; rtRT-PCR; HI assay (turkey RBC)[jj], sequencing	Swine workers (one was immunized in 2008, other two never received an influenza vaccination)[kk]	Saskatchewan, Canada	Bastien et al. 2010 [91]
2009–11	3/3	swH1N1[ll]	Not specified	Not specified	Three adult, male swine workers exposed to ill, influenza-confirmed pigs	Switzerland	European Centre for Disease Prevention and Control 2012 [86]
Aug- Dec 2011	12/12[mm]	H3N2v[nn]	ILI, vomiting, diarrhoea	Rapid tests; rtRT-PCR; sequencing	50% exposed and 50% not exposed to swine; (11 children, one adult male); Most attending agricultural fair	Hawaii, Illinois, Indiana, Iowa, Maine, Maryland, Michigan, Minnesota, Ohio, Pennsylvania, Utah, West Virginia, Wisconsin, United States	United States Centers for Disease Control and Prevention 2012 [99],2013 [25]
2012	309/309				Most attending agricultural fair		
2013	19/19[oo]						
Total	**455/401**						33

Where more than one human case is stated, diagnostic tests were performed for all cases as stated in the Methods section, unless otherwise specified.

BSL: biosafety level; cl: classical swine lineage; HA: haemagglutination; HeLa: Henriette Lacks cervical cancer cells; HI: haemagglutination inhibition; ILI: Influenza-like illness; MAb: monoclonal antibodies; MDCK: Madin Darby canine kidney; MN: microneutralisation; n.a.: not applicable; Nl: neuraminidase inhibition; RBC: red blood cells; RT-PCR: reverse transcriptase polymerase chain reaction; rtRT-PCR: real-time reverse transcriptase polymerase chain reaction; sw: swine; SwL: swine-like; tr: triple reassortant; WI-38: human embryo lung fibroblast.

a   In most cases the number tested reflects only the confirmed cases reported in the reviewed paper where the authors did not report on the true number of suspected cases tested.

dd Contacts of the patient and people exposed to swine during the event were serologically screened.

ee Distinct from A(H1N1)pdm09 and similar to triple-reassortant swine viruses circulating in the United States shortly before .

ff Phylogenetically close to A/Switzerland/8808/02 (European avian-like lineage) [19].

gg In addition, 27 of 34 visitors of the county fair participated in a survey: none reported ILI.

hh No household members were ill at the time.

ii Distinct from A(H1N1)pdm09: NS, NP, M, PA, PB1 and PB2 were similar to a North-American swine triple reassortant and HA and NA were most similar to A/Brisbane/59/2007 (H1N1)-like viruses.

jj For antigenic characterisation.

kk Mild respiratory illness was present in less than 1% of the swine herd the workers were exposed to (no confirmation whether it was due to influenza A infection).

ll Infected with European SIV similar to viruses identified in ill pigs the workers were exposed to.

mm Eleven children (including two children attending the same daycare centre) and one adult male.

nn Influenza A H3N2 variant (comprises genes from avian, swine and human origin) with M gene derived from A(H1N1)pdm09.

oo Case count as available on 31 January 2014.

Authority (EFSA). The main objective of FLURISK is the development of an evidence-based influenza risk assessment framework (IRAF) to assess the potential of animal influenza viruses to cross the species barrier and cause sustained infections in humans. The work presented here aims at describing available evidence for animal-to-human influenza virus transmissions.

Methods

Search strategy
We performed a literature search using Medline, Embase, SciSearch and CabAbstracts. Search terms included 'influenza', 'influenza virus', 'animals', 'swine', 'birds', 'poultry', 'wild bird', 'water bird', 'waterfowl', 'goose', 'duck', 'chicken', 'turkey', 'environment', 'animal-to-human', 'transmission-to-humans', 'interspecies transmission', 'human', 'case', 'seroprevalence', 'serosurveillance', 'prevalence', 'incidence', 'risk factor', 'exposure' and various subtypes of influenza virus; the terms were used alone or in combinations using Boolean operators. Full search details are available from the corresponding author on request. Only articles published in English were included and the search covered all years available in the respective databases, Medline from 1946, Embase from 1947, SciSearch from 1980, CabAbstracts from 1973, all up to February 2012. The search algorithm automatically discarded duplicates. Newly published evidence that came to our attention between February 2012 and January 2014 was also included. Case counts of avian influenza A(H7N9) and A(H5N1) cases were updated on 31 January 2014 based on the latest figures reported by the European Centre for Disease Prevention and Control (ECDC) [23] and by the World Health Organization (WHO) [24]. Case counts of human infections with swine influenza variant A(H3N2)v were retrieved on 31 January 2014 from the website of the United States (US) Centers for Disease Control and Prevention (CDC) as posted on 18 October 2013 [25. Grey literature was searched in a non- systematic way.

Inclusion and exclusion criteria
Included were papers indicating evidence of human infection with animal influenza viruses (selection criterion 1, Figure 1). Two investigators first screened all papers by title and, when necessary, by abstract. All articles meeting this first criterion were reviewed for details of the methods used to diagnose the infection. Experimental and observational studies describing human infection with animal influenza viruses other than influenza A(H5N1) were included. Articles solely describing human infection with A(H5N1) were excluded, and for influenza A(H5N1) and A(H7N9), the official WHO and ECDC statistics from notifications under the International Health Regulations were used for completeness. Commentaries, reviews, articles dealing with influenza in animals only, studies solely assessing human-to-human transmission of an animal influenza virus (i.e. most of the literature on influenza

A(H1N1)pdm09), and articles referring to study subjects described in prior original publications were excluded (selection criterion 2, Figure 1). Studies based on serological evidence only were excluded to ensure high specificity of the findings. Papers were screened for information on the time period when the study was conducted, total number of people sampled, patient information, nature of exposure (e.g. occupational, recreational), possible exposure to diseased animals, influenza virus subtypes included in testing, number of virologically confirmed cases, information on vaccination history if stated, methods used for confirmation, geographic region and study design. Available data were extracted and summarised in tables. Grey literature such as ProMED, and reference lists from articles were screened for possible additional relevant papers. Virus detection by culture or (real-time) reverse transcription polymerase chain reaction (rtRT-PCR) and sequencing was considered to be definitive proof of infection, listed as virological evidence (Tables 1 and 2).

Search output and article selection
The initial search yielded 6,955 articles, with 4,905 articles resulting from the Medline search, and the others from additional searches (Figure 1). Search outputs from Embase, SciSearch and CabAbstracts yielded 631, 553 and 866 references, respectively. After screening of titles, abstracts and application of the second selection criterion, a total of 89 publications were selected. The majority of these would also have been identified solely through the Medline search.

Thirty additional studies were retrieved through scanning of reference lists of articles identified via the literature review, were retrieved from grey literature or came to our attention after February 2012. Of these 119, 59 publications and reports described virological evidence for infection of humans and met all other inclusion criteria; 60 papers provided some evidence for human infection, but only based on antibody testing and will therefore be described elsewhere.. Seven publications containing both serological and virological evidence were counted once in the total reference count but were included twice in the subdivision according to type of evidence in Figure 1.

Most studies discussed in a review of case reports of SIV infections in humans by Myers et al. [26] were also identified in our literature search. For completeness of the human case count, virologically confirmed civilian (n=23) and military cases of Fort Dix (n=5), although discussed in detail in the review by Myers et al. [26], were also included in the current review [21,27-42] (Table 2). For two virus-confirmed cases from the review by Myers et al. [26], the reference could not be retrieved or did not provide full confirmation; these cases were therefore excluded from our listing in Table 2 [43,44].

Humans naturally infected with avian influenza virus subtypes other than A(H5N1) and swine influenza virus subtypes, 1959–2014 (n=771)

Source virus	Number of human cases infected with										
Avian											
Subtype	LP H6N1	H7N2	HP H7N3	LP H7N3	HP H7N7	LP H7N7	LP H7N9[a]	H9N2	H10N7	H10N8	**Total**
	1	4	3	2	89	4	251	15	4	2	**375**
Swine											
Subtype	H1N1	H1N2	H3N2	H3N2v[b]							**Total**
	47	2	7	340							**396**

HP: highly pathogenic; LP: low pathogenic.

[a] as of 27 January 2014 [23].

[b] as of 18 October 2013 [25].

Results

The evidence for virologically confirmed infections of humans with avian or SIV is listed in Tables 1, 2 and 3. The exposure status of infected patients is summarised in Table 4. A total of 386 cases of human infection with non-A(H5N1) AIV were described, of which 375 were caused by natural infection and 11 were infected experimentally (Table1).

Regarding human infections with SIV, a total of 401 naturally (n=396) and experimentally (n=5) infected cases were detected in the published and grey literature in English. This included, three virologically confirmed SIV A(H1N1) cases originally published in Russian by Chuvakova et al. [27] because they were listed in the review by Myers et al. [26]. The majority of cases (n=340) were naturally infected by a SIV variant A(H3N2)v [25]. Recognised in US swine in 2010, this variant combines seven genes from the contemporary North-American A(H3N2) SIV lineage and has acquired the M gene of the A(H1N1)pdm09 virus [25]. The remaining 56 naturally infected, virologically confirmed human cases were caused by different circulating SIV or SIV reassortants (Table 2). Five persons were experimentally infected with SIV [45]. The majority of

AIV- and SIV-infected patients had been exposed to animals (Table 4).

Human infections with avian influenza viruses

Infections with highly pathogenic avian influenza virus A(H5N1)

To date, highly pathogenic avian influenza (HPAI) A(H5N1) viruses are the most frequently diagnosed zoonotic influenza virus infections related to avian exposure [46], although this picture may change in the near future given the recent upsurge in low pathogenic avian influenza (LPAI) A(H7N9) cases. The HPAI A(H5N1) viruses first attracted major attention in the scientific community in 1996, when a large number of domestic waterfowl died in the course of an A(H5N1) outbreak in Guangdong province in southern China. In 1997, HPAI A(H5N1) resurfaced in Hong Kong SAR, China (in the following referred to as Hong Kong); it caused a massive die-off in poultry and crossed the species barrier for the first time, infecting 18 humans, of whom six died [47,48]. From mid-2003 to March 2004, HPAI A(H5N1) spread to seven south-east Asian countries with outbreaks in poultry and waterfowl, and the first confirmed human cases, were reported in Thailand and Vietnam in 2004 [49]. In 2005, HPAI A(H5N1) accounted

Exposure status of patients infected with avian influenza virus, excluding 251 A(H7N9) and including 11 experimentally infected cases, and with swine influenza virus, 1959–2014 (n=536)

Source	Number of cases					
	Exposed	Not exposed	Exposure status unknown	Likely exposed (H3N2v)	Other[a]	**Total**
Avian	114	3	5	n.a.	13	**135**
Swine	45	20	2	328	6	**401**

n.a.: not applicable.

[a] Experimental (avian n=11, swine n=5) or laboratory exposure (avian n=2), or human-to-human transmission (swine n=1).

for the death of a large number of migratory waterfowl at Qinghai lake, China. Shortly after this event, the virus rapidly spread to other Asian countries, Africa, Europe, the Middle East, Mongolia and Russia [50]. Over time, the viruses evolved into multiple lineages, some of which persisted and have become endemic in China, Bangladesh, Egypt, India, Indonesia and Vietnam [51].

As of 10 December 2013, the WHO has listed 648 HPAI A(H5N1) infected cases from 15 countries, confirmed according to WHO criteria and covering a time span of 10 years [24]. In total, 59% of the reported cases died [24]. Indonesia, Egypt and Vietnam reported 195, 173 and 125 cases, respectively, accounting for about 75% of the total influenza A(H5N1) human case count. These three countries also reported the majority of fatalities [24].

Infections with H7 subtype avian influenza viruses
In total, we identified 353 human cases with virologically confirmed H7 infection (Table 1). The majority of these cases (n=251) were reported in China, followed by 95 cases in Europe, six in North America and one in Australia [17,18,23,52–59]. In China, all cases were caused by the recently emerged subtype A(H7N9) [23]. Of the remaining 102 cases, 93 cases had influenza A(H7N7), five had influenza A(H7N3) and four influenza A(H7N2) (Table 3). The first two human cases infected with influenza A(H7N7) were reported in 1959 and 1977. One of these patients had keratoconjunctivitis, thought to be caused by the AIV infection [52,53]. This predilection for the ocular mucosa was confirmed when a person involved in an experimental infection of a seal with an avian-like influenza A(H7N7) developed conjunctivitis, and virus was cultured from a conjunctival swab [54,60]. In the United Kingdom (UK) in 1996, LPAI A(H7N7) virus infection was associated with mild conjunctivitis in a woman who cleaned a duck house and mentioned getting a piece of straw in her eye [55].

Among European cases, 89 humans were infected in the course of a large outbreak with HPAI A(H7N7) in poultry in the Netherlands in 2003 [17]. In contrast to the severe consequences in poultry, only mild symptoms were seen in 88 of the infected people. There was one exception. a veterinarian who died of acute respiratory distress syndrome and multiple organ failure. This person had contracted a virus with several mutations, including a known virulence marker in PB2 [56]. Most of these mutations had accumulated during circulation of the virus in poultry, showing that the public health risk may change over the course of an outbreak [61]. In February 2004, a mixed LPAI and HPAI A(H7N3) virus outbreak was reported in poultry in British Columbia, Canada [18]. Enhanced surveillance for influenza-like illness (ILI) and conjunctivitis in the course of this outbreak led to the identification of two poultry workers showing symptoms of unilateral conjunctivitis. Neither had used the recommended goggles or taken prophylactic oseltamivir. Interestingly,

both virus types led to human infection: the isolate cultured from the first worker had the LPAI phenotype, whereas the strain retrieved from the second worker was classified as HPAI [19,62,63]. In 2006 and 2012, LPAI A(H7N3) was associated with one patient in the UK and HPAI A(H7N3) with two patients in Mexico. In both instances, exposure to infected poultry was documented and all patients presented with conjunctivitis [57,59]. Finally, LPAI A(H7N2) was reported as the infectious agent causing mild influenza-like symptoms and conjunctivitis in four cases in the UK in 2007 [58].

The assumption that LPAI influenza viruses were mostly associated with mild disease was challenged with the emergence of influenza A(H7N9) viruses in March 2013, when China notified the WHO of three cases infected with LPAI A(H7N9) who were severely ill and eventually died [64]. During the first wave of infections from February to May 2013, 133 human cases were reported and an additional two cases in July and August [23]. Phylogenetic studies concluded that all genes of this newly detected virus were of avian origin [64]. In October 2013, the second wave started and was still ongoing at the time of writing (31 January 2014) [23]. Between February 2012 and 27 January 2014, a total of 251 influenza A(H7N9) cases were reported, 56 of whom died [23]. Infections occurred in Anhui (n=4), Beijing (n=3), Fujian (n=15), Guangdong (n=32), Guizhou (n=1), Hebei (n=1), Henan (n=4), Hong Kong (n=3), Hunan (n=4), Jiangsu (n=31), Jiangxi (n=5), Shandong (n=2), Shanghai (n=42) and Zhejiang (n=102). Two cases were imported from mainland China into Taiwan [23]. In response to these events, China culled thousands of birds and closed several poultry markets [65], although only 39 of 48,000 samples representing 1,000 poultry markets tested positive. Most human cases had a history of exposure to birds or live bird markets [23]. As of 31 January 2014, no conclusive evidence of human-to-human transmission has been reported and the ecology of the viruses remains to be resolved.

Infections with H9 subtype avian influenza viruses
In total, we detected 15 human cases infected with AIV A(H9N2) (Table 1, Table 3). Since the mid-1990s, influenza viruses of the H9 subtype have established stable lineages in poultry in Asia and have occasionally infected humans and swine (Table 1) [16,66-69]. As of 31 January 2014, human A(H9N2) cases have only been detected in Asia, particularly in China. Six cases were identified via the literature search [16,66-68]. Of those, three reported poultry exposure and all presented with mild ILI (Table 1). Reviews conducted by Peiris [46] and Cheng et al. [68] identified six additional human infections in China reported in the Chinese literature [70,71]. Three additional cases from Bangladesh, Hunan and Shenzhen, two with and one without poultry exposure, complete the total count of fifteen human cases caused by AIV A(H9N2) [69,72,73] (Table 3). Infections with AIV A(H9N2) viruses gained public health interest when researchers found that strains circulating in Asian poultry had a receptor specificity similar to

human influenza A viruses, which is considered one of the essential features of a human-to-human transmissible virus [74]. So far, however, no sustained human-to-human transmission of A(H9N2) influenza viruses has been reported.

Infections with other avian influenza virus subtypes

Experimental inoculation of human volunteers with influenza strains A(H4N8), A(H6N1) or A(H10N7) resulted in mild clinical symptoms and virus shedding in eleven volunteers [75]. In 2004, the National Influenza Center in Egypt and the WHO Influenza Collaborating Centre in the UK announced the isolation of influenza A(H10N7) virus from two children presenting with fever and cough in Egypt [76]. In Australia, virus of the same subtype could be detected by PCR in two abattoir workers with conjunctivitis who were exposed to infected poultry [20] (Table 3). In December 2013 and January 2014, human infection with A(H10N8) virus was reported for the first time in Jiangxi province, China [77,78]. Both patients were female and had visited a poultry and an agricultural market, respectively, before onset of illness. One of them was immunocompromised and had died whereas the other case was still in critical condition as of 31 January 2014. In 2013, CDC Taiwan reported a human case of AIV A(H6N1) infection causing mild pneumonia, although an avian source could not be identified [79,80] (Table 3).

Human infection with swine influenza viruses

An overview of all studies describing virologically confirmed human SIV cases is given in Table 2. In total, we identified 396 SIV-confirmed patients who were naturally infected (401 including experimental infections) (Table 2). Beare et al. [45] successfully recovered SIV from five of 20 human volunteers after experimental infection: of seven volunteers infected with SIV A(H3N2) related to A/Hong Kong/1/68, three tested virus-positive), and of 13 infected with a classical swine A(H1N1) virus strain, two tested positive. Of the naturally infected cases, 47 were infected with SIV A(H1N1), two with SIV A(H1N2), seven with SIV A(H3N2) and 340 with SIV A(H3N2)v (Table 2, Figure 2). The majority of these cases were reported in North America, 11 in Europe and six in Asia. One of the six Asian cases was infected with SIV A(H3N2) from the European lineage (Figure 2) [39]. SIV epidemiology differs between continents and was extensively reviewed for North America, Europe and Asia [81-84]. In addition to the studies discussed in the review by Myers et al. [26] we identified fourteen studies and reports describing a further 28 human SIV cases; 368 when taking into account 340 cases with SIV A(H3N2)v infection. Details on these studies are described in more detail in the following sections grouped by continent.

Infections with swine influenza A H1 subtype viruses

Asia: A 25 year-old male from the Philippines and a four year-old male from Thailand were infected with swine-like A(H1N2) and A(H1N1), respectively [85]. The isolated viruses carried HA genes most closely related to classical swine viruses circulating in Asia and North America. NA genes were most similar to circulating European SIV. Both cases showed mild ILI and neither of them had direct contact with swine, although occasional contact with backyard swine could not be ruled out.
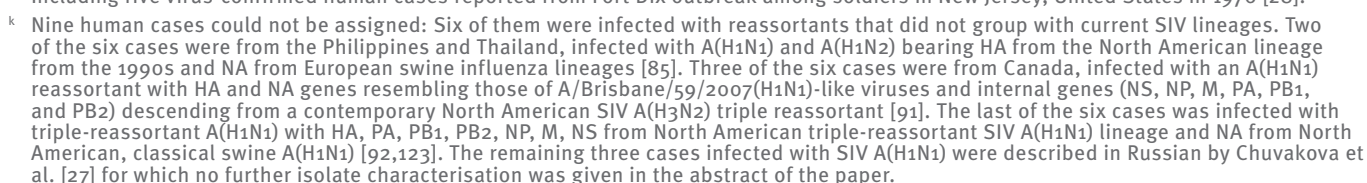
Europe: In Spain, a 50 year-old woman developed ILI after having been closely exposed to swine on a family farm [22]. No symptoms in swine were observed and sequencing of the isolate revealed that it was closely related to avian-like SIV A(H1N1) circulating in swine in western Europe. Three cases from Switzerland were detected who had worked with influenza-confirmed swine [86].

North America: For the US, 19 confirmed cases of SIV A(H1N1) infection were described in the published literature. This number could possibly be higher because Vincent et al. [87] reported on 26 human cases presenting with ILI after exposure to ill swine on a county fair in Ohio. The authors described that isolation and sequencing was performed for at least two of the human cases. Since the exact number of virologically confirmed cases was not given, we only added the two confirmed patients to the overall SIV A(H1N1) count (Table 3). Sequences from swine and human isolates from this outbreak were identical and were similar to triple–reassortant (tr) viruses currently circulating in swine herds in the US [87,88]. Another triple–reassortant A(H1N1) SIV was detected in a 17 year-old male from Wisconsin who assisted in butchering healthy appearing swine [89]. The patient presented with acute, mild respiratory illness without fever. Similarly, Dawood et al. [90] reported infection with trSIV A(H1N1) in a 19 year-old asthmatic male who visited a swine show in South Dakota. Symptoms included fever, ILI, vomiting and diarrhoea. No respiratory illness was observed in swine at this event. A trSIV A(H1N1) was also detected in three infected swine workers in Sasketchewan, Canada [91]. Household members did not report any signs of disease. Mild respiratory illness was reported in less than 1% of the swine; however, no confirmatory test had been conducted in ill swine. Unlike trSIV identified earlier in North America, this isolate contained an HA and a NA belonging to the A/Brisbane/58/2007 A(H1N1) lineage, whereas the remaining genes were derived from trSIV A(H3N2) viruses circulating in North America since 1998. Gray et al. [92] found another trSIV A(H1N1) in the course of a prospective survey, which was isolated from an ill swine farmer exposed to swine showing respiratory symptoms. Routine national influenza surveillance reported another 10 human cases infected with trSIV A(H1N1), distinct from A(H1N1)pdm09, and one case caused by trSIV A(H1N2). The majority of those twelve patients stated exposure to swine prior to disease onset and all made a full recovery [93].

The CDC reported additional human infections with SIV-variant viruses of subtype A(H1N1)v and A(H1N2)v identified in the US since 2005 [94]. These figures have

FIGURE 2

Timeline of emergence of swine influenza virus lineages circulating in Europe and North America indicating natural human infections from swine

HA: haemagglutinin; NA: neuraminidase; SIV: swine influenza virus; v: variant; hu: human.

Years on main arrow denote human influenza pandemics: A(H1N1) in 1918, A(H2N2) in 1957, A(H3N2) in 1968 and A(H1N1)pdm09 in 2009. Pictograms denote the origin of viral genes. Items in grey font indicate that the virus did not establish itself in the swine population and therefore did not circulate any further. Boxed items indicate infection in humans. Double-ended arrows indicate that four viruses were introduced in 1998 in the swine population.

Superscript letters refer to the genome segment constellation:

a   Classical SIV A(H1N1) constitutes a reassortant between human A/BM/1918 and unknown virus.

b   Recent phylogenetic evidence suggests that classical SIVA(H1N1) may have been present in Europe already in the 1930s and not around 1950 as previously assumed [122].

c   Classical SIV A(H1N1) was re-introduced into Europe via Italy in 1976 and circulated in European countries until it was replaced by avian-like SIV(H1N1) in 1979 (was not replaced in England) [122].

d   HA and NA from human HongKong/68-like virus, remaining genes from European avian-like swine A(H1N1).

e   HA from human A(H1N1) (England/80-like), NA from European reassortant swine A(H3N2), remaining genes from European avian-like swine A(H1N1).

f   HA, NA of human A(H3N2) origin, remaining genes from classical swine A(H1N1) and avian influenza origin.

g   HA, NA from classical SIV A(H1N1), remaining genes from triple-reassortant or swine A(H1N2).

h   HA, NA from seasonal human influenza viruses, remaining genes from triple-reassortant swine A(H3N2).

i   A(H3N2)variant: M gene from A(H1N1)pdm09, remaining genes from triple-reassortant swine A(H3N2), N2 antigenically different from triple-reassortant A(H3N2) from 1998.

j   Including five virus-confirmed human cases reported from Fort Dix outbreak among soldiers in New Jersey, United States in 1976 [28].

k   Nine human cases could not be assigned: Six of them were infected with reassortants that did not group with current SIV lineages. Two of the six cases were from the Philippines and Thailand, infected with A(H1N1) and A(H1N2) bearing HA from the North American lineage from the 1990s and NA from European swine influenza lineages [85]. Three of the six cases were from Canada, infected with an A(H1N1) reassortant with HA and NA genes resembling those of A/Brisbane/59/2007(H1N1)-like viruses and internal genes (NS, NP, M, PA, PB1, and PB2) descending from a contemporary North American SIV A(H3N2) triple reassortant [91]. The last of the six cases was infected with triple-reassortant A(H1N1) with HA, PA, PB1, PB2, NP, M, NS from North American triple-reassortant SIV A(H1N1) lineage and NA from North American, classical swine A(H1N1) [92,123]. The remaining three cases infected with SIV A(H1N1) were described in Russian by Chuvakova et al. [27] for which no further isolate characterisation was given in the abstract of the paper.

not been included in this review due to missing case history and in order to avoid double counting of cases described in the published literature.

Human infections with swine influenza A H3 subtype viruses

North America: In our search we detected two cases of trSIV A(H3N2) from Canada [95,96] and one from Kansas, US [97] infected before 2011. In Canada, a six year-old boy who lived on a swine farm presented with parotitis, nasal congestion, cough and pharyngitis, but had no fever. The swine appeared clinically healthy [95]. No swine exposure was reported in the second Canadian patient, a seven month-old child, who lived on a community farm and showed ILI symptoms [96]. Similarly, the third case from Kansas presented with ILI and is likely to have contracted trSIV A(H3N2) from swine he was exposed to at a county fair [97]. It is assumed that swine harboured the virus; PCR results performed on swine samples were negative but sera showed raised titres against SIV A(H3N2) indicating prior infection.

Between July and August 2011, a SIV variant, which accounted for the majority of reported human SIV A(H3N2) cases, appeared in the US, possibly reflecting enhanced surveillance activities in the country. This SIV A(H3N2) variant, A(H3N2)v, was first found in two children presenting with fever and respiratory signs [98,99]. Sequencing showed that this variant contained seven genes derived from the contemporary trSIV A(H3N2), circulating in the US swine population since 1998, as well as the M,gene from the A(H1N1) pdmo9 virus. Since its first occurrence in 2011, A(H3N2) v has been detected in 340 humans according to data as of 18 October 2013 [25]. Since July 2012, 17 patients have been hospitalised and one patient has died due to SIV A(H3N2)v infection. Most cases have reported prolonged exposure to swine before getting ill.

Human infections following exposure to other animals

We have identified three studies describing human susceptibility to equine influenza virus, demonstrated by experimental infection with equine subtype A(H3N8) [100-102]. The literature search did not reveal evidence of humans naturally infected with equine influenza virus.

Discussion

Here we present a review of the literature for studies presenting any evidence for human infection with animal influenza viruses. Virological techniques, e.g. virus culture, PCR and sequencing provide more solid evidence of infection, whereas serological methods can help reaching a diagnosis after the virus has been cleared from the body. Virus isolation is still the gold standard in detecting AIV infection. Human cases with virological evidence identified by PCR only should be interpreted with caution as detection of viral RNA without additional serological evidence (seroconversion, more than fourfold rise in the titre of paired samples) does not necessary imply infection, although current diagnostic methods heavily rely on case identification by PCR [103,104]. Serological results can be misleading because of the existence of cross–reactive antibodies and thus provide less solid evidence than direct detection of the infecting virus itself [105]. Therefore, we limited the current paper to studies providing virological evidence only.

Most evidence of human infection with AIV is associated with subtypes H5 and H7. Both subtypes can be linked to devastating outbreaks in poultry with high mortality, if transition from a low to a highly pathogenic state occurs [106]. Pathogenicity shown in poultry clearly does not reflect disease severity in humans: before the emergence in LPAI A(H7N9) as a cause of severe human illness, LPAI and HPAI viruses of subtype H7 had in the majority of cases been associated with mild eye infections or ILI [107]. The LPAI A(H7N9) infections diagnosed to date, however, have been unusually severe [23,64]. In addition to the severity of illness associated with these and also A(H5N1) viruses, the widespread circulation of different lineages, made possible by mutations and reassortments, justifies enhanced surveillance activities, given that few genetic changes may lead to a human-to-human transmissible virus [108,109].

Nevertheless, the evidence from experimental infections and anecdotal natural infections shows that other AIV may infect humans as well. There is insufficient systematic surveillance data to address the question whether the identified human cases reflect the level of virus circulation among wild or domestic birds, or whether certain subtypes infect humans preferentially.

Regarding SIV, there is ample evidence of human infection with A(H3N2), A(H1N1) and A(H1N2) subtypes, as well as reassortants derived from these endemic SIV lineages. Nevertheless, one has to be aware that the true number of human SIV cases is probably higher than reported since clinical symptoms of SIV are indistinguishable from seasonal influenza [86]. Whereas recent human cases in Europe were detected almost accidentally, the larger number of cases reported in the US since 2005, especially for influenza A(H3N2)v since 2011, may be the result of increased surveillance activities [86,110]. Swine were assumed to play an important role as intermediate hosts or 'mixing vessels' for strains of human, avian and swine origin, because they possess avian and human influenza-specific receptors in the tracheal epithelium [111]. However, recent research showed that the distribution of sialic acid receptors in the porcine respiratory tract is similar to that in humans, leading to the conclusion that humans are equally likely to constitute 'mixing vessels' [112,113]. The fact that influenza viruses can circulate unnoticed in swine populations [114] warrants close surveillance in this animal species as well. Co-circulation of different influenza virus strains in swine may facilitate the generation of new variants that could potentially

pose a threat for public health [115]. For instance, it is assumed that influenza A(H1N1)pdm09 was present in swine herds for months before it emerged as a pandemic strain in humans [116]. Conversely, Nelson et al. [117] reported at least 49 transmission events of influenza A(H1N1)pdm09 from humans to swine between 2009 and 2011, as well as at least 23 separate introductions of human seasonal influenza into swine since 1990.

Although there is some evidence for infection in swine with non-H1 and non-H3 subtype viruses (H9N2, H4N6) [115,118], we found no case reports describing human infection with these influenza A virus subtypes after swine exposure. Since most human infection events are associated with swine exposure, awareness of risk factors and personal protective equipment is paramount to limiting the chance of infection and preventing people working with or recreationally exposed to swine (including children) from becoming 'bridging links' between swine and community contacts and vice versa [92,119].

There are a few limitations to this review. The language restriction set to papers published in English only and the unsystematic search of the grey literature probably lead to the omission of additional documented human infections with animal influenza virus. Although this limitation may affect the total count of human cases, the aim of this review was to identify animal influenza subtypes, which crossed the species barrier to humans, and to our knowledge, all relevant subtypes were covered by this review.

Conclusions

There is evidence of infection of humans with animal influenza viruses belonging to various subtypes. All reported SIV cases have been exclusively associated with subtypes H1 and H3, and most AIV cases were caused by subtypes H5 and H7. Whether this reflects the prevalence of these viruses in birds kept or sold for consumption or a preferential ability to transmit to humans cannot be concluded from the available evidence. Given the often, mild illness associated with non-H5 and non-H7 animal influenza virus infections in humans, such cases likely are underreported [120]. Standardisation of diagnostic methods has significantly improved case ascertainment in recent years, but the monitoring of the evolution of these viruses is less advanced. Recent research pointed out that the majority of Asian and African countries have contributed only few sequences to surveillance networks and do not regularly sequence viruses as part of their surveillance programme [121]. Genetic sequencing is paramount to identifying changes with potential effect on the phenotype of circulating influenza viruses, and could thereby strengthen worldwide epidemic and pandemic preparedness [121]. To be prepared for a potentially emerging influenza virus of animal origin in humans, enhanced global surveillance in animal populations is therefore indicated to monitor evolution and circulation of viruses with yet unknown public health risks.

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