Systematic review and meta-analyses of cases and deaths associated with highly pathogenic avian influenza H5N1 in humans and poultry

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Abstract

From 2003 to date (2015), confirmed highly pathogenic avian influenza (HPAI) H5N1 outbreaks in poultry and humans have been reported, however, certain quantitative parameters remain lacking. We obtained 846 reports of HPAI H5N1 outbreaks in poultry in Africa (2006–2015), and 844 reports in humans globally (2003–2015) from different databases. Data were filtered and analysed using meta-analyses. The outputs were generated for each country included in the study and for overall morbidities, mortalities and case fatalities (for poultry and humans). Approximately 11.6 million poultry were included in the analyses as susceptible with 1.9 million cases and 1.7 million deaths in poultry. In humans, 449 deaths were linked to influenza A H5N1 infections. For all poultry outbreaks in 2006–2015 in Africa, an overall mean apparent morbidity of 48.7% (n = 1 850 589) was estimated, with overall mean apparent mortality being 40.2% (n = 1 705 388) and overall mean case fatality rate (CFR) for HPAI H5N1 outbreaks in poultry being 86.4% (n = 1 705 388). In humans, the overall mean CFR for A H5N1 globally for 2003–2015 was 62.3% (n = 449). Indonesia, Egypt and Vietnam had higher proportions of all human deaths associated with the A H5N1 and Egypt had a significant age–sex bias. Improved reporting and effective quantitation remain key to understanding the characteristics of the virus.

Keywords: Case fatality Rate, HPAI H5N1, Humans, Poultry, Meta-analyses

Introduction

African countries have experienced multiple outbreaks of highly pathogenic avian influenza (HPAI) H5N1 from 2006 [1], and to date 12 African countries have been infected [2, 3]. HPAI H5N1 outbreaks have caused an alarming endemic situation in parts of Africa (especially Egypt) and Asia (Bangladesh, China, Indonesia, Vietnam and eastern India) [4], and other parts of Africa have had infections and re-infections (Nigeria, Cote d'Ivoire, Ghana, Libya, Burkina Faso, Togo and Benin) [3]. To date, only a few countries have reported single or unrelated HPAI H5N1 outbreaks in Africa including Cameroon, Djibouti and Niger [3]. In 2015 alone, outbreaks of avian influenza (H5N1, H5N2, H5N3, H5N6, H5N1, H7N3 and H7N7) were reported in 32 countries including 6 from Africa (Burkina Faso, Cote d'Ivoire, Ghana, Libya, Niger and Nigeria) [3].

In addition to outbreaks in poultry, transmission to humans has been reported worldwide [5, 6]. As of September 2015, a total of 844 confirmed cases with 449 deaths (cumulative proportion of fatal cases: 53.2%) of H5N1-infected patients had been reported to the World Health Organization from 16 countries [7]. Routine surveillance, either passive or active, is an integral part of the means for detecting cases of HPAI H5N1 outbreak as early as possible [8, 9]. However, it is unlikely that continuous and sustained surveillance is practiced in parts of Africa where competition for limited resources is great and priorities are often weighed in favour of other competing interests apart from animal health and welfare.

Reports of HPAI H5N1, and also other influenza outbreaks in animals and humans, are routinely submitted to international organizations and held by national agricultural and health authorities. Nevertheless, these may not be comprehensive enough, due to, e.g., differences in capacities of human health and veterinary services, and censorship [10]. However, for predictive modelling, disease control, policy decisions and to understand the characteristics of the infectious pathogens, certain parameters such as the actual case morbidity and fatality in poultry and humans will have to be determined. However, to date these data are lacking in peer-reviewed literature. This study was therefore designed to determine the apparent morbidity, apparent mortality, true case fatality rate (CFR) (for both poultry and humans) of avian influenza H5N1 in Africa and to assess how interventions affect the situation of fatality in poultry and humans.

Methodology

Data gathering and generation

Up-to-date aggregate data were extracted and compiled from the databases and websites of the World Organization for Animal Health [3], World Health Organization [7] and the Food and Agriculture Organization EMPRES-i websites [2]. Data were cross-matched with records in the repository of the national agricultural authorities (where available) or with peer-reviewed studies. Data were quality-checked using filtration to remove duplicates and non-validated data. For a situation of HPAI H5N1 infection to qualify as a case, it was checked that laboratory confirmation [serology, virus isolation, reverse transcription–polymerase chain reaction (RT–PCR)] had been conducted to support suspicion based on the documented report from the authorities. A single case in poultry was considered an outbreak if a single or group of poultry was kept together in a single location at a unit time, but a case in humans was counted on an individual basis [11]. A total of 846 reports of HPAI H5N1 outbreaks in poultry in Africa, and 844 reports for confirmed HPAI H5N1 human infection cases globally, were entered and used for this study. All reported cases were harmonized into a single Microsoft Excel spreadsheet and only validated quantitative data were used.

Statistics

The data included the number of birds that were susceptible, the number of actual cases and deaths recorded per outbreak per year and per country. Apparent morbidity, apparent mortality and case fatality for the HPAI H5N1 outbreak in poultry in Africa were calculated based on the above data. Similarly, data (cases and deaths) on influenza A H5N1 infections in humans globally in 2003–2015 were collected. All data were analysed using the fixed-effect model (precision-based estimates) in the Meta-analyses software of Excel [12]. Comparisons between individual studies were calculated in WinPepi v11.24 [13]. The outputs were generated as country-based morbidity, mortality and case fatality with 95% confidence intervals. Cumulative events for apparent morbidity, mortality and case fatality for humans and poultry were also produced in forest plots with measures of central tendencies.

Results

During this period of outbreaks of HPAI H5N1 (2006–2015) in Africa, approximately 11.6 million poultry were reported as susceptible, 1.9 million cases were documented and 1.7 million deaths of poultry were recorded. Globally, 844 cases and 449 deaths linked to influenza A H5N1 infections were recorded in humans.

For the study period 2006–2008, Burkina Faso was the country with the highest apparent morbidity in Africa (100.0%; n = 130), followed by Cameroon (86.2%; n = 50) and Niger (9.6%; n = 2700) (Table 1). In the 2014–2015 outbreaks, the highest apparent morbidity was recorded in Cote d'Ivoire (98.7%; n = 51 555), followed by Burkina Faso (64.2%; n = 143 163) and the least apparent morbidity was observed in Nigeria (10.0%; n = 95 334) (Table 1). For all the outbreaks in 2006–2015, an overall mean apparent morbidity of 48.7% ($CI_{95\%}$: 47.8–49.6) was estimated (n = 1 850 589) (Table 1, Figure 1, Appendix 1a).

Similarly, the highest apparent mortality for 2006–2008 was recorded in Burkina Faso (94.6%; n = 123), followed by Cameroon (86.2%; n = 50) and lowest mortality was reported in Niger (9.0%; n = 2530). In the epidemic period of 2014–2015, Burkina Faso (63.8%; n = 142 246), Cote d'Ivoire (58.1%; n = 30 335) and Nigeria (9.7%; n = 92 312) reported apparent mortality (Table 2). The overall mean apparent mortality was 40.2% ($CI_{95\%}$: 39.3–41.1; n = 1 705 388) (Table 2, Figure 2, Appendix 1b).

The overall mean CFR for HPAI H5N1 outbreaks in poultry in Africa between 2006 and 2015 was 86.4% ($CI_{95\%}$: 85.5–87.3; n = 1 705 388). Country-specific CFRs for the epidemic periods 2006–2008 and 2014–2015 were about 100% for most countries including Djibouti, Cameroon, Egypt, Ghana, Burkina Faso, Sudan and Togo (Table 3, Figure 3, Appendix 1c). However, Cote d'Ivoire had a CFR of 39.4%. By far, Egypt had the highest proportions of poultry morbidity (58.3%), mortality (63.0%) and case fatality (63.0%) in Africa Figure 4.

With regards to cases of human fatalities globally, the overall mean CFR for influenza A H5N1 in humans across the globe in 2003–2015 was 62.3% ($CI_{95\%}$: 61.3–63.2;

Table 1 Apparent morbidity in poultry due to HPAI H5N1 infection, Africa, 2006–2015

Serial number	Study	Events	Sample size	Outcome	SE	CI lower	CI upper	Forest plot ID	Rate	*P*-value
1	Nigeria, 2015	95 334	949 221	0.100	0.000	0.100	0.101	16	10.04	<0.0001
2	Nigeria, 2006–2008	349 246	652 353	0.535	0.001	0.534	0.537	15	53.54	<0.0001
3	Egypt, 2006–2008	1 079 490	9 398 800	0.115	0.000	0.115	0.115	14	11.49	<0.0001
4	Benin, 2007	351	684	0.513	0.027	0.459	0.567	13	51.32	<0.0001
5	Burkina Faso, 2006	130	130	1.000	0.088	0.828	1.172	12	100.00	<0.0001
6	Burkina Faso, 2015	143 163	222 875	0.642	0.002	0.639	0.646	11	64.23	<0.0001
7	Cameroon, 2006	50	58	0.862	0.122	0.623	1.101	10	86.21	<0.0001
8	Cote D'Ivoire, 2006–2007	1823	3189	0.572	0.013	0.545	0.598	9	57.17	<0.0001
9	Cote D'Ivoire, 2015	51 555	52 218	0.987	0.004	0.979	0.996	8	98.73	<0.0001
10	Djibouti, 2006	4	22	0.182	0.091	0.004	0.360	7	18.18	1.00
11	Ghana, 2007	12 884	34 706	0.371	0.003	0.365	0.378	6	37.12	<0.0001
12	Ghana, 2015	16 556	55 053	0.301	0.002	0.296	0.305	5	30.07	<0.0001
13	Libya, 2014–2015	30	62	0.484	0.088	0.311	0.657	4	48.39	0.15
14	Niger, 2006	2700	28 000	0.096	0.002	0.093	0.100	3	9.64	<0.0001
15	Sudan, 2006–2007	84 900	173 197	0.490	0.002	0.487	0.493	2	49.02	<0.0001
16	Togo, 2007–2008	12 373	22 700	0.545	0.005	0.535	0.555	1	54.51	<0.0001
	Summary			0.487	0.005	0.478	0.496	Central tendency	48.73	

χ^2 for comparison of data = 1 134 183; degree of freedom = 15; *P*-value for heterogeneity test ≤ 0.0001; heterogeneity index (Higgins & Thompson's *H*): *H* = 275.0 (95% CI: 273.0–277.0), quantification of heterogeneity squared (I^2) = 100.0% (95% CI: 100.0–100.0%); *P*-value for individual study was calculated using Holm's multiple-comparison procedure.

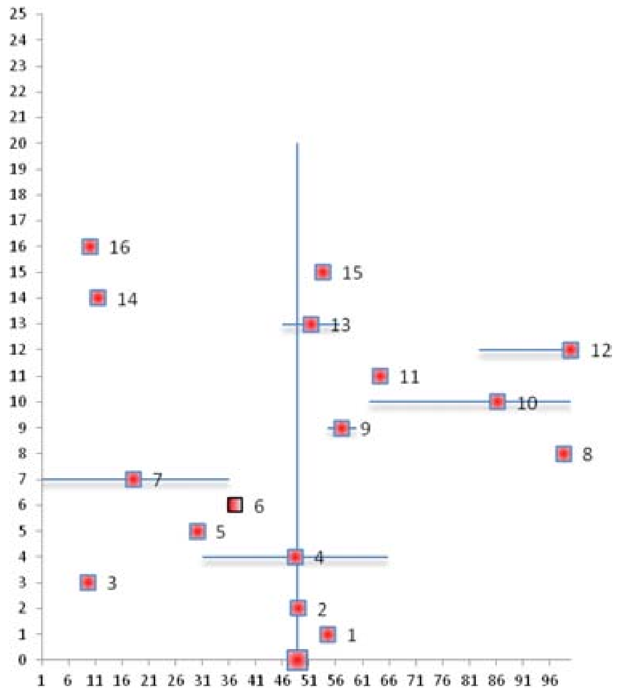

Figure 1 Forest plot for apparent morbidity in poultry due to HPAI H5N1 infection, Africa, 2006–2015.

n = 449). Nigeria, Lao PDR and Canada had 100% CFR, whereas Indonesia had 83.9% and Bangladesh 14.3% CFR. By proportion, Indonesia, Egypt and Vietnam had 37.2, 25.8 and 14.3% of all human deaths associated with the A H5N1, respectively Table 4.

Discussion

Our analyses have revealed some relatively obscure facts concerning the epidemiology and bio-characteristics of avian influenza H5N1 in poultry in Africa and explored the human case fatalities globally. Significant differences exist between the apparent morbidities, mortalities and case fatalities from those that had been previously validated under experimental conditions. While these parameters appeared lower in our estimates, much higher values have been obtained in previous experiments using the H5N1 virus of the clade 2.2.1 [14–18], and it has been confirmed that the virus is a pathogen with very high morbidity and mortality with short incubation period [19]. It is thought that in the course of active and passive surveillance, infected, infectious, as well as yet-uninfected, but in-contact animals were included in the denominators with effect on absolute pathogenicity of the virus.

Furthermore, the time to respond (from the notification of outbreaks until the culling of in-contact survivors) significantly affected the observed apparent morbidities and mortalities. Similar findings have been documented previously [20]. Our overall evaluation revealed that in countries where veterinary infrastructures, human and

Table 2 Apparent mortality in poultry due to HPAI H5N1 infection, Africa, 2006–2015

Serial number	Study	Events	Sample size	Outcome	SE	CI lower	CI upper	Forest plot ID	Rate	*P*-value
1	Nigeria, 2015	92 312	949 221	0.097	0.000	0.097	0.098	16	9.73	< 0.0001
2	Nigeria, 2006–2008	236 850	652 353	0.363	0.001	0.362	0.365	15	36.31	< 0.0001
3	Egypt, 2006–2008	1 073 621	9 398 800	0.114	0.000	0.114	0.114	14	11.42	< 0.0001
4	Benin, 2007	180	684	0.263	0.020	0.225	0.302	13	26.32	0.03
5	Burkina Faso, 2006	123	130	0.946	0.085	0.779	1.113	12	94.62	< 0.0001
6	Burkina Faso, 2015	142 246	222 875	0.638	0.002	0.635	0.642	11	63.82	< 0.0001
7	Cameroon, 2006	50	58	0.862	0.122	0.623	1.101	10	86.21	< 0.0001
8	Cote D'Ivoire, 2006–2007	719	3189	0.225	0.008	0.209	0.242	9	22.55	< 0.0001
9	Cote D'Ivoire, 2015	30 335	52 218	0.581	0.003	0.574	0.587	8	58.09	< 0.0001
10	Djibouti, 2006	4	22	0.182	0.091	0.004	0.360	7	18.18	< 0.0001
11	Ghana, 2007	12 884	34 706	0.371	0.003	0.365	0.378	6	37.12	< 0.0001
12	Ghana, 2015	16 238	55 053	0.295	0.002	0.290	0.299	5	29.50	< 0.0001
13	Libya, 2014–2015	23	62	0.371	0.077	0.219	0.523	4	37.10	0.75
14	Niger, 2006	2530	28 000	0.090	0.002	0.087	0.094	3	9.04	< 0.0001
15	Sudan, 2006–2007	84 900	173 197	0.490	0.002	0.487	0.493	2	49.02	< 0.0001
16	Togo, 2007–2008	12 373	22 700	0.545	0.005	0.535	0.555	1	54.51	< 0.0001
	Summary			0.402	0.005	0.393	0.411	Central Tendency	40.22	

χ^2 for comparison of data = 739 654; degree of freedom = 15; *P*-value for heterogeneity test $\leqq$ 0.0001; heterogeneity index (Higgins & Thompson's *H*): *H* = 222.1 (95% CI: 220.1–224.0), quantification of heterogeneity squared (I^2) = 100.0% (95% CI: 100.0–100.0%); *P*-value for individual study was calculated using Holm's multiple-comparison procedure.

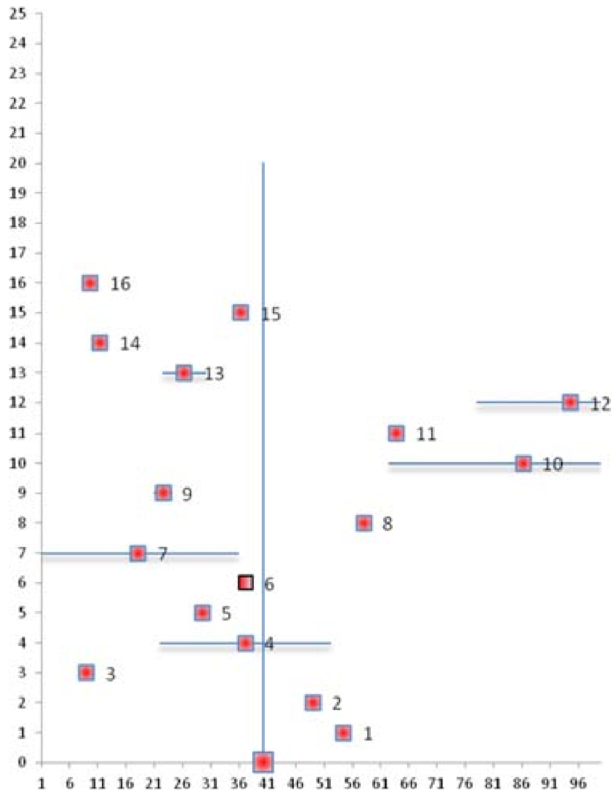

Figure 2 Forest plot for apparent mortality in poultry due to HPAI H5N1 infection, Africa, 2006–2015.

technical capacities, and interaction with the stakeholders were comparatively better, apparent morbidities, mortalities and case fatalities appeared to be comparatively lower.

Based on the aggregated data for the susceptible poultry populations, approximately 11.6 million birds were involved in the HPAI H5N1 outbreaks in Africa in 2006–2015. In addition, millions of in-contact domestic poultry and other birds were also culled. However, they were not analysed in this study since it was technically difficult to classify these birds in terms of epidemiological status [susceptible (S), exposed (E), infected (I) and recovered (R)] at the time of intervention, nor was it possible to assess the control measures including (but not limited to) the restriction of bird movement, stamping out of all laboratory confirmed cases and in-contact birds, decontamination of all infected premises and education of farmers [21, 22].

Although the overall mean apparent morbidity of HPAI H5N1 outbreaks in poultry in Africa from 2006–2015 was 48.7%, a majority of the affected countries had relatively higher apparent morbidity than this (see Table 1 and Figure 1, details in Appendix). This deviation from the average and variations in country-level values of apparent morbidity, as well as between outbreaks in one same country, can be attributed to lessons learnt from previous experience and quicker responses of the intervention teams in subsequent outbreaks. Furthermore, it is

Table 3 Case fatality in poultry due to HPAI H5N1 infection, Africa, 2006–2015

Serial number	Study	Events	Sample size	Outcome	SE	CI lower	CI upper	Forest plot ID	Rate	*P*-value
1	Nigeria, 2015	92 312	95 334	0.968	0.003	0.962	0.975	16	96.83	< 0.0001
2	Nigeria, 2006–2008	236 850	349 246	0.678	0.001	0.675	0.681	15	67.82	< 0.0001
3	Egypt, 2006–2008	1 073 621	1 079 490	0.995	0.001	0.993	0.996	14	99.46	< 0.0001
4	Benin, 2007	180	351	0.513	0.038	0.438	0.588	13	51.28	< 0.0001
5	Burkina Faso, 2006	123	130	0.946	0.085	0.779	1.113	12	94.62	1.00
6	Burkina Faso, 2015	142 246	143 163	0.994	0.003	0.988	0.999	11	99.36	< 0.0001
7	Cameroon, 2006	50	50	1.000	0.141	0.723	1.277	10	100.00	1.00
8	Cote D'Ivoire, 2006–2007	719	1823	0.394	0.015	0.366	0.423	9	39.44	< 0.0001
9	Cote D'Ivoire, 2015	30 335	51 555	0.588	0.003	0.582	0.595	8	58.84	< 0.0001
10	Djibouti, 2006	4	4	1.000	0.500	0.020	1.980	7	100.00	1.00
11	Ghana, 2007	12 884	12 884	1.000	0.009	0.983	1.017	6	100.00	< 0.0001
12	Ghana, 2015	16 238	16 556	0.981	0.008	0.966	0.996	5	98.08	< 0.0001
13	Libya, 2014–2015	23	30	0.767	0.160	0.453	1.080	4	76.67	1.00
14	Niger, 2006	2530	2700	0.937	0.019	0.901	0.974	3	93.70	1.00
15	Sudan, 2006–2007	84 900	84 900	1.000	0.003	0.993	1.007	2	100.00	< 0.0001
16	Togo, 2007–2008	12 373	12 373	1.000	0.009	0.982	1.018	1	100.00	< 0.0001
	Summary			0.860	0.005	0.851	0.869	Central tendency	86.01	

χ^2 for comparison of data = 36 786; degree of freedom = 15; *P*-value for heterogeneity test ≦ 0.0001; heterogeneity index (Higgins & Thompson's *H*): *H* = 49.5 (95% CI: 48.1–51.0), quantification of heterogeneity squared (I^2) = 100.0% (95% CI: 100.0–100.0%); *P*-value for individual study was calculated using Holm's multiple-comparison procedure.

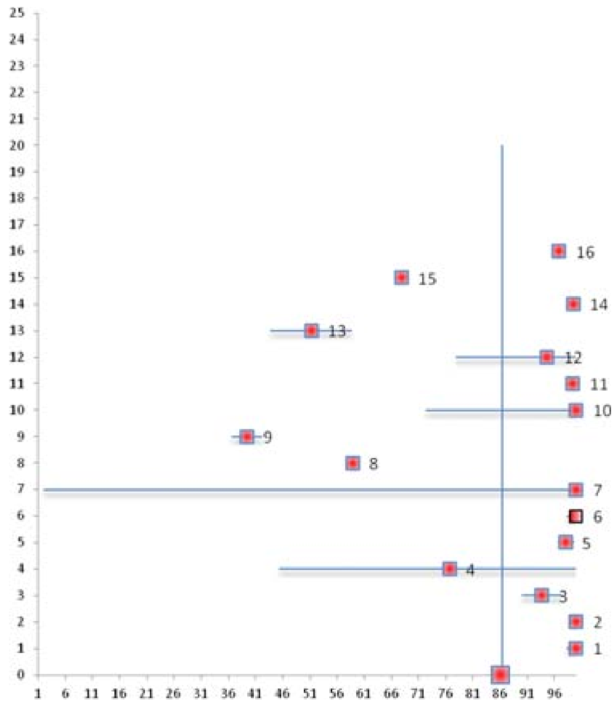

Figure 3 Forest plot for case fatality in poultry due to HPAI H5N1 infection, Africa, 2006–2015.

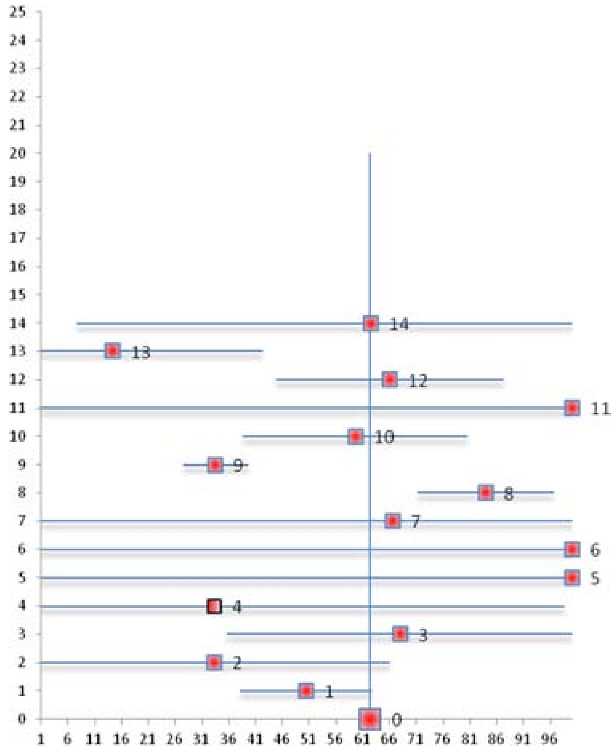

Figure 4 Forest plot for case fatality in poultry due to HPAI H5N1 infection globally, 2006–2015.

possible that compliance with some biosecurity measures have increased based on previous expert evaluations with consequent impact on reduced infection transmission [23]. Contrastingly, in Cote d'Ivoire in 2006 and 2015,

Table 4 Case fatality in humans due to HPAI H5N1 infection globally, 2006–2015

Serial number	Study	Events	Sample size	Outcome	SE	CI lower	CI upper	Forest plot ID	Rate	*P*-value
1	Azerbaijan	5	8	0.625	0.280	0.077	1.173	14	62.50	1.00
2	Bangladesh	1	7	0.143	0.143	−0.137	0.423	13	14.29	0.03
3	Cambodia	37	56	0.661	0.109	0.448	0.874	12	66.07	1.00
4	Canada	1	1	1.000	1.000	−0.960	2.960	11	100.00	0.99
5	China	31	52	0.596	0.107	0.386	0.806	10	59.62	1.00
6	Egypt	116	346	0.335	0.031	0.274	0.396	9	33.53	<0.0001
7	Indonesia	167	199	0.839	0.065	0.712	0.966	8	83.92	<0.0001
8	Iraq	2	3	0.667	0.471	−0.257	1.591	7	66.67	1.00
9	Lao PDR	2	2	1.000	0.707	−0.386	2.386	6	100.00	1.00
10	Nigeria	1	1	1.000	1.000	−0.960	2.960	5	100.00	0.99
11	Pakistan	1	3	0.333	0.333	−0.320	0.987	4	33.33	1.00
12	Thailand	17	25	0.680	0.165	0.357	1.003	3	68.00	1.00
13	Turkey	4	12	0.333	0.167	0.007	0.660	2	33.33	1.00
14	Vietnam	64	127	0.504	0.063	0.380	0.627	1	50.39	1.00
	Summary			0.623	0.005	0.613	0.632	Central tendency	62.26	

χ^2 for comparison of data = 94.9; degree of freedom = 13; *P*-value for heterogeneity test $\leqq$ 0.0001; heterogeneity index (Higgins & Thompson's *H*): *H* = 2.7 (95% CI: 2.2–3.4), quantification of heterogeneity squared (I^2) = 86.3% (95% CI: 78.6–91.2%); *P*-value for individual study was calculated using Holm's multiple-comparison procedure.

apparent morbidities of 57.2 and 98.7% were estimated, respectively.

The overall mean apparent mortality for the HPAI H5N1 outbreaks in poultry in Africa was 40.2%, with differing country-level outcomes (Table 2, Figure 2). Specifically, the mean value of apparent mortalities in Nigeria and Burkina Faso dropped significantly during the epidemic periods of 2006–2008 and 2015 ($P < 0.0001$), however, these values were more than double in Cote d'Ivoire. These observed increases in apparent morbidity and mortality may be follow from delays and inconsistencies in intervention, increased mean distances from the central disease coordination and management centres, location of outbreaks and the occurrence of multiple overwhelming outbreaks [24]. For instance, the outbreaks in Cote d'Ivoire in 2006 primarily occurred in Abidjan, but in 2015, multiple outbreaks occurred in many localities within about a 5-h drive from Abidjan. Rivas *et al.* [25] confirmed that such distances can play a role in the dissemination of outbreaks to new locations, and Brown *et al.* [9] stated that multiple empirically-dispersed disease surveillance and detection centres in each country will assist in facilitating rapid and effective controls of outbreaks. The spatio-temporal dynamics of policy decisions on diseases may have influenced the outcomes of HPAI H5N1 infections in Africa.

The overall mean CFR of HPAI H5N1 outbreaks in poultry in Africa in 2006–2015 was 86.0%. This is comparable to data from other countries. It is worth noting that in certain countries, outbreaks in poultry have been associated with cases and deaths in infected wild birds [26].

Similarly, due to the zoonotic nature of HPAI H5N1 and increased human–animal interactions, a total of 449 deaths associated with A H5N1 infections have occurred in humans globally in 2003–2015, with an estimated CFR of 62.3% based on reported cases. Our results are comparable to those of Van Kerkhove *et al.* [27]. However, Li *et al.* [28] had earlier argued for a lower estimate of 14–33% due to uncertainties around reporting, and we agree with this postulation. We are aware that our results may have been influenced and biased due to factors like underreporting (especially in cases with milder symptoms), misclassification of cases and its effects on denominators, and censoring effect from local and national authorities where final outcomes cannot be immediately ascertained. However, we tried to filter all data, remove duplicates and validate records based on laboratory-confirmed cases before including data in the evaluation. A CFR in the range determined by Li *et al.* [28] (14–33%) is high enough to warrant the attention of health authorities in case of an epidemic in humans and for an effective control to be implemented [6, 9]. Although the virus is yet to adapt effectively to infect and transmit between humans, it and other forms of influenza viruses continue to threaten humans and livestock [29–32].

Although the CFR for human infections was relatively high and varied from one country to another, some of the observed differences may be attributed to delayed diagnosis, and misdiagnosis with respiratory infections that present similar signs and symptoms [27]. Since avian influenza H5N1 and other animal influenza viruses continue to threaten humans, reduced human–animal interactions must be implemented and modern farming methods must consider human health in their management procedures. It should be noted that people in close contact with poultry are at high risk of infections, and the elderly, children and individuals with chronic illnesses have higher risks of developing complications, such as bronchitis and chest infection, which may lead to death. To date, Bangladesh, China, Egypt, part of India, Indonesia and Vietnam are considered endemic for HPAI H5N1 virus [4, 33].

In Egypt, human infection with H5N1 avian influenza virus was confirmed in poultry and humans, and the influenza-related human morbi–mortality approached zero towards the end of 2008. However, such trend changed significantly between the end of 2014 and November 2015 with a total of 173 human cases and 53 deaths reported as of November 2015. Particularly between November 2014 and 30 April 2015, a total of 165 human cases were reported and 48 deaths were confirmed by the national health authorities – the highest number of human cases ever reported from any country over a similar period. It is possible that close human–animal interactions that exist in Egypt were responsible for this observation. However, between 2006 and 2015, Egypt still reported some of the lowest overall mortality rates. In addition, Egypt has reported the lowest median age of people infected (6 years) and globally the country also has the highest number of infected young people and females [34, 35].

This work was also subject to some other limitations. Data mining was difficult because good-quality and consistent information was scarce in and the skills of veterinary and human health authorities were varied. Benet *et al*. [36] have earlier highlighted some limitations to effective circulation of critical epidemiological information in developing countries and aspects affecting disease reporting include: independence of health services, coherence of the decision-making chain, coordination among role players, integration between risk assessment and management, and traceability. Also, some countries suspended further reports to the international organizations like the OIE. For instance, Egypt has suspended regular reports to the OIE since July 2008, a period when endemicity of HPAI H5N1 was declared in Egypt [37], and finally, reports from the national authorities do not sometimes correspond to those officially declared to the OIE.

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Appendix 1a.

Apparent morbidity of HPAI H5N1 in poultry in Africa using 846 reports, 2006–2015.

Study	Events	Sample size	Outcome (es)	SE	Var	W	w*es	w*(es2)	w2	wv	wv*es	wv*(es2)	wv2
Nigeria, 2015	95 334	949 221	0.100434	0.000325	1.06×10^{-7}	9 451 198	949 221	95 334	8.93×10^{13}	51.48727	5.171069	0.519351	2650.939
Nigeria, 2006–2008	349 246	652 353	0.535364	0.000906	8.21×10^{-7}	1 218 523	652 353	349 246	1.48×10^{12}	51.48538	27.56339	14.75643	2650.744
Egypt, 2006–2008	1 079 490	9 398 800	0.114854	0.000111	1.22×10^{-8}	81 832 570	9 398 800	1 079 490	6.7×10^{15}	51.48752	5.913549	0.679195	2650.965
Benin, 2007	351	684	0.513158	0.02739	0.00075	1332.923	684	351	1 776 684	49.57268	25.43861	13.05402	2457.451
Burkina Faso, 2006	130	130	1	0.087706	0.007692	130	130	130	16 900	36.88067	36.88067	36.88067	1360.183
Burkina Faso, 2015	143 163	222 875	0.642347	0.001698	2.88×10^{-6}	346 970	222 875	143 163	1.2×10^{11}	51.47991	33.06795	21.24108	2650.181
Cameroon, 2006	50	58	0.862069	0.121915	0.014863	67.28	58	50	4526.598	29.16691	25.14389	21.67577	850.7086
Cote D'Ivoire, 2006–2007	1823	3189	0.571653	0.013389	0.000179	5578.563	3189	1823	3 1120 369	51.01669	29.16382	16.67157	2602.703
Cote D'Ivoire, 2015	51 555	52 218	0.987303	0.004348	1.89×10^{-5}	52 889.53	52 218	51 555	2.8×10^{9}	51.43748	50.78439	50.13959	2645.814
Djibouti, 2006	4	22	0.181818	0.090909	0.008264	121	22	4	14 641	36.11851	6.567002	1.194	1304.547
Ghana, 2007	12 884	34 706	0.371233	0.003271	1.07×10^{-5}	93 488.55	34 706	12 884	8.74×10^{9}	51.45921	19.10334	7.091783	2648.05
Ghana, 2015	16 556	55 053	0.300728	0.002337	5.46×10^{-6}	183 065.5	55 053	16 556	3.35×10^{10}	51.47307	15.47941	4.655099	2649.477
Libya, 2014–2015	30	62	0.483871	0.088342	0.007804	128.1333	62	30	16 418.15	36.72887	17.77203	8.59937	1349.01
Niger, 2006	2700	28 000	0.096429	0.001856	3.44×10^{-6}	29 0370.4	28 000	2700	8.43×10^{10}	51.47842	4.963991	0.478671	2650.028
Sudan, 2006–2007	84 900	173 197	0.490193	0.001682	2.83×10^{-6}	35 3323.9	173 197	84 900	1.25×10^{11}	51.48005	25.23517	12.37011	2650.195
Togo, 2007–2008	12 373	22 700	0.545066	0.0049	2.4×10^{-5}	41 646.33	22 700	12 373	1.73×10^{9}	51.42398	28.02946	15.27791	2644.425
	1 850 589	11 593 268	0.487282										
k	16				Sums:	93 871 404	11 593 268	1 850 589	6.79×10^{15}	754.1766	356.2777	225.2846	36 415.42
df	15												
										v	0.019422		
Q	41 8801.9			Qv	56.97679								
I2	99.99642			I2v	73.67349								
es (fixed)	0.123502			es (random)	0.472406								
SEes (fixed)	0.000103			SEes (random)	0.036414								
CI (fixed)	0.123299	0.123704		CI (random)	0.401036	0.543777							

Appendix 1b.

Apparent mortality of HPAI H5N1 in poultry in Africa using 846 reports, 2006–2015.

Study	Events	Sample size	Outcome (es)	SE	Var	w	w*es	w*(es2)	w2	wv	wv*es	wv*(es2)	wv2
Nigeria, 2015	92 312	949 221	0.09725	0.00032	1.02×10^{-7}	9 760 600	949 221	92 312	9.53×10^{13}	78.66748	7.650434	0.744007	6188.573
Nigeria, 2006–2008	236 850	652 353	0.36307	0.000746	5.57×10^{-7}	1 796 768	652 353	236 850	3.23×10^{12}	78.66467	28.56081	10.36958	6188.131
Egypt, 2006–2008	1073 621	9 398 800	0.11423	0.00011	1.22×10^{-8}	82 279 912	9 398 800	1 073 621	6.77×10^{15}	78.66804	8.986218	1.026492	6188.661
Benin, 2007	180	684	0.263158	0.019615	0.000385	2599.2	684	180	6 755 841	76.35707	20.09397	5.287886	5830.403
Burkina Faso, 2006	123	130	0.946154	0.085312	0.007278	137.3984	130	123	18 878.31	50.02567	47.33198	44.78334	2502.568
Burkina Faso, 2015	142 246	222 875	0.638232	0.001692	2.86×10^{-6}	349 206.8	222 875	142 246	1.22×10^{11}	78.6504	50.19722	32.03748	6185.885
Cameroon, 2006	50	58	0.862069	0.121915	0.014863	67.28	58	50	4526.598	36.26488	31.26283	26.95071	1315.142
Cote D'Ivoire, 2006–2007	719	3189	0.225463	0.008408	7.07×10^{-5}	14 144.26	3189	719	2×10^{8}	78.233	17.63861	3.976846	6120.402
Cote D'Ivoire, 2015	30 335	52 218	0.58093	0.003335	1.11×10^{-5}	89 886.91	52 218	30 335	8.08×10^{9}	78.59933	45.6607	26.52567	6177.854
Djibouti, 2006	4	22	0.181818	0.090909	0.008264	121	22	4	14 641	47.67332	8.667877	1.575978	2272.746
Ghana, 2007	12 884	34 706	0.371233	0.003271	1.07×10^{-5}	93 488.55	34 706	12 884	8.74×10^{9}	78.60198	29.17962	10.83243	6178.271
Ghana, 2015	16 238	55 053	0.294952	0.002315	5.36×10^{-6}	18 6650.6	55 053	16 238	3.48×10^{10}	78.63498	23.19355	6.840988	6183.459
Libya, 2014–2015	23	62	0.370968	0.077352	0.005983	167.1304	62	23	27 932.58	53.49029	19.84317	7.361177	2861.212
Niger, 2006	2530	28 000	0.090357	0.001796	3.23×10^{-6}	30 9881.4	28 000	2530	9.6×10^{10}	78.64815	7.106422	0.642116	6185.532
Sudan, 2006–2007	84 900	173 197	0.490193	0.001682	2.83×10^{-6}	353 323.9	173 197	84 900	1.25×10^{11}	78.65061	38.554	18.89891	6185.918
Togo, 2007–2008	12 373	22 700	0.545066	0.0049	2.4×10^{-5}	41 646.33	22 700	12 373	1.73×10^{9}	78.5198	42.79848	23.328	6165.359
	1 705 388	11 593 268	0.402196										
k	16				Sums:	95 278 601	11 593 268	1 705 388	6.87×10^{15}	1128.35	426.7259	221.1816	82 730.11
df	15												
										v	0.012712		
Q	294 747.4			Qv	59.79991								
I2	99.99491			I2v	74.91635								
es (fixed)	0.121678			es (random)	0.378186								
SEes (fixed)	0.000102			SEes (random)	0.02977								
CI (fixed)	0.121477	0.121878		CI (random)	0.319837	0.436535							

Appendix 1c.

Case fatality of HPAI H5N1 in poultry in Africa using 846 reports, 2006–2015.

Study	Events	Sample size	Outcome (es)	SE	Var	w	w*es	w*(es2)	w2	wv	wv*es	wv*(es2)	wv2
Nigeria, 2015	92 312	95 334	0.968301	0.003187	1.02×10^{-5}	98 454.93	95 334	92 312	9.69×10^{9}	28.17804	27.28482	26.41992	794.0018
Nigeria, 2006–2008	236 850	349 246	0.678175	0.001393	1.94×10^{-6}	514 979	349 246	236 850	2.65×10^{11}	28.18456	19.11407	12.96269	794.3696
Egypt, 2006–2008	1 073 621	1 079 490	0.994563	0.00096	9.21×10^{-7}	1 085 391	1 079 490	1 073 621	1.18×10^{12}	28.18537	28.03213	27.87973	794.4153
Benin, 2007	180	351	0.512821	0.038223	0.001461	684.45	351	180	468 471.8	27.07129	13.88271	7.11934	732.8548
Burkina Faso, 2006	123	130	0.946154	0.085312	0.007278	137.3984	130	123	18 878.31	23.38821	22.12885	20.93729	547.0085
Burkina Faso, 2015	142 246	143 163	0.993595	0.002634	6.94×10^{-6}	144 085.9	143 163	142 246	2.08×10^{10}	28.18059	28.00009	27.82074	794.1458
Cameroon, 2006	50	50	1	0.141421	0.02	50	50	50	2500	18.02501	18.02501	18.02501	324.901
Cote D'Ivoire, 2006–2007	719	1823	0.394405	0.014709	0.000216	4622.154	1823	719	21 364 311	28.01527	11.04936	4.35792	784.8552
Cote D'Ivoire, 2015	30 335	51 555	0.588401	0.003378	1.14×10^{-5}	87 618.86	51 555	30 335	7.68×10^{9}	28.17704	16.57939	9.755326	793.9456
Djibouti, 2006	4	4	1	0.5	0.25	4	4	4	16	3.502891	3.502891	3.502891	12.27025
Ghana, 2007	12 884	12 884	1	0.00881	7.76×10^{-5}	12 884	12 884	12 884	1.66×10^{8}	28.12458	28.12458	28.12458	790.9919
Ghana, 2015	16 238	16 556	0.980792	0.007697	5.92×10^{-5}	16 880.23	16 556	16 238	2.85×10^{8}	28.13912	27.59864	27.06853	791.81
Libya, 2014–2015	23	30	0.766667	0.159861	0.025556	39.13043	30	23	1531.191	16.3843	12.5613	9.630329	268.4454
Niger, 2006	2530	2700	0.937037	0.018629	0.000347	2881.423	2700	2530	8 302 598	27.91306	26.15557	24.50874	779.1389
Sudan, 2006–2007	84 900	84 900	1	0.003432	1.18×10^{-5}	84 900	84 900	84 900	7.21×10^{9}	28.17675	28.17675	28.17675	793.9293
Togo, 2007–2008	12 373	12 373	1	0.00899	8.08×10^{-5}	12 373	12 373	12 373	1.53×10^{8}	28.12204	28.12204	28.12204	790.8493
	1 705 388	1 850 589	0.860057										
k	16				Sums:	2 065 986	1 850 589	1 705 388	1.49×10^{12}	397.7681	338.3382	304.4118	10 587.93
df	15												
										v	0.035478		
Q	47 738.62			Qv	16.62422								
I2	99.96858			I2v	9.770215								
es (fixed)	0.895742			es (random)	0.850592								
SEes (fixed)	0.000696			SEes (random)	0.05014								
CI (fixed)	0.894378	0.897105		CI (random)	0.752317	0.948866							

Appendix 1d.

Case fatality of HPAI H5N1 in humans using 842 reports, 2006–2015.

Study	Events	Sample Size	Outcome (es)	SE	Var	w	w*es	w*(es2)	w2	wv	wv*es	wv*(es2)	wv2
Azerbaijan	5	8	0.625	0.279508	0.078125	12.8	8	5	163.84	8.341429	5.213393	3.258371	69.57944
Bangladesh	1	7	0.142857	0.142857	0.020408	49	7	1	2401	16.08578	2.297969	0.328281	258.7524
Cambodia	37	56	0.660714	0.108621	0.011798	84.75676	56	37	7183.708	18.6717	12.33666	8.151005	348.6322
Canada	1	1	1	1	1	1	1	1	1	0.959915	0.959915	0.959915	0.921437
China	31	52	0.596154	0.107072	0.011464	87.22581	52	31	7608.341	18.78886	11.20105	6.67755	353.0212
Egypt	116	346	0.33526	0.031128	0.000969	1032.034	346	116	1065095	23.40414	7.846473	2.63061	547.7536
Indonesia	167	199	0.839196	0.064939	0.004217	237.1317	199	167	56 231.46	21.75067	18.25307	15.31791	473.0916
Iraq	2	3	0.666667	0.471405	0.222222	4.5	3	2	20.25	3.788155	2.525437	1.683624	14.35012
Lao PDR	2	2	1	0.707107	0.5	2	2	2	4	1.845841	1.845841	1.845841	3.407128
Nigeria	1	1	1	1	1	1	1	1	1	0.959915	0.959915	0.959915	0.921437
Pakistan	1	3	0.333333	0.333333	0.111111	9	3	1	81	6.541521	2.180507	0.726836	42.7915
Thailand	17	25	0.68	0.164924	0.0272	36.76471	25	17	1351.644	14.50147	9.860999	6.705479	210.2926
Turkey	4	12	0.333333	0.166667	0.027778	36	12	4	1296	14.38098	4.793659	1.597886	206.8125
Vietnam	64	127	0.503937	0.062992	0.003968	252.0156	127	64	63 511.88	21.86914	11.02067	5.553723	478.2592
	449	842	0.622604										
k	16				Sums:	1845.229	842	449	1 204 950	171.8895	91.29556	56.39694	3008.586
df	15												
										v	0.041759		
Q	64.78538			Qv	7.907194								
I2	76.84663			I2v	−89.7007								
es (fixed)	0.456312			es (random)	0.531129								
SEes (fixed)	0.02328			SEes (random)	0.076274								
CI (fixed)	0.410684	0.50194		CI (random)	0.381633	0.680626							