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REVIEW

Avian Influenza Human Infections at the Human-Animal Interface

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Background. Avian influenza A viruses (AIVs) are among the most concerning emerging and re-emerging pathogens because of the potential risk for causing an influenza pandemic with catastrophic impact. The recent increase in domestic animals and poultry worldwide was followed by an increase of human AIV outbreaks reported.

Methods. We reviewed the epidemiology of human infections with AIV from the literature including reports from the World Health Organization, extracting information on virus subtype, time, location, age, sex, outcome, and exposure.

Results. We described the characteristics of more than 2500 laboratory-confirmed human infections with AIVs. Human infections with H5N1 and H7N9 were more frequently reported than other subtypes. Risk of death was highest among reported cases infected with H5N1, H5N6, H7N9, and H10N8 infections. Older people and males tended to have a lower risk of infection with most AIV subtypes, except for H7N9. Visiting live poultry markets was mostly reported by H7N9, H5N6, and H10N8 cases, while exposure to sick or dead bird was mostly reported by H5N1, H7N2, H7N3, H7N4, H7N7, and H10N7 cases.

Conclusions. Understanding the profile of human cases of different AIV subtypes would guide control strategies. Continued monitoring of human infections with AIVs is essential for pandemic preparedness.

Keywords. avian influenza; human infection; review.

Avian influenza A viruses (AIVs) are pathogens that infect a wide range of avian species. Spillover to human populations and other species occurs occasionally, resulting in disease of varying severity. There is a potential for AIV to lead to devastating human losses if a novel AIV emerged with the ability for sustained human-to-human transmission [1, 2]. AIVs have been identified among wild birds, poultry, and a few mammals since the 1870s [3], and have been linked with the emergence of global influenza pandemics [4, 5]. Fears of a new influenza pandemic from an avian source increased in 1997 following the occurrence of human infections with influenza A(H5N1) virus in Hong Kong [6]. If H5N1 acquired the ability to transmit efficiently from person-to-person, while maintaining its high pathogenicity, the consequences would be more devastating than the 1918 pandemic, which caused more than 50 million deaths worldwide [7].

While influenza pandemics of the 20th century are thought to have been caused by avian-origin viruses, the 2009 influenza A(H1N1) pandemic was caused by a swine-origin virus [8], although the clinical manifestations were relatively mild. Nevertheless, concerns continue that an avian influenza virus could cause the next pandemic. Among more than 100 subtypes of AIVs detected in birds [9], a relatively small number have been identified as causing human infections. Most of these viruses were assessed to be of low concern, largely due to low severity in humans or limited cross-species transmissibility. Since 2013, a newly emerged strain of avian influenza A(H7N9) virus has caused more than 1500 human cases and 600 deaths in China, while H5N1 has been responsible for more than 800 cases and 400 deaths worldwide since its first appearance. In February 2018, the World Health Organization (WHO) reported the first human infection with H7N4, becoming the 11th identified AIV subtype responsible for human infection [10].

To improve the understanding of the epidemiology of human infections with AIVs, we systematically reviewed information on 11 different AIV subtypes that have been known to cause human infections.

METHODS

Search Strategy

Human cases of avian influenza and outbreaks were identified using WHO reports [11–13], FluTrackers [14], and publications of related studies on PubMed. Articles were identified using the query ("avian" OR "A") AND "influenza" AND ("individual" OR "individuals" OR "worker" OR "workers" OR "patient" OR "patients" OR "persons" OR "person" OR "human" OR "man" OR "woman" OR "men" OR "women"), with a publication date

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up to 31 July 2019. References cited in the resulting articles were also reviewed.

WHO situation updates for avian influenza [11], WHO monthly risk assessment summary for human animal interface [13], and WHO weekly epidemiological reports [12] were also used to provide information on the human cases for different AIV subtypes. When case information was missing in the WHO report, we reviewed Flutrackers and publications for complementary information. FluTrackers is a website where publicly available information on influenza and other emerging pathogens is curated [15].

Selection Criteria

All confirmed human AIV cases with illness onset before 31 July 2019 were included in the analysis. Cases identified through serological studies with symptomatic infections that were reported by WHO as confirmed cases were also included. Duplicated results and results not written in English were excluded from the study. We excluded reviews but we reviewed the reference list for relevant publications. Case reports for human AIV infections were included if they were the source of WHO updates or provided supplementary information on the WHO report. The earliest publication was selected if there were multiple publications on the same case(s), unless additional information was provided in the more recent publications. Multiple publications were used to obtain all relevant information on a case if they could be linked to the same case using the province, age, sex, and date of illness onset. For H5N1, H5N6, and H7N9 cases, as the total number of human infections was provided in the WHO reports, no additional case was further added to the database. Additional information on an H5N1 or H7N9 case from publications was included if the reported case could be linked to the WHO report. For other AIV subtypes, publications that reported information on cases that could not be linked to the WHO report were still added in the analysis, as no official number of human infections for those subtypes was provided by WHO. Publications reporting general information on outbreaks such as the number of cases and mean age were excluded, as individual data were not available.

Data Variables and Extractions

Individual data, including age, sex, country, state/province, AIV subtype, illness onset date, outcome (death, recovery, or unknown), and information related to the exposure were collected. FluTrackers was used to update the clinical outcome of the cases when not provided by WHO. When individual information on a case was not available, we still included the case as aggregated data based on illness onset date. When the exact age was not available, we assigned them to age groups 0–14, 15–29, 30–44, 45–59, and older than 60 years whenever possible.

For H5N1 and H7N9, we used the total number of human infections and deaths provided by WHO. Additional information was searched for the cases reported by WHO, linked by illness onset date, age, sex, and state/province.

RESULTS

WHO reports provided individual information for 2504 human AIV cases but some individual information was missing for H6N1, H7N3, H7N7, and H10N7 subtypes. We further searched for relevant publications from PubMed, which returned 7316 results (Figure 1). After selecting relevant articles, these were integrated with WHO reports and other supplementary sources, from which we extracted information on 2644 reported human cases infected with 11 subtypes of AIV as of 31 July 2019. Among them, 881 and 1568 cases were infected with H5N1 and H7N9, respectively, with fewer cases infected with H7N7, H9N2, H5N6, and other subtypes (Table 1 and Table 2).

Human AIV cases have been reported in more than 20 countries (Figure 2A). Four countries reported infections with more than 2 AIV subtypes: mainland China (n = 6), Egypt (n = 3), United Kingdom (n = 3), and Canada (n = 3). However, for Canada, only 1 subtype has caused infection locally, whereas the 2 other subtypes were imported from China [16–18].

In mainland China, although there were 6 different AIV subtypes in total, no provinces have reported more than 4 subtypes (Figure 2B). Eight provinces have reported infections with 4 subtypes, 3 provinces with 3 subtypes, 9 provinces with 2 subtypes, and 7 provinces with 1 subtype. Provinces with the highest number of subtypes causing infections were all located in the southeast part of China. In the north of China, only Beijing reported 3 subtypes causing infections, the highest number in this region.

Human infections with different AIV subtypes have been reported in the same province in mainland China within a short period. For instance, in Hunan province, human infections with 3 AIV subtypes (H5N1, H5N6, and H7N9) were reported in February 2014. Aswan in Egypt reported human infections with 2 subtypes (H5N1 and H9N2) in January 2015. Overall, 6 provinces from mainland China, Egypt, and Taiwan reported human infections with at least 2 AIV subtypes within a 1-month period 17 times, and Guangdong province, China reported such occurrence 7 times. Zhejiang province, China reported the highest number of human AIV infections (n = 277). State/provinces could not be determined for 274 cases (10.4%).

H5N1

Between 1997 and March 2019, 881 human infections with H5N1 were identified, with a case fatality risk (CFR) of 52.4% (462/881) among laboratory-confirmed cases (Table 1). The H5N1 cases were reported from 17 countries, with Egypt (n = 359), Indonesia (n = 200), Vietnam (n = 127), Cambodia (n = 56), and mainland China (n = 52) reporting almost all of the cases (815/881, 92.5%) [19–23]. The highest number of H5N1 human infections was reported in 2015 with 145 cases (Table 2), mainly from Egypt (n = 136). Since then, fewer than 20 H5N1

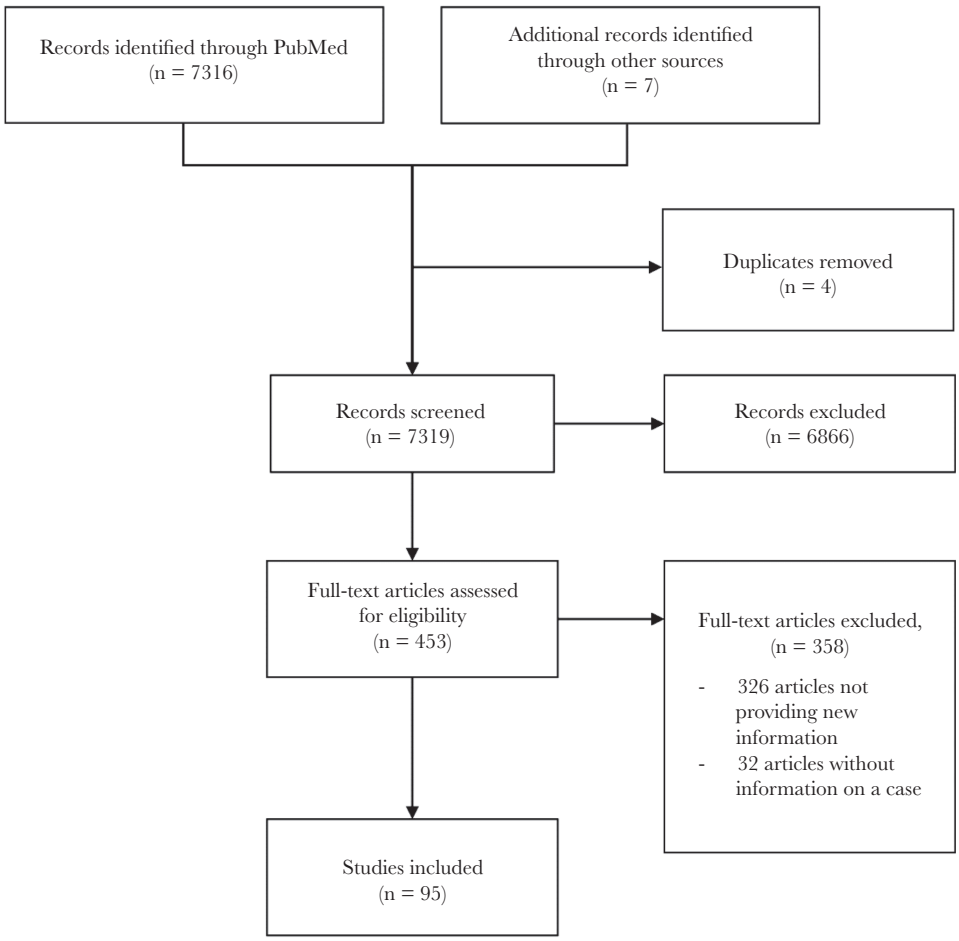

Figure 1. Flow diagram of the review.

cases were reported. A clear seasonal pattern was found in China, Egypt, Vietnam, Cambodia, and Thailand, with a peak around winter, although the timing may differ across countries.

The majority of H5N1 cases occurred in children and younger adults (Figure 3). Egypt has been reporting a higher proportion of H5N1 female cases generally than Southeast

Table 1. Human Cases and Deaths per Subtype From 1996 to July 2019[a]

Subtype	Year of First Human Identification	Location of First Human Case Identification	Country With Highest Number of Human Cases	No. Deaths/Cases (%)
H7N7	1996	United Kingdom	Netherlands	1/93 (1.1)
H5N1[b]	1997	Hong Kong SAR	Egypt	462/881 (52.4)
H9N2	1998	China	China	1/58 (1.7)
H7N2	2002	United States	United States	0/8 (0.0)
H7N3	2004	Canada	Canada	0/5 (0.0)
H10N7	2004	Egypt	Egypt/Australia	0/4 (0.0)
H7N9[b]	2013	China	China	616/1568 (39.3)
H6N1	2013	Taiwan	Taiwan[c]	0/1 (0.0)
H10N8	2013	China	China[c]	2/3 (66.7)
H5N6	2014	China	China[c]	14/22 (63.6)
H7N4	2018	China	China[c]	0/1 (0.0)

[a]Subtypes are ordered by the isolation date of the first human case.

[b]The number of deaths was identified from 1 or multiple sources (see Supplementary Material).

[c]Only 1 country reported human infections.

Table 2. Number of Cases per Year per Subtype[a]

Subtype	1996–2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	Total
H5N1	18	6	46	98	115	88	44	73	48	62	32	39	52	145	10	4	…	1	881
H5N6	…	…	…	…	…	…	…	…	…	…	…	…	3	5	9	2	3	…	22
H6N1	…	…	…	…	…	…	…	…	…	…	…	1	…	…	…	…	…	…	1
H7N2	1	1	…	…	…	4	…	…	…	…	…	…	…	…	2	…	…	…	8
H7N3	…	…	2	…	1	…	…	…	…	…	2	…	…	…	…	…	…	…	5
H7N4	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	1	…	…	1
H7N7	1	89	…	…	…	…	…	…	…	…	…	3	…	…	…	…	…	…	93
H7N9[b]	…	…	…	…	…	…	…	…	…	…	…	158	339	190	265	599	2	1	1554
H9N2	8	1	1	…	…	1	1	2	…	1	…	2	2	12	10	7	7	3	58
H10N7	…	…	2	…	…	…	…	…	2	…	…	…	…	…	…	…	…	…	4
H10N8	…	…	…	…	…	…	…	…	…	…	…	1	2	…	…	…	…	…	3
Total	28	97	51	98	116	93	45	75	50	63	34	204	398	352	296	613	12	5	2644

[a]The cases were identified from a single or multiple sources (see Supplementary Table 1).

[b]Not including 14 cases reported between 2014 and 2015 with no clear date of illness onset.

Asia and China. However, these 3 regions consistently reported cases in children and younger adults. Among the cases with relevant information available, 98.9% were 60 years or younger (n = 791), 46.0% were male (n = 369), and 97.4% were linked to any kind of poultry exposure (n = 582) (Table 3). The most recent H5N1 human case was identified in Nepal in March 2019 [24].

H7N9

Between 2013 and March 2019, 1568 laboratory-confirmed human infections with H7N9 were reported of which 616 died of the disease (CFR, 39.3%) (Table 3). Only 31 of those cases were reported outside of mainland China: 21 cases from Hong Kong, 5 cases from Taiwan, and 5 cases from Canada, Macao, and Malaysia combined. All of these cases were considered to have been epidemiologically linked to mainland China [20]. Of the 31 cases, 30 were in mainland China in the 2 weeks prior to symptom onset and the other case was a poultry vendor from Macao who imported a batch of poultry from mainland China that was later found positive for H7 (Supplementary Table 3). After the first epidemic wave in early 2013, occurrence of H7N9 infections in mainland China exhibited a seasonal pattern with outbreaks starting in winter (November–December) every year [25]. A surge of H7N9 human infections in the 2016/2017 winter resulted in 38.2% of the total cases (n = 599). Only 3 H7N9 cases have been reported since the introduction of a bivalent H5/H7 vaccine among poultry in late 2017.

Age and sex distributions differed greatly between those infected with H5N1 and H7N9 (Figure 4, P values < .005 for both sex and age from χ^2 tests). While most of the H5N1 cases were among young people and there were no difference between sexes, more H7N9 cases were among older people (60 years or older, 40.4%, 555/1376) and male (70.0%, 1085/1550). Poultry exposure was reported by 98.7% (1070/1084) of the cases and visiting live poultry markets was reported by 38.5% (417/1084) of the cases (Table 3). The most recent H7N9 human case was identified in Gansu province, mainland China in March 2019 [26].

Other Virus Subtypes

Among other AIV subtypes reported in humans, the most common were H7N7 (48%) and H9N2 (30%). The WHO reported 93 human cases of H7N7 between 1997 and April 2018 (Table 2). The first human case was reported from Ireland in 1996 with a 43-year-old woman presenting with conjunctivitis after preparing duck meat [27]. The virus was confirmed to be a low-pathogenic AIV. The largest H7N7 outbreak occurred in Netherlands in 2003; 89 cases were identified, among which 86 were poultry workers and 3 had no contact with the infected poultry but were family relatives of the infected poultry workers [28]. In 2013, 3 new cases were reported from Italy, also among poultry workers [29]. The CFR for laboratory-confirmed H7N7 human cases was 1.1% (Table 3). None of the cases were older than 60 years, and 5 out of 8 cases were male. The majority of the cases (76/79, 96.2%) reported previous exposure to poultry.

H9N2 human infections were firstly identified in Guangdong province of mainland China in 1998 [30] and Hong Kong in 1999 [31]; 50 human cases (Table 2) have been reported thereafter, with the latest infection reported in March 2019 in Oman. China including Hong Kong represented more than 86.2% (n = 50) of the cases, with Guangdong being the province reporting the highest number of human cases (n = 21). Human infections with H9N2 were clinically mild. Two human infections were identified through information in genome banks [32]. Of 43 cases with a known clinical outcome, only 1 death was recorded (Table 3), indicating a CFR of 2.3%. Of the cases, 5.6% (3/54) were older than 60 years while 75.9% (41/54) were younger than 15 years (Figure 4), 40% (22/55) were male, and 88.6% (31/35) reported previous exposure to poultry. No clear

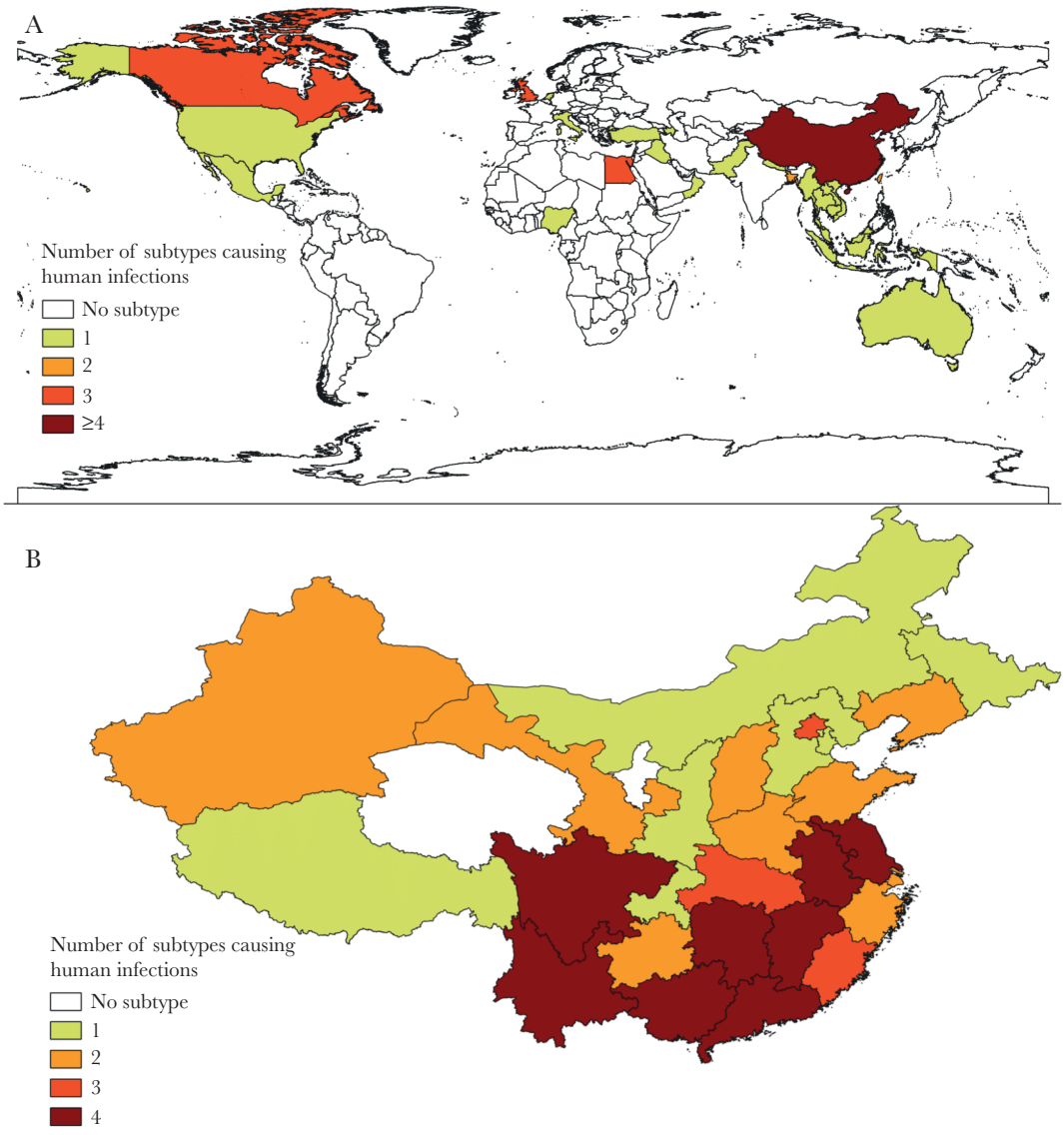

Figure 2. Number of subtypes reported causing human infections (*A*) per country and (*B*) per province in mainland China.

seasonal pattern was found in China or Egypt, or at the global level. We further compared 35 cases with available information on virus lineage. The BJ94(Y280) lineage has caused 24 human infections in China only, whereas the G1 lineage caused 11 human infections in 4 different countries. There was no significant difference in the case characteristics across lineage, except that more cases infected with the BJ94(Y280) lineage were male (Supplementary Table 4).

Seven other subtypes caused 44 human infections and of these only H5N6 and H10N8 caused deaths (n = 16). Four of the subtypes (H6N1, H10N8, H5N6, and H7N4) were first reported after 2012 and only in China, whereas the other 3 subtypes (H7N2, H7N3, and H10N7) were reported before 2005 and outside of China (Table 1). There was no clear sex difference in these cases of different AIV subtypes. No case older than 60 years were found among H7N2, H7N3, H10N7, and H6N1 cases, while few cases older than 60 years were reported among H5N6 cases (4.5%) (Table 3). Poultry exposure was commonly reported for all subtypes, except H6N1 where no exposure information was available. A majority of H7N2, H7N3, and H10N7 cases reported occupational exposure, but few among H5N6 cases (5.9%). All 3 H10N8 cases and few H5N6 cases (41.2%) reported visiting live poultry markets prior to symptom onset. Exposure to sick or dead birds was commonly reported for H7N2, H7N3, H7N4, H7N7, and H10N8 cases (70%–100% for all subtypes) but not for H5N6 cases (17.6%). Backyard poultry exposure was reported only among H5N6 and H7N4 cases. We did not investigate seasonal patterns for subtypes with low numbers of cases.

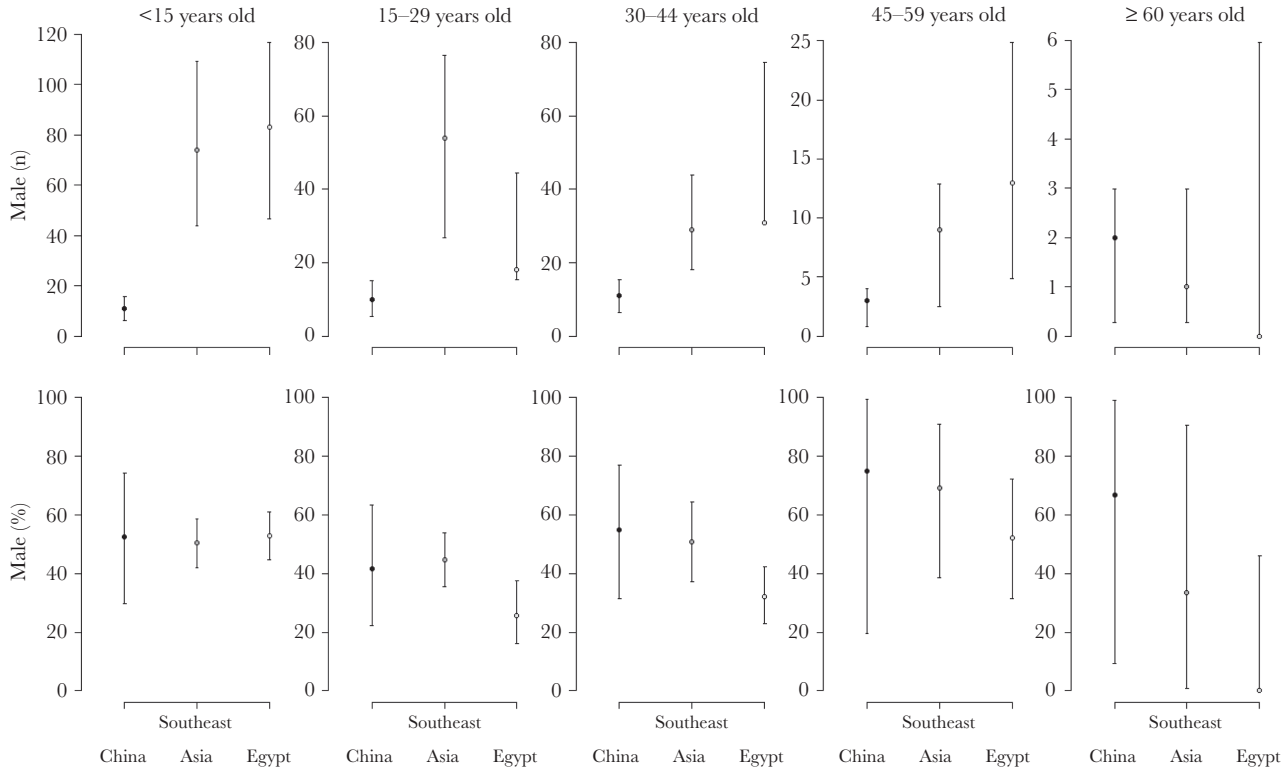

Figure 3. The reported number, proportion, and 95% confidence intervals of male human H5N1 cases per age category, for the 3 regions with the highest number of cases: China, Southeast Asia, and Egypt. Regions are ordered per number of cases in ascending order.

DISCUSSION

In this study, 2644 human cases of AIVs from more than 20 years of surveillance and monitoring were studied and compared. While few AIV subtypes were identified in humans before the year 2000 (H5N1, H7N7, and H9N2), more subtypes have been reported in the last 6 years (H5N6, H6N1, H7N4, H7N9, and H10N8) (Table 1). It is likely that the increase in detections in recent years is due to improved diagnostics such as polymerase chain reaction (PCR) and improved access to these diagnostics, particularly in Southeast Asia. While H5N1 has been known for its severity among human populations, H7N9 led to the largest number of cases and deaths, implying a higher transmission between poultry and human. Among the 1568 H7N9 cases, at least 20 infections have been reported as probable human-to-human transmission (Table 3), with identification of several clusters of human infections supporting this claim [33, 34].

While Asia was a major source for human infections with many AIV subtypes, other regions have also reported multiple subtypes, such as Europe with only H7 cases and at least 3 different subtypes causing human AIV infections in the UK (Figure 2). South America was the only continent not having any human AIV infections reported, whereas Africa, apart from Egypt, reported only 1 human AIV case (H5N1) in Nigeria. The locations of human infections are largely consistent with AIV outbreaks among poultry [35].

Age distribution was strongly heterogeneous among most of the AIV subtypes with a considerable number of human infections. H5N1 and H9N2 were mainly reported in young people, whereas H7N9 was mainly reported in older adults (Figure 4). A few studies have presented the possibility of routine surveillance being biased towards older and more severe cases for H7N9, whereas mild cases in young people are under-ascertained [36, 37], partly explaining the observed age distribution. Another possible explanation is the influences of imprinting by childhood exposure to human AIVs explaining the susceptibility to H5, H9, and H7 in different age groups [38]. However, this does not explain the observed sex difference in the H7N9 cases. By using phylogenic similarity, hemagglutinin proteins could be divided in 2 groups: H5, H6, and H9 subtypes belong to group 1 whereas H7 and H10 belong to group 2. Similar patterns in age and sex distributions are observed among human infections with H5N1 and H9N2 (group 1), but not for H7N9 (group 2) (Supplementary Table 5). Performing paired subtype Mann-Whitney U tests on age distributions per sex showed statistically significant differences between male and female age distributions for H5N1 versus H7N9, H5N1 versus H9N2, and H7N9 versus H9N2, and male

Table 3. Epidemiological Features of the Human Cases per Subtype[a]

Characteristics	H5N1	H7N9	H7N7	H9N2	H5N6	H10N8	H6N1	H7N4	H7N2	H7N3	H10N7
Cases	881	1568	93	58	22	3	1	1	8	5	4
Deaths/ total cases (CFR %)	462/881 (52.4)	616/1568 (39.3)	1/93 (1.1)	1/43 (2.3)	14/20 (70.0)	2/2 (100.0)	0/1 (0.0)	0/1 (0.0)	0/8 (0.0)	0/5 (0.0)	0/4 (0.0)
Male/ total cases (%)	369/803 (46.0)	1085/1550 (70.0)	5/8 (62.5)	22/55 (40.0)	11/22 (50.0)	1/3 (33.3)	0/1 (0.0)	0/1 (0.0)	2/2 (100.0)	3/4 (75.0)	…
>60 y/ total cases (%)	9/800 (1.1)	555/1376 (40.4)	0/93 (0.0)	3/54 (5.6)	1/22 (4.5)	2/3 (66.7)	0/1 (0.0)	1/1 (100.0)	0/2 (0.0)	0/4 (0.0)	0/2 (0.0)
Exposure[b]/ total cases (%)											
Any poultry exposure	567/582 (97.4)	1070/1084 (98.7)	76/79 (96.2)	31/35 (88.6)	17/17 (100.0)	3/3 (100.0)	…	1/1 (100.0)	5/7 (71.4)	5/5 (100.0)	2/2 (100.0)
Occupational	22/582 (3.8)	89/1084 (8.2)	75/79 (94.9)	1/35 (2.9)	1/17 (5.9)	0/3 (0.0)	…	0/1 (0.0)	5/7 (71.4)	5/5 (100.0)	2/2 (100.0)
Visiting LPM	41/582 (7.0)	417/1084 (38.5)	0/79 (0.0)	6/35 (0.0)	7/17 (41.2)	3/3 (100.0)	…	0/1 (0.0)	0/7 (0.0)	0/5 (0.0)	0/2 (0.0)
Sick or dead bird	330/582 (56.7)	3/1084 (0.3)	75/79 (94.9)	3/35 (8.6)	3/17 (17.6)	0/3 (0.0)	…	1/1 (100.0)	5/7 (71.4)	5/5 (100.0)	2/2 (100.0)
Backyard poultry	113/582 (19.4)	163/1084 (15.0)	1/79 (1.3)	5/35 (14.3)	1/17 (5.9)	0/3 (0.0)	…	1/1 (100.0)	0/7 (0.0)	0/5 (0.0)	0/2 (0.0)
Infected humans	17/582 (2.9)	27/1084 (2.5)	3/79 (3.8)	0/35 (0.0)	0/17 (0.0)	0/3 (0.0)	…	0/1 (0.0)	0/7 (0.0)	0/5 (0.0)	0/2 (0.0)

Abbreviations: CFR, case fatality risk; LPM, live poultry market.

[a]The cases were identified from a single or multiple source (see Supplementary Table 1). Some denominators were smaller than the total number of cases for each subtype due to missing data.

[b]See Supplementary Table 2 for definitions of exposure.

age distributions for H5N1 versus H5N6 (P value < .005) but not for female age distributions for H5N1 versus H5N6 (P value = .059) (Supplementary Table 6). The data for human infections with H7N7 were not sufficient to make a comparison, and the number of cases for the other subtypes was also insufficient to perform an analysis.

Exposure to poultry was the major source of infection for most of the AIV subtypes, implying limited human-to-human transmission. Poultry workers in mainland China have been shown to be at higher risk of AIV infection [39]. However, several clusters have been reported for H5N1, H7N7, and H7N9 [33, 34, 40–42], with few cases reporting exposure to another human case as the only known exposure. For instance, 3 H7N7 cases were family members of poultry workers in the Netherlands [42], and women from the same family in Vietnam have been reported as H5N1 cases, confirmed by WHO as human-to-human transmission [43]. Controlling risk associated with exposure to poultry is therefore a priority. In response to avian influenza outbreaks, different interventions have been used. In Hong Kong, following the H5N1 outbreaks before 2000 there were calls for a series of control measures, such as banning overnight holding of poultry and rest days in live poultry markets, and temporary suspension of importation from mainland China, in addition to culling [22]. Mainland China responded to outbreaks in different ways: live poultry market closures in some critical cities with H7N9 outbreaks [44, 45], and poultry vaccination leading to a substantial reduction in H7N9 infections in human and in poultry since 2017 [46]. In Egypt, a vaccination policy was introduced following H5N1 outbreaks but the overreliance on this single intervention may have led to a mixed impact [47, 48].

One priority for public health authorities when faced with a new AIV subtype is to determine the risk of pandemic emergence. The Influenza Risk Assessment Tool (IRAT) developed by the US Centers for Disease Control and Prevention rated different influenza subtypes according to the risk of acquiring the ability to spread efficiently in human (emergence) and the potential severity of human disease (impact) [49]. H7N9 was evaluated as the subtype with the highest pandemic potential, due to a combination of the high disease severity (39% of deaths) and potential for human-to-human transmission. Some of the subtypes have not yet been assessed due to a lack of knowledge (eg, H6N1) or recent emergence (eg, H7N4). H7N3 and H7N2 caused mild symptoms with conjunctivitis, which made identification difficult. On the contrary, H10N8 was of higher concern because 3 cases were reported close in location and time with 2 fatal outcomes. The results from IRAT may guide prioritization of control policies when multiple viruses are cocirculating.

Our review has several limitations. First, we examined laboratory-confirmed AIV human cases only, which ignored subclinical seropositive cases. This may underestimate the number of AIV infections among humans. Second, not all

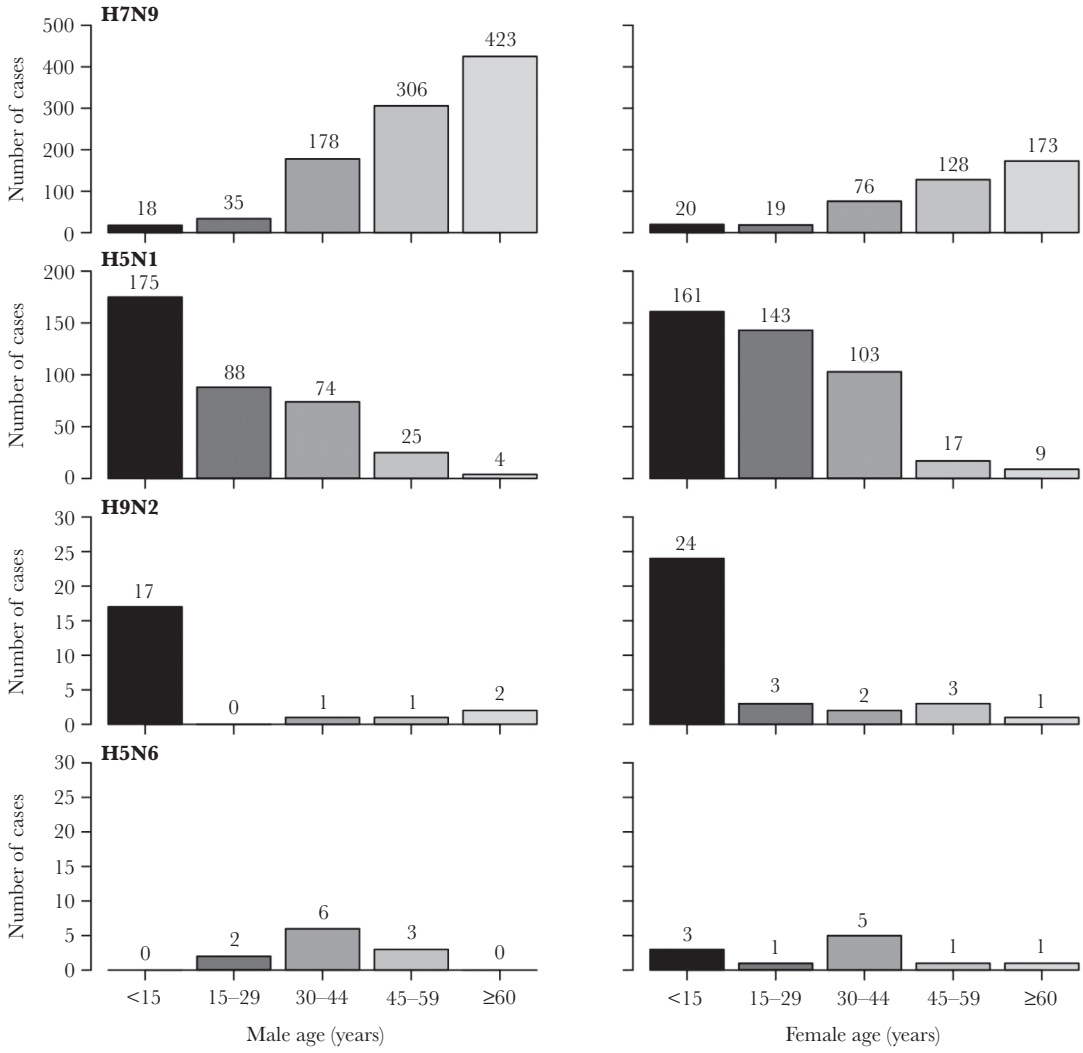

Figure 4. Distribution of the human cases per age categories and sex for H7N9, H5N1, H9N2, and H5N6. Subtypes are ordered according to the total number of cases reported in descending order.

information could be recovered from the WHO reports and other publications, especially for exposure history.

In addition to the review of human cases of different AIV subtypes, our review highlighted an important aspect of pandemic potentials for avian influenza, that is cocirculation of AIV subtypes. We did not focus on poultry outbreaks; however, spillover events of different AIVs to humans indicated even more virus reassortment potential at the human-animal interface [50]. These included H5N1, H5N6, H7N9, and H9N2 in mainland China, and also H5N1 and H9N2 in Egypt. It was later shown that the viruses isolated from an H10N8 human case was phylogenetically clustered with H9N2 viruses previously identified in the same province [51]. While Zhejiang province in mainland China reported the highest number of human AIV infections in the study period, a much higher number of occurrences of human infections with more than 1 AIV subtypes within a short period were reported in Guangdong province, probably indicating a higher diversity of AIVs. The number of cases reported from these provinces indicates an animal-to-human interface that could possibly facilitate animal-to-human transmission. Moreover, many H7N9 cases were imported from China, indicating a higher risk of virus spread within or out of that particular region, hence surveillance and interventions at the human-animal interface should be sustained and strengthened under the One Health approach.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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