

Review

Epidemiological Risk Factors for Animal Influenza A Viruses Overcoming Species Barriers

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Abstract: Drivers and risk factors for Influenza A virus transmission across species barriers are poorly understood, despite the ever present threat to human and animal health potentially on a pandemic scale. Here we review the published evidence for epidemiological risk factors associated with influenza viruses transmitting between animal species and from animals to humans. A total of 39 papers were found with evidence of epidemiological risk factors for influenza virus transmission from animals to humans; 18 of which had some statistical measure associated with the transmission of a virus. Circumstantial or observational evidence of risk factors for transmission between animal species was found in 21 papers, including proximity to infected animals, ingestion of infected material and potential association with a species known to carry influenza virus. Only three publications were found which presented a statistical measure of an epidemiological risk factor for the transmission of influenza between animal species. This review has identified a significant gap in knowledge regarding epidemiological risk factors for the transmission of influenza viruses between animal species.

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INTRODUCTION

Wild birds of the Orders Anseriformes and Charadriiformes are the natural reservoir for most Influenza A viruses (IAVs) (family *Orthomyxoviridae*), and subtypes H1–H16 have been isolated from wild birds (Alexander and Brown 2000; Suarez 2000, 2010). Bats have recently been identified as hosts for subtypes H17 and H18 (Tong et al. 2012; Tong et al. 2013). Influenza A viruses can infect mammalian species either endemically or cause sporadic outbreaks (and occasional spillover from host species) (Ducatez et al. 2008) in, for example, pigs (H1, H2, H3), horses (H3 and H7), dogs (H3), marine mammals (including pinnipeds and cetaceans) (H3, H7, H10 and H13) and humans (H1, H2, H3) (Alexander and Brown 2000; Daly et al. 2008; Reperant et al. 2009; Crispe et al. 2011; Freidl et al. 2014). Occasional spillover infections of various subtypes in a range of mammalian species have been identified including H5 in domestic cats and less commonly, zoo felids (Keawcharoen et al. 2004; Kuiken et al. 2004; Thanawongnuwech et al. 2005; Songserm et al. 2006; Yingst et al. 2006; Klopfleisch et al. 2007b). Transmission of IAVs between humans and other mammals has also been demonstrated in both directions (Alexander and Brown 2000; Van Reeth et al. 2007). Transmission generally occurs through direct contact or indirect contact via environmental contamination or ingestion of infected material (Keawcharoen et al. 2004; Thanawongnuwech et al. 2005; Songserm et al. 2006; Daly et al. 2008; Crispe et al. 2011).

Various studies have been conducted to identify risk factors for transmission of IAVs between species, including from animals to humans and between animal species. Much of this work has focused on intrinsic or virological risk factors (Munoz et al. 2015) while epidemiological (environmental or host) risk factors have been less studied. These include direct/indirect exposure through, for example, backyard farming, keeping poultry in the home, preparation of food for consumption and live poultry markets, occupational exposure and environmental exposures such as through swimming and bathing (Mounts et al. 1999; Dudley 2008; Gray et al. 2008; Vong et al. 2009; Zhou et al. 2009; Gerloff et al. 2011; Khan et al. 2012; Krueger et al. 2013).

The primary aim of this literature review was to identify epidemiological risk factors associated with trans-

mission of IAVs between species, including from animals to humans. A further objective of this review was to identify knowledge gaps of influenza epidemiology to which future research could be directed.

METHODS

Literature searches were performed between February 2012 and September 2015 to identify relevant papers describing epidemiological risk factors associated with an IAV being transmitted between species. The primary method of reference identification was electronic searches carried out in Web of Knowledge (which simultaneously searches Web of Science 1995, Current contents 1998, CAB abstracts 1910, Medline 1950) to search all available published literature on epidemiological risk factors associated with jump of IAVs between species (Table 1). Search terms also used to identify papers with epidemiological risk factors associated with the transmission of IAVs from animals to humans included: “influenza”, “influenza virus”, “animals”, “swine”, “birds”, “poultry”, “wildbird”, “waterbird”, “waterfowl”, “goose”, “duck”, “chicken”, “turkey”, “environment”, “animal-to-human”, “transmission-to-humans”, “interspecies transmission”, “human”, “case”, “seroprevalence”, “serosurveillance”, “prevalence”, “incidence”, “risk factor” and “exposure”.

The first literature searches were carried out for all papers published between 1910 and the dates of searching. Language restrictions were not placed on the searches if the abstract was available in English; however, articles were not translated. Review articles were generally not included because the aim of this study was to identify primary studies that identified and measured risk factors; however, one review was screened to identify additional references. If screening of the title and/or abstract met the inclusion criteria, full text was assessed for eligibility.

The following inclusion criteria were applied for the review: no timeframe, global geographic scope, avian and mammalian species (including risk factors for the virus to spread from animals to humans), all subtypes, exposures (environmental, husbandry, biosecurity, marketing/trade, disease management related), study design (observational) and types of literature (published, grey). Articles related to Influenza B and C and experimental studies were excluded.

The first searches were not successful in locating relevant epidemiological risk factor information (only one anecdotal report found). Further approaches in finding relevant publications included reviewing (1) Reference lists of publications retrieved through the original literature search; (2) References known to co-authors of this study; (3) Databases held by laboratories, research institutions or international organisations, e.g. EMPRES-i¹ (FAO 2012), and (4) Proceedings from conferences on influenza from 2012.

In the original literature searches carried out in 2012, a total of 731 references from online searches were screened for eligibility; of these, 444 abstracts were reviewed and 85 papers read in full. In addition, 58 papers were reviewed in their entirety after screening a review article (Reperant et al. 2009) and other references recommended by co-authors. More than half of the publications reviewed related to Highly Pathogenic Avian Influenza (HPAI) H5N1. In searches carried out to include papers published between 2012 and 2015, additional 222 abstracts were reviewed and 110 papers read in full.

Eligible papers were grouped into two broad categories (some papers were relevant to more than one category and so may be counted more than once): (1) cross-species transmission among animals (not necessarily referring to sustained transmission and could relate to a single event) ($n = 21$) and (2) cross-species transmission of animal influenza viruses to humans ($n = 39$).

RESULTS

Risk Factors for the Transmission of Influenza A Viruses Between Animal Species

A total of 21 papers described epidemiological risk factors that could be associated with IAVs transmitting between animals (Table 2). Most papers described observational or circumstantial evidence and three reported a statistical measure of risk factors identified (Biswas et al. 2011; Aguirre-Ezkauriatza et al. 2012; Zhou et al. 2015). Eleven papers presented circumstantial evidence, speculating on factors influencing the transmission of IAVs between species, but with no direct evidence. Ten publications pre-

sented observational reports of the epidemiological risk factors in a particular incident. Generally, publications referred to one incident (some a single case, others with large mortalities) and due to the genetic characteristics of the virus (e.g. relatedness to another strain), led to possible hypotheses of transmission routes from one species to another.

Twenty papers described incidents involving proximity to infected animals, and seven described the feeding or ingestion of infected animal organs. Three papers referred to the transmission of IAV (of swine or turkey origin, in both directions) potentially from close proximity of farms or to external water sources (Karasin et al. 2000; Suarez et al. 2002; Yassine et al. 2011). As pigs have receptors for both avian and human influenza viruses, they could play an important role in transmission of IAV between birds and mammals (Myers et al. 2007; Van Reeth 2007).

Four papers described transmission between marine mammals (Geraci et al. 1982; Hinshaw et al. 1986; Callan et al. 1995); three involved harbour seals (*Phoca vitulina*) and one, pilot whales (*Globicephala melaena*). All four papers suggested close contact (direct or indirect) with coastal birds or bird faeces at feeding or haul-out sites as the source of infection. Geraci et al. (1982) referred to H7N7 infection in harbour seals potentially being infected from water- and shore birds. More recently, avian H3N8 virus has emerged in harbour seal populations in the USA causing high mortality. Although no epidemiological risk factors were stated, recovered isolates were similar to a virus that has been circulating in North American waterfowl since at least 2002 but showed mutations thought to be associated with its adaptation to the mammalian host (Anthony et al. 2012). In 2014, Zohari et al. (2014) first reported IAV isolation of H10N7 in harbour seals (*Phoca vitulina*) from a mass mortality event in Sweden, the first reported in Europe and the first known isolation of the H10 subtype virus in seals. Genetically, this virus is closely related to Eurasian IAVs from wild and domestic birds, supporting the theory that the subtype has been transmitted from birds to seals by direct or indirect contact.

Close contact to coastal birds and crows (*Corvus corvus*) was thought to be a potential route of transmission in farmed mink (*Mustela lutreola*) in Sweden (Klingeborn et al. 1985). Yoon et al. (2012) speculated that a source for H1N2 infection in mink in the USA was uncooked turkey meat. Although the virus was considered to be of swine origin as the strain was closely related to the US endemic swine influenza virus (SIV), there was no obvious source to

¹FAO EMPRES-i compiles and displays information from numerous sources (FAO representatives or country missions, FAO reports, OIE, official government sources, European Commission, FAO reference centres, laboratories and FAO collaborators) to provide full and accurate information on the animal disease situation worldwide.

Table 1. Summary of Search Strings Used

Date of search and search number	Search string
24/02/2012	
1	Topic = ((influenza* OR flu* OR orthomyxovir*)) AND Topic = ((jump* NEAR species) OR cross?species OR inter?species)
2	Topic = (influenza* OR flu* OR orthomyxovir*) AND Topic = (jump* NEAR species OR cross?species OR inter?species) NOT Topic = (human) AND Topic = (pandemic)
3	Topic = (influenza* OR flu* OR orthomyxovir*) AND Topic = (jump* NEAR species) OR Topic = (cross?species OR inter?species) NOT Topic = (human)
4	Topic = (influenza* OR flu* OR orthomyxovir*) AND Topic = (“risk factors” or “risk” or “factors”) AND Topic = (pandemic) AND Topic = (spread) AND Topic = (zoonotic)
15/03/2012	
5	Topic = (influenza* or orthomyxovir*) AND Topic = (bird or avian) AND Topic = (equine or horse) AND Topic = (canine or dog) AND Topic = (felid or cat)
20/03/2012	
6	Topic = (transmission of influenza from birds to cats)
7	Topic = (transmission of influenza from horses to dogs)
8	Topic = (transmission of influenza from birds to swine)
9	Topic = (transmission of influenza from birds to seals)
16/05/2014	Search strings related to searches 1–9 repeated
10	
29/04/2015	Search strings related to searches 1–9 repeated
11	
11/09/2015	
12	TS = “influenza A” AND TS = (“risk factor*” OR determinant*) AND TS = (transmission OR spread) AND TS = (zoono* OR “animal to human” OR “animal-to-human”) NOT TS = (anthropono* OR “reverse zoono*” OR “human to animal” OR “human-to-animal”) <i>and</i> TS = (H7N9 NOT H5N1) AND TS = (“risk factor*” OR determinant*) AND TS = (transmission OR spread) AND TS = (zoono* OR “animal to human” OR “animal-to-human”) NOT TS = (anthropono* OR “reverse zoono*” OR “human to animal” OR “human-to-animal”)

the mink (no pork by-products fed, or swine herds nearby). Authors speculated the source of infection was uncooked turkey meat since cross-species transmission of SIV particularly of this subtype is known to occur in US swine herds.

Feeding on infectious tissues from birds or horses (*Equus ferus*) has been linked to cross-species transmission of HPAI H5N1 virus in leopards (*Panthera pardus*), tigers

(*Panthera tigris*), stone martens (*Martes foina*), cats (*Felis catus*) and H3N8 virus in dogs (*Canis lupus*) (Keawcharoen et al. 2004; Songserm et al. 2006; Yingst et al. 2006; Klopfleisch et al. 2007a; Daly et al. 2008). Proximity to horses has also been described as a possible cause of transmission of H3N8 virus to dogs (Kirkland et al. 2010; Crispe et al. 2011). Although the role of dogs was not clearly demonstrated in the epidemiology of the disease, the permanent

Table 2. Summary of Potential Risk Factors Associated with Influenza Viruses Transmitting Between Animal Species

Subtype	Country	Donor Species	Recipient Species	Observational or Circumstantial Evidence	Author
H1N2	USA	Pig (<i>Sus scrofa domestica</i>)	Nicholas turkey breeder hens (<i>Meleagris gallopavo</i>)	Circumstantial: proximity of turkey and swine farms	Suarez et al. (2002)
H1N2	USA	Uncooked turkey meat	Mink (<i>Mustela lutreola</i>)	Circumstantial: speculative that source was uncooked turkey meat—the IAV was also of swine origin	Yoon et al. (2012)
H3N2	Not specified (review)	Turkey (<i>Meleagris gallopavo</i>)	Pig (<i>Sus scrofa domestica</i>)	Circumstantial: proximity of turkey and swine farms	Yassine et al. (2011)
H3N3	USA	North American coastal birds	Harbour seal (<i>Phoca vitulina</i>)	Circumstantial: haul-out sites—close contact with coastal birds	Callan et al. (1995)
H3N8	Mexico	Dog (<i>Canis lupus familiaris</i>)	Horse (<i>Equus ferus</i>)	Observational: higher seroprevalence in horses associated with permanent presence of dogs in the stables (MH-OR 1.327; $P < 0.0001$)	Aguirre-Ezkauriatza et al. (2012)
H3N8	Australia	Horse (<i>Equus ferus</i>)	Dog (<i>Canis lupus familiaris</i>)	Observational: seropositive dogs were in close proximity to infected horses	Crispe et al. (2011)
H3N8	UK	Horse (<i>Equus ferus</i>)	Dog (<i>Canis lupus familiaris</i>)	Observational: feeding of infected horse meat week before clinical signs/possible aerosol transmission (housing proximity to horses)	Daly et al. (2008)
H3N8 (EIV)	Australia	Horses (<i>Equus ferus</i>)	Dog (<i>Canis lupus familiaris</i>)	Observational: seropositive dogs were in close proximity to infected horses	Kirkland et al. (2010)
H4N6	Canada	Waterfowl (Anatidae)	Pig (<i>Sus scrofa domestica</i>)	Circumstantial: proximity of affected farm to lake with waterfowl, and raw lake water being pumped into the farm	Karasin et al. (2000)
HPAI H5N1	Bangladesh	Crow (Corvidae)	Chicken (<i>Gallus gallus domesticus</i>)	Observational: increased association of HPAI H5N1 infection with dead crow seen at or near farm (OR 47.4, CI 4.7–480.3)	Biswas et al. (2011)
H5N1	Thailand	Birds	Leopard (<i>Panthera pardus</i>) and tiger (<i>Panthera tigris</i>)	Observational: direct infection through ingestion of infected bird carcasses	Keawcharoen et al. (2004)
H5N1	Germany	Wild waterfowl (Anatidae)	Stone marten (<i>Martes foina</i>)	Circumstantial: potential route through scavenging of infectious material	Klopfleisch et al. (2007a)
H5N1	Germany	Wild waterfowl (Swans, ducks, geese) (Anatidae)	Domestic cat (<i>Felis catus</i>)	Circumstantial: proximity to wild birds—scavenging	Klopfleisch et al. (2007b)
H5N1	Thailand	Pigeon (<i>Columbus livia</i>)	Cat (<i>Felis catus</i>)	Circumstantial: Ingestion of infected birds	Songserm et al. (2006)

Table 2. continued

Subtype	Country	Donor Species	Recipient Species	Observational or Circumstantial Evidence	Author
H5N1	Iraq	Goose (<i>Anser anser domesticus</i>)	Cat (<i>Felis catus</i>)	Observational: H5N1 detected from a goose from the same dwelling	Yingst et al. (2006)
H5N1	China	Poultry	Cat (<i>Felis catus</i>)	Observational: cats in live poultry markets were more likely to have evidence of previous infection than those sampled from poultry farms in rural areas (OR 2.9)	Zhou et al. (2015)
H7N7	USA	Tern (<i>Sterna</i> sp.) or marine mammal	Harbour seal (<i>Phoca vitulina</i>)	Circumstantial: Terna (<i>Sterna</i> sp.) associate with seals in water and on land, therefore could be source of infection (or another marine species could have carried the virus)	Geraci et al. (1982)
H10 (Six strains)	Sweden	Crows (<i>Corvus corvus</i>) and gulls (<i>Laridae</i> sp.)	Mink (<i>Mustela lutreola</i>)	Circumstantial: unknown route of transmission but proximity to coastal birds/crows and mink cages kept outside (food attracting birds)	Klingeborn et al. (1985)
H10N5	China	Birds	Pigs (<i>Sus scrofa domestica</i>)	Observational: isolated the IAV in pigs, suggesting likely interspecies transmission as has rarely been isolated in mammals	Wang et al. (2012)
H10N7	Sweden	Sea birds	Harbour seal (<i>Phoca vitulina</i>)	Observational: isolated the subtype in seals in mass mortality event—first known isolation of this subtype in seals	Zohari et al. (2014)
H13	USA	Gulls (<i>Laridae</i> sp.)	Pilot whale (<i>Globicephala melaleona</i>)	Circumstantial: increased probability of faecal-oral transmission of virus through seawater	Hinshaw et al. (1986)

Table 3. Statistical Measures of Risk Factors for the Jump of Influenza Viruses from Animal to Human: A Summary of Published Studies and Statistically Significant Results

AI subtype	Study population	Country of origin	Year of study	Risk factors	Measure of risk (e.g. ARR, RR, OR)	95% CI	Author
AIV	207 workers (Cross-sectional study; 105 live bird market and 102 poultry farm workers)	India	2008	Logistic regression model—awareness of AI	OR		Kumar et al. (2013)
				Education (11 + compared to 0–3 (ref.) and 4–10 year (ns))	43.66	8.46–225.31	
				Duration of work in poultry 5–10 years (ref. <5 year > 10 year)	3.03	1.19–7.73	
				Non-labourers (ref. labourers)	4.22	1.49–11.97	
				Urban location (ref. rural)	7.75	1.45–41.55	
				Logistic regression model—good biosecurity practice	11.9	5.15–27.03	
				Education (11 + compared to 0–3 (ref.) and 4–10 year (ns))	6.92	2.34–20.45	
				Urban location (ref. rural)	5.71	2.66–12.35	
pH1N1/SIV	211 swine contacts, 224 matched controls	Luxembourg	2009	Risk factor analysis	OR		Gerloff et al. (2011)
				Odds of having antibodies against pandemic H1N1 (2.4 × to 3.9 × greater for swine workers (SW) than controls)	2.4	1.4–4.2	
				Odds of having antibodies against SIV—(1.3 × to 9.9 × greater for swine workers (SW) than for controls)	3.9	1.3–12	
				Farm worker versus slaughterhouse workers	1.3	0.8–1.9	
					9.9	0.5–38.9	

Table 3. continued

AI subtype	Study population	Country of origin	Year of study	Risk factors	Measure of risk (e.g. ARR, RR, OR)	95% CI	Author
H3N2	SIV positive pH1N1 positive Male SW's—odds of being: SIV positive pH1N1 positive 26.5% of SW's self-reported receiving ≥ 1 dose of seasonal influenza vaccine during the past 5 years. Among vaccinated SW's, odds of having antibodies against			SIV	2.3	1.1–5	Bowman et al. (2014b)
				pH1N1	1.2	0.6–2.5	
				Among vaccinated SW's, odds of having antibodies against	1.1	0.6–2.3	
				SIV	1.7	0.8–3.5	
				pH1N1	1.3	0.7–2.5	
Influenza A virus, H4, H5, H6, H9 and H10	Swine nasal swabs and associated metadata collected at 40 Ohio fairs 95 cases (exposed turkey workers), 82 controls (unexposed)	USA	2012	Breeding show	OR	2.417–infinity	Bowman et al. (2014b)
				Number of pigs	21.676	1.002–1.026	
Influenza A virus, H4, H5, H6, H9 and H10	95 cases (exposed turkey workers), 82 controls (unexposed)	USA	2007–08	Seropositive for avian H5 among all growers	OR	1.5–13.3	Kayali et al. (2010)
				Seropositive for the following AI subtypes among small growers:			
				H4	3.9	1.2–12.8	
				H5	6.2	2.0–19.6	
				H6	15.3	2.0–115.2	
H9	3.9	1.2–12.8					

Table 3. continued

AI subtype	Study population	Country of origin	Year of study	Risk factors	Measure of risk (e.g. ARR, RR, OR)	95% CI	Author
HPAI H5N1	Cohort study (293 Government workers (GW) and 1525 poultry workers (PW) involved in poultry slaughter Nested case control analysis of poultry workers 81 cases, 1231 controls	Hong Kong	1997–98	After adjusting for antibodies titres, exposure to chicken and exposure to swine, small growers has higher odds for infection with an avian H10 virus compared with controls	OR 5.8	1.2–27.7	Buxton Bridges et al. (2002)
				Male	1.3	0.8–2.1	
				Current smoker (A risk factor for H5 antibody among GWs not PWs)	1.1	0.7–1.7	
				Work in retail poultry operation versus wholesale poultry farm/hatchery	2.7	1.5–4.9	
				> 10% mortality in poultry	2.2	1.3–3.7	
				Touching poultry	5.8	0.9–113.6	
				Butchering poultry	3.2	1.6–5.9	
				Feeding poultry	2.4	1.4–4.1	
				Collecting eggs	1.2	0.6–2.2	
				Cleaning poultry stalls	1.6	0.9–2.7	
				Touching poultry intestines	1.7	0.9–2.9	
				Handling money	1.6	1.0–2.5	
				Preparing poultry for restaurants	1.7	1.1–2.7	
HPAI H5N1	28 cases, 106 controls	Vietnam	2004	Preparing sick or dead poultry for consumption ≤ 7 days before onset of illness Having sick or dead poultry in the household ≤ 7 days before onset of illness	OR 8.99 4.94	0.98–81.99 1.21–20.20	Dinh et al. (2006)

Table 3. continued

AI subtype	Study population	Country of origin	Year of study	Risk factors	Measure of risk (e.g. ARR, RR, OR)	95% CI	Author
HPAI H5N1	99 human cases	Vietnam	2003–04	No indoor water source in household Poultry outbreaks reported in the same district	6.46 OR	1.20–34.81	Minh et al. 2009
				1 week later	6.15	3.33–11.38	
				4 weeks later	2.48	1.20–5.13	
				Odds of a report of a human case following poultry outbreaks in the same or neighbouring district			
				In the same week	2.75	1.43–5.30	
				1 week later	2.56	1.31–5.00	
				4 weeks later	2.7	1.56–4.66	
HPAI H5N1	15 cases, 41 controls	Hong Kong	1997	Exposure to live poultry in market ($P = .045$)	OR 4.5	1.2–21.7	Mounts et al. (1999)
				Played in indoor playground ($P = .013$)	0	0.0–0.5	
HPAI H5N1	7 cases, 24 controls	Cambodia	2006	Swimming or bathing in ponds ($P = .03$)	OR 11.3	1.25–102.18	Vong et al. (2009)
				People gathering poultry and placing in cages and/or poultry areas ($P = .05$)	5.8	0.98–34.12	
HPAI H5N1	28 urban and rural cases, 134 urban and rural controls	China	2008	Multivariate analysis (all participants)	OR		Zhou et al. (2009)
				Direct contact with sick or dead poultry ($P < .001$)	506.6	15.7–16319.6	
				Indirect exposure to sick or dead poultry ($P = .002$)	56.9	4.3–745.6	
				Visiting a wet poultry market ($P = .001$).	15.4	3.0–80.2	
				Multivariate analysis (rural participants)			

Table 3. continued

AI subtype	Study population	Country of origin	Year of study	Risk factors	Measure of risk (e.g. ARR, RR, OR)	95% CI	Author
H6N2	Serosurveillance study (15,689 serum samples)	China	2009–2011	Direct contact with sick or dead poultry ($P < .001$), Indirect exposure to sick or dead poultry ($P = .008$) Occupation:	67.3 25.4 OR	5.8–783.8 2.4–274.3	Xin et al. (2015)
				Live poultry market	2.10	1.27–3.47	
				Poultry farm	0.40	0.18–0.87	
				Backyard poultry farm	1.05	0.61–1.82	
				Poultry slaughter factory	0.38	0.47–3.54	
				Wild bird habitat	1.28	0.39–2.11	
				Other	0.91	0.39–2.11	
				Male	1.18	0.72–1.94	
				Age youth (15–24)	0.75	0.19–3.00	
				Adult (25–59)	1.27	0.54–2.94	
				North China (South as ref.)	0.59	0.30–1.15	
Influenza A virus H6 and H7	Prospective study (poultry exposed 385, unexposed 418) 803 cases, 66 controls	USA	2004	Associated with elevated antibodies titres (Adjusted OR)	OR		Gray et al. (2008)
				Positive for H1N1:			
				H5	2	1.2–3.4	
				H7	3.1	1.4–7	
				Touching live poultry or game birds (H5)	1.2	1.02–1.5	
				Hunting wild birds (H7)	2.8	1.2–6.5	
				Working with poultry since 2000			
				H6	3.4	1.4–8.5	
				H7	2.5	1.1–5.7	
				Chronic medical condition (H6)	5.2	1.9–13.9	

Table 3. continued

AI subtype	Study population	Country of origin	Year of study	Risk factors	Measure of risk (e.g. ARR, RR, OR)	95% CI	Author
H7N9	Cross-sectional study	China	2013	Live bird market density (markets per km ²)	OR 1.08	1.04–1.12	Fuller et al. (2014)
H7N9	Case-control study 25 cases, 93 controls	China	2013	Chronic medical conditions (hypertension excluded) ($P = 0.021$) Direct contact with poultry ($P = 0.012$) Environment-related exposures ($P = 0.064$)	OR 6.0 9.1 4.2	1.3–27.3 1.6–50.9 0.9–19.6	Ai et al. (2013)
H7N9	Case-control study 89 cases, 339 controls	China	2013	Chronic obstructive pulmonary disease (COPD) Immunosuppressive medication Obesity Visit to live poultry market Direct/indirect contact with poultry Age (continuous)	OR 5 7 3.7 3.4 2.9 Adjusted OR 1.03	1.7–14.4 1–44.7 1.3–10.8 1.8–6.7 1.3–6.3 1.002–1.1	Liu et al. (2014)
H9N2	800 participants (prospective cohort study)	Thailand	2010	Influenza vaccine in last 12 months Exposed to poultry in the last year: 21–12,000 birds/day (mean 933) 7–20 birds/day (mean 14) 1–6 birds/day (mean 4)	5.5 1.1 2.3 0.9 OR	2.3–13.1 0.4–3.0 1.04–5.2 0.3–3.3	Krueger et al. (2013)
H9N2	800 participants (rural cohort)	Cambodia	2008	Older age > 60 year Older age 40–59 (compared to 20–39 years (ref cat)) Elevated H1N1 HI titre Elevated H3N2 HI titre Elevated H2N2 MN titre	6.9 5.2 3.8 0.3 5.5	1–48 1–27 1.4–10.2 0.1–0.9 1.8–16.4	Blair et al. (2013)

Where a study found significant factors in their multivariate analyses, these have been included in the table. Please refer to the paper for full description of results including univariate analyses

presence of dogs in stables (in the US–Mexico Border) was found to be significantly associated with an increase in H3N8 seroprevalence in horses (MH-OR 1.327; (Aguirre-Ezkauriatza et al. 2012)). Proximity to wild birds (and the potential for scavenging) was also a potential risk for cats to be infected with influenza virus HPAI H5N1 virus (Klopfleisch et al. 2007b). A sero-epidemiological study carried out in Southern China (Sun et al. 2014) found little or no evidence of transmission of H5N1 virus to cats. Only one of 1680 blood samples from cats tested positive by haemagglutination inhibition (HI) test, and none could be confirmed by neutralisation test/assay (NT). In China, Zhou et al. (2015) studied H9N2, H3N2 and H5N1 viruses and identified that cats found in live poultry markets were more likely to have evidence of previous H5N1 virus infection than those sampled from poultry farms in rural areas (OR 2.9, $P < 0.05$).

IAV of subtype H10N5 was isolated from pigs and is a virus rarely isolated from mammals, and thus provides an example of likely interspecies transmission to pigs (Amir-salehy et al. (2012); Wang et al. (2012); Zhang et al. (2013); Feng et al. (2014); Panahi et al. (2014)).

A study by Biswas et al. (2011) in Bangladesh hypothesised that crows (*Corvus splendens*) played a role in the epidemiology of HPAI H5N1. In 2008, mass mortality events in crows were reported in eight districts where H5N1 HPAI virus was also detected. Indeed, the presence of dead crows at or near a farm was associated with increased odds of HPAI H5N1 virus occurrence in commercial chickens (OR 47.4).

Risk Factors for the Transmission of Influenza A Viruses from Animals to Humans

A total of 39 papers were identified that considered epidemiological risk factors for cross-species transmission from animals to humans. Eighteen reported a statistical measure of the risk factors described (Table 3), 16 of which referred to avian to human transmission and around half referred to HPAI H5N1 virus in Asia, which is unsurprising given the widespread distribution and impact of this virus in the region.

Direct or Indirect Exposure to Poultry (or Other Species)

Sixteen papers referred to exposure to poultry as a risk for human infection and the odds (OR) for associated risk ranged from 1.1 to 506.

Most publications investigating transmission of HPAI H5N1 virus from animals to humans focused on direct or indirect exposure to poultry as a significant risk factor for infection, including housing poultry in the family home or in the neighbourhood, preparation of poultry for consumption, contact with sick or dead birds and live bird markets (Dudley 2008; Khan et al. 2012).

A large number of surveys and studies describing the risk of HPAI H5N1 virus transmitting from poultry to humans have been documented in the literature. Khan et al. (2012) described aspects of family (backyard) poultry management that are known through other studies to be associated with transmission of infection; close proximity of poultry housing to owners living quarters, providing feed to healthy and sick birds and slaughtering birds inside the home.

Study results from Krueger et al. (2013) found that an increase in H9N2 virus antibodies in Thai villagers was associated with exposure to 7–20 birds/day (OR 2.3) compared to 1–6 birds/day (OR 0.9) or 21–12,000 birds/day (OR 1.1), suggesting backyard type flocks pose a higher risk of infecting humans, possibly due to closer physical contact with the birds as well as contact during the slaughtering process.

In China, direct or indirect exposure (within 1 m) to sick and dead poultry was a significant risk factor for HPAI H5N1 virus infection among all participants, both urban and rural (Zhou et al. 2009). In Egypt, Tseng et al. (2010) found that in 84.6% of confirmed cases of HPAI H5N1 virus infection in humans between 2006 and 2009, there had been contact with sick or dead poultry or birds. Backyard and rooftop-owned birds were suggested as a more significant risk factor for human infection of HPAI H5N1 virus rather than those from poultry farms. Minh et al. (2009) found that the presence of outbreaks in poultry in the same or neighbouring district in Vietnam was associated with increased likelihood of human infection.

Exposure to poultry through visits to wet poultry markets was also found to be significantly associated with the transmission of HPAI H5N1 virus and other IAV subtypes to humans (FAO 2006; Zhou et al. 2009). Mounts et al. (1999) found that exposure to live poultry in Hong Kong (by visiting either a retail poultry stall or a market selling live poultry) in the week before illness was significantly associated with HPAI H5N1 virus infection (OR 4.5). The handling of poultry (placing in cages and/or poultry areas) (OR 5.8, $P = .05$) and the cleaning of cages and poultry areas (OR 5, $P = 0.09$) has also been associated

with increased odds of HPAI H5N1 virus infection in humans, in Cambodia (Vong et al. 2009). With the emergence of H7N9 in 2013 in China, studies describing cases of human infection often report recent exposure to poultry through visiting live poultry markets as a key epidemiological characteristic (Guan et al. 2013; Li et al. 2014; Zhuang et al. 2013; Gong et al. 2014; Wang et al. 2015). The odds of exposure and thus infection were found to be higher in people that had visited live poultry markets (OR ranging from 3.4 to 9). Ai et al. (2013) carried out a case-control study to identify risk factors for human infection with H7N9 virus. In their multivariate analyses, the odds of H7N9 virus infection were nine times higher where direct contact with poultry occurred in live poultry markets (OR 9.1). Liu et al.'s (2014) case-control study in 2013 found that the odds of H7N9 virus infection were 3.4 times higher (OR 3.4) where visits to live poultry markets had occurred, even after adjusting for poultry contact and other confounding factors.

Occupational Exposure

Occupational exposure to infected birds or pigs has been implicated as increasing the risk for human infection. Buxton Bridges et al. (2002) found that most occupational duties involving poultry exposure in Hong Kong were associated with increased odds of being seropositive for HPAI H5N1 virus. In a stratified analysis, risk factors most highly associated with H5 seropositivity were butchering poultry and exposure to diseased poultry with greater than 10% mortality. Some potential evidence of protective risk factors was found; not living on a poultry farm (OR 0.4, CI 0.1–2.1) and no febrile respiratory illness (fever/chest infections) since November 1997 (OR 0.8, CI 0.5–1.3), although the 95% confidence intervals for the factors included 1, so further study or analysis would be required to clarify these associations. Mounst et al.'s (1999) study in Hong Kong found that activities relating to poultry preparation or eating, travel with and contact with wild birds, for example, through hunting, were not significantly different between cases and controls.

Occupational exposure at live bird markets has been associated with increased risk of IAV transmission to humans. In 2013, human infections of H7N9 virus were reported in Eastern China, which led to live bird market closures in heavily affected areas (Chowell et al. 2013). Evidence points to an avian reservoir with the virus found in chickens at some live bird markets thought to be the

main source of human infections (Lam et al. 2013). Fuller et al. (2014) identified that the risk of H7N9 virus infection in humans increased by 8% for each additional live bird market per km² (OR 1.08).

In a study on H6N2 virus in China (Xin et al. 2015), the authors found that seropositivity was highest in workers in live poultry markets, backyard poultry farmers and workers in wild bird habitats, with an increased risk for human infection (OR 2.1, 1.1 and 1.3, respectively), compared to exposure through occupations such as poultry farming (OR 0.4), poultry slaughter factory (OR 0.4) and others (OR 0.9).

Elevated antibody titres to H6 and H7 viruses have been associated with the following factors in a study conducted in rural United States (USA): working with poultry, chronic medical conditions, and hunting of wild birds (Gray et al. 2008). A further study in the USA found that turkey workers involved in small-scale production of backyard or free range flocks (flocks of <1000) were considered to have an increased risk of IAV infections, from increased antibody titres against H4, H5, H6, H9 and H10 IAV subtypes. Adjusted odds ratios (after adjusting for antibody titres against human influenza H1N1 virus and/or exposure to chickens and swine) varied between 3.9 and 15.3 for the IAV strains when compared to non-exposed controls (Kayali et al. 2010). Involvement in depopulation following an outbreak is also a potentially high-risk activity, and Bos et al. (2010) found a higher probability of infection was associated with clinical inspection (7.6%) and active culling of poultry (6.2%) during the HPAI H7N7 virus Netherlands epizootic in 2003. The probability of infection through depopulation was negligible where biosecurity was described as “managed” (0.0%), and where there was cleaning assistance during depopulation (0.0%).

One study conducted in Luxembourg identified a statistical measure for infection from pigs to humans where the odds of having antibodies to pandemic (p)H1N1 virus were 2.4–3.9 times greater in swine workers than controls, and to swine influenza virus (SIV) were 1.3–9.9 times greater (Gerloff et al. 2011). When comparing occupations among cases (swine workers), farm workers were more likely to be SIV (OR 2.3) or pH1N1 virus (OR 1.2) seropositive than slaughterhouse workers. Male slaughterhouse workers were more likely to be SIV (OR 1.7) and/or pH1N1 seropositive (OR 1.1) than controls (Gerloff et al. 2011).

In Olsen et al.'s (2002) study on pig farm owners in the USA, the number of seropositive samples (to swine and

human H1 influenza viruses) in farm participants (cases) was significantly higher than in urban control cohorts.

Kumar et al. (2013) investigated awareness of IAVs in South India using multivariate analyses. There was a greater awareness in people with increased education (11 + years (y) vs. 0–3 years, OR 43.66), time spent working with poultry (5–10 years (OR 3.03) and >10 years (OR 4.22), non-labourers (OR 7.75) compared to labourers and urban location (OR 11.9) compared to rural. This may indicate risks to rural farmers who may not have a great awareness of risks associated, or ways to reduce the risk of transmission in their flock or to themselves.

Exposure to Non-Poultry Species

Ramirez-Martinez et al. (2013) investigated seropositivity of dog owners for pH1N1, H1N1 and H3N2 viruses and found no evidence associating seropositivity with factors such as age, sex and whether dogs leave the home in a 24-h period. The only statistically significant factor was vaccination of the dog owners in the last 6 months against subtype pH1N1 virus.

Burnell et al. (2014) found that despite prolonged exposure to horses known to have acute EIV infections, human subjects did not show evidence (serologic response) of recent infection.

Exposure of swine influenza H3N2 virus at swine agricultural fairs (both to humans and from humans to swine) has been implicated as a risk factor in the USA where a particular virus strain was circulating among exhibition swine in 2012 (Ohio, USA). The virus was isolated from swine at ten fairs, and seven of the ten fairs were epidemiologically linked to human infections (Bowman et al. 2014a). Most human cases were directly or indirectly exposed to swine. In a second study by Bowman et al. (2014b), multivariate analysis identified that for every increase of 20 pigs at a fair, the odds of infection in pigs increased by 1.01 times.

Water Sources

Environmental exposure such as swimming and bathing in contaminated water (Dudley 2008) has also been implicated as an epidemiological risk factor for human infection with HPAI H5N1 virus. Vong et al. (2009) indicated that HPAI H5N1 virus seropositive persons (cases) were more likely to report swimming or bathing in ponds (OR 11.3) than control subjects. Using ponds as a water source had

increased odds but was not statistically significant (OR 6.8, $P = 0.08$). Khan et al. (2012) describe survey results where sharing the same water as poultry for bathing, washing clothes and fishing posed a risk for transmission for HPAI H5N1 from poultry to humans. In a study by Zhou et al. (2014), H9N2 virus seropositive participants indicated that they sometimes bathed or swam in swine farm ponds, and sometimes had close poultry contact. Other factors such as age, gender and history of pig or bird contact were not significantly associated with IAV infection among swine farm residents tested. Lack of an indoor water source has also been identified as a risk factor for infection, linked to poor hand washing practices (Mounts et al. 1999; Buxton Bridges et al. 2002; Dinh et al. 2006).

Human Demographics

Human demographic factors such as age and gender are also described in papers as potentially associated with transmission of IAVs. Smallman-Raynor and Cliff (2007) reported on the skewed age distribution of confirmed HPAI H5N1 virus infection cases towards children and young adults from 229 cases from ten countries across Africa, Asia and Europe. Lohiniva et al. (2013) reported 54% of cases of HPAI H5N1 were in children <15 years. Chen et al. (2007) also found that children and young adults had a higher probability of infection when investigating 224 cases across Vietnam, Cambodia, China, Indonesia and Thailand between 2004 and 2006.

In comparison with HPAI H5N1 virus where younger adults and children have increased likelihood of infection, studies on cases of H7N9 virus infection have found that the risk of transmission was higher in people aged over 60 (Cowling et al. 2013; Li et al. 2014; Zhuang et al. 2013; Gong et al. 2014). A study of cases of H9N2 virus exposure in Cambodia by Blair et al. (2013) also found that people over the age of 60 had increased serological evidence of previous infection (OR 6.9).

In a cross-sectional survey of 3600 backyard poultry owners in Cambodia, males had a higher exposure risk potential to HPAI H5N1 virus than females across all age groups ($P < 0.001$) (Van Kerkhove et al. 2008). Also, males between the ages of 26–40 reported practices of contact with poultry which were associated with increased risk potential of H5N1 transmission. A higher proportion of H7N9 virus infection cases have been identified in males (Li et al. 2014; Zhuang et al. 2013; Wang et al. 2015).

Location of residents (urban vs. rural) has been identified as a potential risk factor for transmission of H7N9 to humans, likely linked to increased exposure to live poultry markets. The proportion of cases that are from urban residents has varied from 65% (30/46) (Gong et al. 2014) to 84% (69/82) (Li et al. 2014).

DISCUSSION

While the emergence of new or zoonotic influenza viruses has been an undeniable threat to human health and prosperity for many years, progress in understanding how, where and why new viruses emerge has been limited. Part of the reason for this is that disease emergence is a complex process and IAVs have a complex ecology, but also this review has highlighted the lack of epidemiological studies for interspecies transmission of IAVs.

We have reviewed the available literature on studies relating to the epidemiological risk factors associated with IAVs being transmitted from one species to another (animal-to-animal and animal-to-human). There was a distinct lack of relevant publications relating to epidemiological risk factors found through initial searches conducted, particularly where cross-species transmission between animals was concerned, and hence, there is potential for bias in the selection of publications obtained. Many publications identified by the initial searches that contained data or information on transmission of IAV between species were focussed on virological rather than epidemiological risk factors, and hence not within the scope of this review (see Munoz et al. (2015) for a review of virological risk factors). While different IAVs can vary in their phenotypic properties affecting risk of interspecies transmission, common patterns and trends among IAVs are likely to occur, particularly for closely related viruses and those within similar host populations.

There were several epidemiological risk factors identified repeatedly across two or more studies, highlighting increased risk of transmission of IAVs between animal species and from animals to humans: (1) transmission of IAVs between animal species was associated with contact between species including ingestion of infectious tissues (Table 2); (2) close contact with coastal birds or bird faeces at feeding or haul-out sites was identified as a source of transmission from birds to marine mammals; (3) close proximity of farms (or to outdoor water sources) was associated with possible transmission between pigs and

turkeys. Exposure to infected species through direct and indirect contact is intuitively a key risk factor for cross-species transmission of IAVs, supported by observational evidence of H3N8 virus infection in dogs with indirect contact with infected horses, and H5N1 virus infection in cats fed on infected poultry meat.

Transmission of IAVs from animal species to humans has been associated with contact and exposure to animals, particularly direct or indirect contact with sick or dead poultry. Most studies were related to HPAI H5N1 virus in poultry in Asia, which is unsurprising given the massive impact of this virus in the region. This geographical bias in study location is an important consideration in achieving a representative perspective in future. An increasing number of studies have been conducted identifying risk factors relating to human behaviours, for example, through visiting live poultry markets (HPAI H7N9), food preparation and sharing water sources (including swimming and bathing in water used by poultry and/or other bird species (HPAI H5N1), occupational risk in swine workers (pH1N1), and exposure at swine agricultural fairs (H3N2).

Age of humans also appears to affect the likelihood of infection of IAVs; with HPAI H5N1, a number of studies described children and young adults as having increased association with infection, compared to HPAI H7N9 and also H9N2 where risk of transmission was higher in people over the age of 60. The older average age of humans infected with H7N9 virus may be linked to a preference by older generations to attend traditional wet markets, whereas younger people may have greater awareness of the risks of IAV transmission.

The lack of published studies with a statistical measure of epidemiological risk factors for transmission of IAVs between animal species was a key finding of this study. There appears to be a significant gap in knowledge on which epidemiological factors are most associated with cross-species transmission, particularly for subtypes other than HPAI H5N1 virus. Among avian influenza viruses, almost all studies involve H5 and H7 subtypes due to their impact on poultry health. The bias studies towards these viruses overlook the potential role of other avian influenza viruses in cross-species transmission. Van Reeth (2013) commented that although interspecies transmission of IAVs occurs regularly, this is with limited spread and often transient infection; only occasionally establishing a stable virus lineage in a new host species. Nonetheless, these “species jumps” can potentially have very severe consequences and are a key step in the disease emergence process.

A number of studies investigating the spatial distribution and co-occurrence of relevant host species (e.g. poultry, pigs and humans) have been conducted to identify geographical “hot spots”, but the myriad of other potentially relevant and confounding factors that show spatial variation leaves plenty of progress to be made for this approach (Hill et al. 2015).

It is difficult to extrapolate and weigh the relative importance of risk factors across publications, particularly when looking at subtypes other than HPAI H5N1, due to different study designs, settings, study size and statistical measures used. More studies that statistically measure potential risk factors for cross-species transmission are needed to improve both the breadth and depth of knowledge of epidemiological risk factors in this field. Carefully designed prospective studies and standardised or even harmonised approaches to risk factor description and measurement, along with detailed analyses of available data from influenza outbreaks, could greatly improve our knowledge in this area and support our ability to manage risk and conduct successful control programmes in the future. Such studies, particularly for viruses other than HPAI H5N1 (particularly H7N9 and H5N8), would help to identify epidemiological risks, both in transmitting between and within species. Results of these studies will help guide policies and control measures to allow more effective disease control and mitigate the risk of emergence.

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