One Health 2 (2016) 55–64

Contents lists available at ScienceDirect

One Health

journal homepage: www.elsevier.com/locate/onehlt

Interventions in live poultry markets for the control of avian influenza: A systematic review

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ARTICLE INFO

Article history:
Received 12 October 2015
Received in revised form 17 February 2016
Accepted 14 March 2016
Available online 22 March 2016

Keywords:
Influenza A virus
Live poultry market
A/H7N9
A/H9N2
Closure
Rest day

ABSTRACT

Background: Live poultry markets (LPMs) pose a threat to public health by promoting the amplification and dissemination of avian influenza viruses (AIVs) and by providing the ideal setting for zoonotic influenza transmission.
Objective: This review assessed the impact of different interventions implemented in LPMs to control the emergence of zoonotic influenza.
Methods: Publications were identified through a systematic literature search in the PubMed, MEDLINE and Web of Science databases. Eligible studies assessed the impact of different interventions, such as temporary market closure or a ban on holding poultry overnight, in reducing i) AIV-detection rates in birds and the market environment or ii) influenza incidence in humans. Unpublished literature, reviews, editorials, cross-sectional studies, theoretical models and publications in languages other than English were excluded. Relevant findings were extracted and critically evaluated. For the comparative analysis of findings across studies, standardized outcome measures were computed as i) the relative risk reduction (RRR) of AIV-detection in LPMs and ii) incidence rate ratios (IRRs) of H7N9-incidence in humans.
Results: A total of 16 publications were identified and reviewed. Collectively, the data suggest that AIV-circulation can be significantly reduced in the LPM-environment and among market-birds through (i) temporary LPM closure, (ii) periodic rest days (iii) market depopulation overnight and (iv) improved hygiene and disinfection. Overall, the findings indicate that the length of stay of poultry in the market is a critical control point to interrupt the AIV-replication cycle within LPMs. In addition, temporary LPM closure was associated with a significant reduction of the incidence of zoonotic influenza. The interpretation of these findings is limited by variations in the implementation of interventions. In addition, some of the included studies were of ecologic nature or lacked an inferential framework, which might have lead to cosiderable confounding and bias.
Conclusions: The evidence collected in this review endorses permanent LPM-closure as a long-term objective to reduce the zoonotic risk of avian influenza, although its economic and socio-political implications favour less drastic interventions, e.g. weekly rest days, for implementation in the short-term.

Contents

Abbreviations: C/D, cleansing and disinfection; GLM, general linear model; IRR, incidence rate ratio; LBM, live bird market; LPM, live poultry market; NDV, Newcastle Disease Virus; OR, odds ratio; PUE, Pneumonia of Unknown Etiology; rLPM, retail live poultry market; RR, relative risk; RRR, relative risk reduction; RT-PCR, reverse transcription polymerase chain reaction; wLPM, wholesale live poultry market.

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http://dx.doi.org/10.1016/j.onehlt.2016.03.002

1. Introduction

Human influenza viruses cause seasonal influenza, a globally widespread respiratory illness giving rise to ~3–5 million cases of severe illness every year [1]. Influenza viruses can also be found in other mammals and birds, and the greatest diversity of influenza viruses occurs in aquatic birds [2]. Most strains of avian influenza viruses (AIVs) do not pose a risk to human health. Some strains however, e.g. subtypes H7N9 [3] and H5N1 [4], have acquired the ability to cross the species-barrier and infect humans who come into close contact with infected birds or contaminated environments [5]. Occasionally, animal influenza viruses cause global pandemics in humans, as happened three times in the 20th century and most recently in 2009 [6,7]. Surveillance of avian influenza viruses is important to identify new strains that may pose a pandemic threat [8].

Because of the high density and variety of avian hosts, live poultry markets (LPMs) support the maintenance, amplification and dissemination of AIVs [8–11]. In addition, LPMs provide frequent opportunities for inter-species transmission events [8–12]. In fact, the emergence of zoonotic influenza outbreaks has often been preceded by long-lasting AIV-circulation in market poultry [13,14].

Considering the unpredictability of the subtype or strain causing the next zoonotic or pandemic influenza threat [15], generic measures to control the endemicity of AIVs at the source, e.g. in market poultry, remain key elements of pandemic preparedness [8,15,16]. Permanent LPM closure encounters strong public resistance [17]. Nonetheless, Chinese LPMs were temporarily closed during both H7N9-waves [18]. Hong Kong's LPMs implemented monthly [19] or bimonthly [20] rest days and an overnight poultry storage ban [21]. Similarly, LPM-systems in the North-Eastern USA have introduced regular depopulation and disinfection of all markets in 2002 [22–24].

This review discusses the impact of different LPM interventions on (i) AIV-circulation in LPMs and (ii) AIV-transmission to humans, drawing implications for policy recommendations based on the collective scientific evidence.

2. Materials and methods

2.1. Literature search

The databases PubMed, Web of Science and MEDLINE were searched for relevant articles through the following search string: ((poultry market) OR (poultry markets)) AND (avian influenza). This search was complemented with different combinations of the following search terms: “live poultry market/markets”, “avian influenza”, “overnight”, “rest day”, “market closure”, “clos*” and “ban”. The literature search was conducted on 25 July 2015.

2.2. Inclusion criteria

Settings: live poultry markets worldwide; no time restrictions;

Interventions: temporary LPM closure, periodic rest days combined with depopulation and disinfection of the markets, sale ban of specific bird species and ban on holding live poultry within LPMs overnight;

Outcomes: AIV-detection rates in birds and/or the market environment or influenza incidence in humans;

Study design: before–after studies assessing the impact of either of the listed interventions on either of the outcomes.

2.3. Exclusion criteria

Unpublished literature, reviews, editorials, cross-sectional studies, theoretical models and publications in languages other than English were excluded.

2.4. Data extraction

All studies were individually assessed with regard to study design and potential bias or confounding. No study was excluded based on these criteria, but major limitations of specific studies are discussed in the text.

The following information was retrieved from the included studies: location, influenza strain, type and date of intervention, data collection methods, main outcomes and findings. Because of the differences in study design, data analysis and reporting methods, the computation of a pooled estimate of intervention effectiveness was not possible within this group of studies. To compare findings across studies, standardized outcome measures were computed as i) relative risk reduction (RRR) of AIV-detection in LPMs and ii) incidence rate ratios (IRRs) of H7N9-incidence in humans. When necessary, raw data was retrieved from supplementary materials.

2.5. Calculation of epidemiologic outcome measures

The following outcome measures were used to summarize the findings:

Average AIV-prevalence before (P_{pre}) or after (P_{post}) the intervention:

- P_{pre} = *total nr. of positive samples before the intervention/total nr. of samples tested before the intervention*
- P_{post} = *total nr. of positive samples after the intervention/total nr. of samples tested after the intervention*

Relative risk (RR):

$$RR = P_{post}/P_{pre}$$

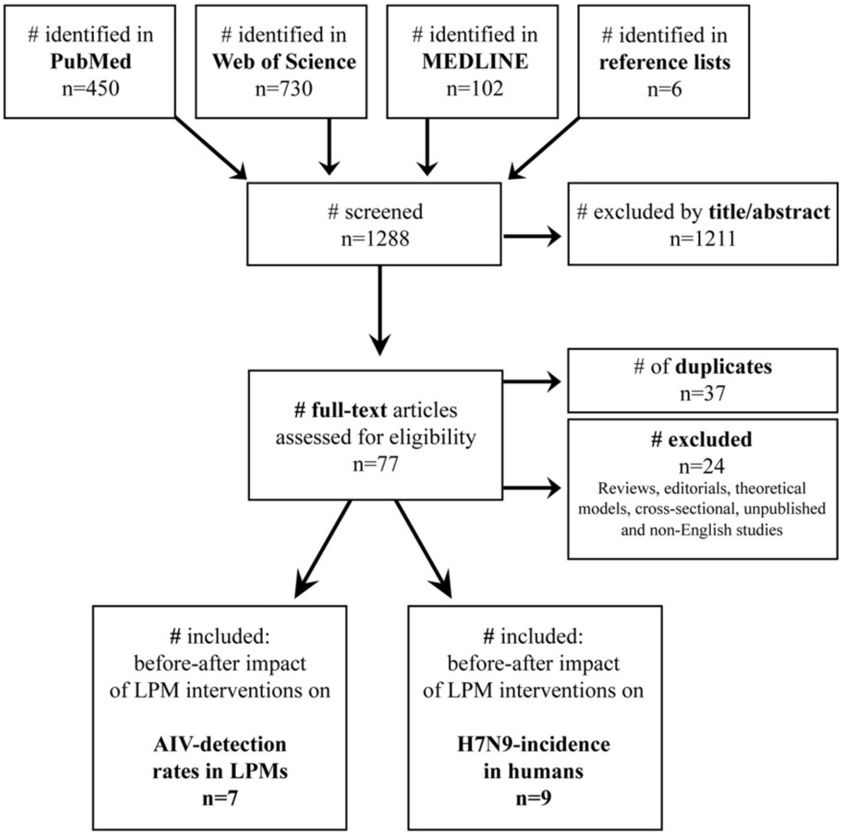

Fig. 1. Visual summary of the literature search and inclusion process.

Relative risk reduction (RRR) for studies with AIV-prevalence as an outcome:

$$\mathrm{RRR} = 1 - \mathrm{RR}$$

The 95% confidence intervals for the RRR were calculated as 1 minus the confidence limits of the relative risk.

Incidence rate ratio (IRR) for studies with H7N9-incidence as an outcome:

IRR = incidence rate after the intervention / incidence rate before the intervention

LPM closure effectiveness was calculated as one minus the incidence rate ratio.

The statistical analysis was conducted with SPSS statistical software, version 20.

3. Results

3.1. Overview of the included studies

The combination of search terms in the three databases delivered a total of 1282 articles, in addition to six publications identified from reference lists (Fig. 1). Ultimately, this review included 16 studies assessing the before–after impact of different interventions in LPMs on the reduction of (i) AIV-detection rates by virus isolation or RT-PCR in the markets ($n = 7$) or (ii) influenza incidence in humans ($n = 9$) (Fig. 1). A detailed description of all included studies is provided in supplementary Tables S1 and S2.

3.2. Impact of LPM interventions on AIV-isolation rates in Hong Kong

Three studies assessed the effectiveness of different LPM interventions in reducing AIV-isolation rates in Hong Kong's LPMs, using the endemic poultry strain H9N2 as indicator for virus survival [19–21]. Kung and colleagues determined the impact of a mandatory rest day combined with depopulation and restocking, introduced in Hong Kong in 2001 [19]. A total of 2218 faecal swabs were sampled from different bird species within a 6-day window prior and after the monthly intervention. The study reported odds ratios (ORs) of H9N2-isolation before and after the rest day [19]. Each month, the risk of H9N2-isolation was significantly reduced by 87–100% after the intervention (p-values ≤ 0.01) [19]. However, isolation rates reached again pre-intervention values within a month [19].

Subsequently, Lau and colleagues utilized faecal bird-samples routinely collected in Hong Kong LPMs between 1999 and 2005 to assess the additive effectiveness of a live quail sale ban and an additional monthly rest day [20]. A multivariable Poisson General Linear Model (GLM) adjusted for several potential confounders of AIV-transmission was used to calculate relative risks (RRs) of weekly H9N2-isolation during the different intervention periods, compared to the time period prior to the implementation of the first rest day [20]. According to this model, the introduction of one monthly rest day resulted in a 27% (p-value = 0.22) or 58% (p-value = 0.001) reduction in H9N2 average isolation rates in chickens and minor poultry, respectively [20]. After the quail sale ban and the second monthly rest day, average isolation rates from both chickens (RR = 0.56; p-value = 0.09) and minor poultry (RR = 0.37; p-value = 0.01) declined further, although these interventions did not affect the circulation of H9N2 significantly [20].

Table 1
Relative risk reduction (RRR) of AIV-detection in studies assessing the immediate effects of interventions. (Sample collection within a <3 week time window.)

Study	Influenza strain	Intervention	Sampling period and AIV detection method	P_{pre}[a]	P_{post}[b]	RRR (95% CI)
Kung et al. (2003)	H9N2	Monthly rest day, depopulation and C/D	Monthly, within a 6-day window before & after rest day (virus isolation)	5.0% (56/1122)	0.4% (4/1096)	0.93 (0.80; 0.97)*
Kang et al. (2015)	H7N9	Two-week LPM closure and C/D	One week before closure and at re-opening (RT-PCR)	14.8% (112/755)	1.7% (5/300)	0.89 (0.73; 0.95)*
Trock et al. (2008)	H7N2, H5N2	LPM depopulation and C/D	1–17 days before the intervention and upon visual C/D approval (virus isolation)	22.5% (306/1362)	0.4% (1/226)	0.98 (0.86; 1.00)*
			1–17 days before the intervention and 0–3 days after C/D approval (virus isolation)	22.5% (306/1362)	4.6% (46/996)	0.79 (0.72; 0.85)*

C/D = cleaning and disinfection.
[a] P_{pre} = prevalence before the intervention.
[b] P_{post} = prevalence after the intervention.
* Significant at the α = 0.05 level.

A follow-up study revealed that a ban on overnight storage of live poultry introduced in 2008 dramatically reduced H9N2-isolation rates by an additional 84% and 100% in chickens and minor poultry, respectively (p-values < 0.05) [21].

3.3. Impact of LPM closures in Mainland China

Following the emergence of H7N9 in early 2013 [25], a weekly 24-h LPM closure was introduced in Guangzhou [26]. Samples were collected during the time period spanning one month before and two months after LPM closure and the prevalence of different AIV strains was assessed by RT-PCR. After the intervention, overall AIV-prevalence was significantly decreased in environmental ($\chi2 = 6.25$; p-value = 0.012), but not animal specimens [26].

In a similar study in Guangdong, 15% (112/755) of samples were H7N9-positive by RT-PCR one week before a 14 day LPM closure period [27], but this proportion was significantly reduced to 1.67% (5/300) at market re-opening ($\chi2 = 37.75$; p-value < 0.01) [27].

3.4. Impact of quarterly LPM depopulation in the USA

In 2002, poultry traders from the New York City area agreed on the quarterly depopulation and disinfection of all live bird markets (LBMs) [23]. Before a depopulation event, H7N2 or H5N2 subtypes could be detected in 22.5% of samples collected in LBMs. The proportion of AIV-positive specimens decreased to 0.4% upon completed disinfection but rose again to ~4.6% within three days [23].

A follow-up study covering a period of 6 years reported a steady decline in the number of H7 and H5 isolations in this LBM system following the implementation of the quarterly depopulation operations, although additional interventions, e.g. all-year round vehicle washing, likely played an important role as well [24].

3.5. Relative risk reduction of AIV isolations through LPM interventions

The relative risk reduction (RRR) of AIV-detection could be calculated from the raw data provided in the papers or the technical appendices of 6/7 publications.

Table 2
Relative risk reduction (RRR) of AIV-detection in studies assessing the long-term effects of interventions. (Sample collection over time periods of >3 weeks.)

Study	Influenza strain	Intervention	Sampling period and AIV detection method	P_{pre}[a]	P_{post}[b]	RRR (95% CI)
Yuan et al. (2014b)	H7N9, H5, H9	Weekly rest day, depopulation and C/D	During the 33 days before and the 3–56 days after the implementation of the weekly rest day (RT-PCR)	rLPMs Total: 5.1% (85/1660)	Total: 4.1% (92/2224)	0.19 (−0.08; 0.39)
				Env: 7.0% (70/1007)	Env: 4.6% (64/1397)	0.34 (0.08; 0.53)*
				Bird: 2.3% (15/653)	Bird: 3.4% (28/827)	−0.47 (−1.74; 0.21)
				wLPMs Total: 3.0% (7/230)	Total: 2.1% (10/484)	0.32 (−0.76; 0.74)
				Env: 3.4% (4/117)	Env: 2.4% (5/209)	0.30 (−1.56; 0.81)
				Bird: 2.7% (3/113)	Bird: 1.8% (5/275)	0.32 (−1.82; 0.83)
Lau et al. (2007)	H9N2	+Monthly rest day, depopulation, C/D	~Daily over a total time period of >6 years, during the time periods before or after the additive implementation of each intervention (chicken samples only) (virus isolation)	5.7% (360/6270)	5.8% (206/3542)	−0.01 (−0.20; 0.14)
		+Ban of live quail sales		5.8% (206/3542)	3.2% (152/4768)	0.45 (0.33; 0.55)*
		+Additional monthly rest day		3.2% (152/4768)	2.0% (261/13,035)	0.37 (0.24; 0.48)*
		All interventions (baseline: no intervention)		5.7% (360/6270)	2.0% (261/13,035)	0.65 (0.59; 0.70)*
Leung et al. (2012)	H9N2	+Monthly rest day, depopulation, C/D	~weekly or monthly over a period of ~11.5 years, during the time periods before or after the additive implementation of each intervention (chicken samples only) (virus isolation)	5.9% (345/5816)	5.7% (246/4334)	0.04 (−0.12; 0.18)
				5.7% (246/4334)	2.6% (110/4297)	0.55 (0.44; 0.64) *
		+Ban of live quail sales		2.6% (110/4297)	2.6% (633/24,286)	−0.02 (−0.24; 0.17)
		+Additional monthly rest day		2.6% (633/24,286)	0.2% (11/4826)	0.91 (0.84; 0.95) *
		+Ban on poultry overnight storage		5.9% (345/5816)	0.2% (11/4826)	0.96 (0.93; 0.98) *
		All interventions (baseline: no intervention)				

C/D = cleaning and disinfection; Env = environmental samples; rLPM = retail LPM; wLPM = wholesale LPM.
[a] P_{pre} = prevalence before the intervention.
[b] P_{post} = prevalence after the intervention.
* significant at the α = 0.05 level.

Table 3
Impact of LPM closure on the risk of H7N9-infection in humans.

Study	Intervention	Data source	Reported outcome	Location	Date of implementation	LPM closure effectiveness[a]
Chowell et al. (2013)	LPM closure and bird culling	Official notifications of laboratory-confirmed H7N9-cases reported to CDC through national surveillance system between March 1st and May 20th, 2013 (n = 73)	Observed daily H7N9-incidence rate after LPM closure compared to incidence rate estimated according to an exponential model fitted to the daily case time series prior to the intervention	Shanghai and Zhejiang provinces	April 6th and 16th, 2013, respectively	Not reported[b]
Yu et al. (2014)	Closure of 780 LPMs, depopulation and disinfection	Illness onset data of laboratory-confirmed and hospitalized H7N9-cases announced by China CDC until June 7th, 2013 (n = 60)	Reduction in mean daily number of infections associated with complete LPM closure (95% CrI)	Shanghai	April 6th, 2013	99% (93%–100%)
				Nanjing	April 8th, 2013	97% (81%–100%)
				Hangzhou	April 15th/24th, 2013	99% (92%–100%)
				Huzhou	April 11th–21st, 2013	97% (68%–100%)
Lau et al. (2014)	LPM closure	Officially announced laboratory-confirmed H7N9-cases from Chinese CDC and from three other line lists constructed with publicly available information, compiled based on reports of laboratory-confirmed H7N9-cases between April 10th and May 31st, 2013	LPM closure effectiveness calculated as 1 minus the ratio of H7N9-incidence after LPM closures versus incidence since first case (p-values from likelihood ratio tests)	Shanghai	April 6th, 2013	China CDC: 94% (<0.001) HealthMap: 93% (<0.001) Virginia Tech: 96% (<0.001) Flu Trackers: 94% (<0.001)
				Nanjing	April 8th, 2013	China CDC: 99% (0.007) HealthMap: 100% (0.034) Virginia Tech: 98% (0.010) Flu Trackers: 64% (0.328)
				Hangzhou	April 15th, 2013	*China CDC: 100% (<0.001)* *HealthMap: 99% (<0.001)* *Virginia Tech: 99% (<0.001)* *Flu Trackers: 100% (<0.001)*
Wu et al. (2014)	LPM closure for ≥7 consecutive days	Confirmed H7N9-cases between 14 days before LPM closure or onset date of first confirmed local case in 2014 (whichever later) and last day of LPM closure or March 7th, 2014 (whichever earlier); data source not reported (n = 69)	LPM closure effectiveness (95% CI), calculated as 1 minus IRR	Guangdong and Zhejiang provinces	Different closing dates in each market between January and early March 2014	97% (87%–100%)
Kucharski et al. (2015)	LPM closure	Symptom onset data; data source not reported	Reduction of market spillover hazard, i.e. the risk of animal-to-human infection (95% CrI)	Shanghai province		*First wave* (*2013*): 99% (95%–100%)
				Zhejiang province	January 22nd–26th, 2014	*First wave* (*2013*): 99% (97%–100%) *Second wave* (*2014*): 97% (92%–99%)
				Jiangsu province		*First wave (2013): 97% (80%–100%)*
				Guangdong province	Guangdong: Guangzhou: February 16th–28th 2014; other cities: 2 week closure in the same period	*Second wave* (*2014*): 73% (53%–89%)

LPM = live poultry market.
CDC = Center for disease control and prevention.
95% CrI = 95% Credibility interval.
95% CI = 95% Confidence interval.
[a] LPM closure effectiveness expressed as 1-IRR; IRR = ratio of H7N9-incidence rate after LPM closure/H7N9-incidence rate before LPM closure.
[b] Quantitative estimate not provided; authors reported a significant deceleration after LPM closure, outside of the confidence bounds predicted by the pre-intervention model.

According to studies collecting samples during the immediate time period before and after the intervention (Table 1), the immediate risk of AIV-detection was always significantly reduced after LPM closure and disinfection, with RRRs ranging between 0.79 and 0.98 (p-values < 0.0001) [19,23,27].

In contrast, long-term risk reduction following the implementation of a regular LPM rest day was less evident (Table 2) [20,21,26]. For instance, weekly rest days in Guangzhou's retail LPMs (rLPM) induced a significant risk reduction of AIV-detection from environmental specimens (RRR = 0.34; 95% CI = 0.08–0.53), but not from animal samples

[26]. Similarly, the introduction of a monthly rest day in Hong Kong's markets did not elicit a significant sustained risk reduction of H9N2-isolation between interventions [20] and the long-term impact of the bimonthly rest day (RRR = 0.37; 95% CI = 0.24–0.48) [20] was not entirely consistent across studies [21]. Over the years, only the overnight poultry storage ban elicited a sustained and highly significant risk reduction of H9N2-isolation (RRR = 0.96; 95% CI = 0.93–0.98) [21].

3.6. Impact of LPM closure on the risk of H7N9 infections in humans

Between April 2013 and early 2014, nine studies were conducted in mainland China to investigate a potential association of LPM closure with reduced H7N9-incidence in humans.

For instance, Chowell and colleagues developed a Bayesian exponential model with intrinsic growth rate fitted to daily case time series reported in the Shanghai and Zhejiang provinces prior to the intervention (Table 3) [28]. Compared to the expected number of H7N9-cases predicted by the statistical model, H7N9-incidence rates were significantly reduced in the post-intervention period [28].

In the same time frame, Yu and colleagues quantified the impact of closure and depopulation of 780 LPMs in four cities in Eastern China [29]. Their model was based on the assumption of constant but different pre- and post-intervention infection forces, which were estimated according to the illness onset time series of hospitalized H7N9-cases in each city. The model matched the observed incidence patterns with a posterior predictive value of 0.9 [29]. This analysis revealed a dramatic decline in H7N9-incidence in humans within 2–3 days from LPM closure, with very few case-onsets after the intervention (Table 3) [29]. This finding was consistent with a 97%–99% risk reduction of human infection following LPM-closure. A similar analysis using several different sources of epidemiologic data confirmed a >90% reduction in H7N9-incidence following LPM closure in three of the four cities (p-values < 0.05) (Table 3) [30]. According to a follow-up study, the effectiveness of LPM closure in the subsequent winter was 97% (95% CI = 89%–100%) [31].

Kucharski and colleagues inferred market spill-over hazard reduction following LPM closure during both H7N9-waves in different Chinese cities [32]. This study used H7N9-symptom-onset data to construct a statistical model of infections, which assumed that (i) the reported cases occurred following animal exposures and human-to-human transmission, (ii) the incubation period distribution of infections acquired from animal exposures had zero variability, and (iii) secondary cases arising from human-to-human transmission would have a serial interval of 7 days. In most instances, LPM closures significantly reduced spill-over hazard by >97% (95% CrIs: 80%–100%) (Table 3) [32].

Four more studies reported a qualitative impact of LPM closure on the reduction of H7N9-transmission to humans (Table 4) [18,33–35]. For instance, Murhekar and colleagues reported a decline in the number of human H7N9-cases in the Shanghai, Zhejiang and Jiangsu provinces after all rLPMs and sale spots were closed [33]. Similarly, two contemporaneous studies reported the decline in H7N9-incidence in Huzhou [34] and Shanghai [18]. Except for one isolated patient, no additional H7N9-case was detected in Huzhou following the sequential closure of 139 LPMs (p-value = 0.01) [34]. In Shanghai, the temporary closure and disinfection of 464 LPMs was combined with a poultry import ban [18]. According to He and colleagues, four H7N9-cases were reported during the first post-intervention incubation period, but no additional cases followed [18]. As soon as the ban was lifted in January 2014, 8 new cases were reported within a month. LPM-closure was re-implemented and H7N9-incidence declined again to zero [18].

Accordingly, the proportion of H7N9-positive cases among cases reported through the national Pneumonia of Unknown Etiology (PUE) Surveillance system from different provinces decreased from 21% one week before LPM closure to 4% or 2% during the first or second week post-intervention, respectively (p-value <0.001) [35].

4. Discussion

4.1. Impact of LPM interventions on AIV isolation rates

Kung and colleagues demonstrated the significant impact of a market rest day in reducing virus isolation rates in LPMs. This study clearly indicated that the viral load in the market is a result of virus amplification within the LPM, rather than a simple reflection of virus infection within incoming poultry [19]. The overall virus isolation rates drifted back to baseline prior to the next rest day, suggesting that the monthly intervention might reduce isolation rates only for a short period of time, as confirmed by later studies [20,21].

The two follow-up investigations from Hong Kong provide data on the long-term impact of LPM interventions, accounting for several confounding factors potentially influencing viral infection in poultry [20,21]. These two studies convincingly demonstrated that both frequent rest days [20,21] and a ban on holding live poultry overnight [21] were effective in reducing H9N2-transmission within the LPM. The overnight ban is particularly effective, because it limits the length of stay of the birds in the markets, removing susceptible or newly infected birds from the LPM before they become infectious themselves. This identifies the birds' length of stay and the AIV-incubation period between infection and onset of transmission as critical control points of AIV-circulation, as also postulated by mathematical models [36].

In concordance with the findings from Hong Kong, studies from mainland China [26,27] and the USA [23,24] confirmed LPMs as a favourable environment for AIV-circulation in poultry and validated market rest days [23,24,26] or prolonged LPM closure [27] as valuable interventions to reduce environment-to-human transmission. The long-term elimination of H7-strains from the American LBM-system demonstrates that eradication of AIVs from market environments is possible through regular interruptions of the constant bird flow and disinfection, although the role of additional measures, e.g. all-year-round vehicle washing, was also evident [23,24].

Despite the immediate risk reduction of AIV-isolation following LPM closure and depopulation, a long-term benefit was not always apparent. For instance, AIV-transmission within bird populations in Chinese markets was not particularly sensitive to regular LPM-depopulation in the long-run [26]. Accordingly, even though the monthly rest day in Hong Kong had an immediate impact on H9N2-circulation [19], it did not significantly reduce average isolation rates over longer time periods [20, 21]. Over the years, the live quail sale ban induced a comparatively much more dramatic risk reduction of AIV-isolation compared to one or even two monthly rest days, although the ban of keeping poultry overnight led to the most sustained impact [21]. The impact of the ban on the sale of live quails was context-dependent, as it was introduced based on previous research demonstrating that quails were the species with the highest virus shedding rates within Hong Kong LPMs at the time of the investigations.

It is important to note that the long-term effectiveness of such interventions is highly dependent of AIV-prevalence among incoming poultry. The studies in Hong Kong were of necessity carried out with subtype H9N2, which is more endemic in incoming poultry than, for example, the more clinically relevant H5N1. When virus prevalence is very high in incoming birds, viral amplification within the LPM would be a less significant factor in determining overall zoonotic exposure. In this case, even the ban on holding live poultry overnight might fail to substantially reduce human exposure (Fig. 2). In the case of AIV strains that have lower prevalence within incoming poultry, it is possible that even the monthly or bimonthly rest days would significantly reduce overall exposure of humans to the zoonotic viruses (Fig. 2).

In addition, the implementation of these interventions is crucial to their effectiveness [37]. For instance, the effectiveness of the overnight ban would be greatly compromised, if residual poultry was simply moved to an “off-site” holding facility and re-introduced

Table 4
Number of human H7N9-cases before and after LPM closure (qualitative studies).

Study	Intervention	Location	Date of implementation	Data collection period before and after the intervention	n_{pre}	n_{post}	Source of epidemiological data
Murhekar et al. (2013)	Closure of LPMs and sale spots; culling of all live birds in wLPMs; safe disposal of culled birds, excreta, feed and water; C/D of materials, transportation tools and market environment	Shanghai	On April 6th, 2013	*Before*: February 19th–April 6th *After*: April 7th–May 2nd	25	6 last case onset: April 13th, 2013;	Not reported
		Zhejiang province (including Hangzhou, Huzhou and Jiaxing)	Between April 11th and 19th, 2013	*Before*: March 7th–April 11th *After*: April 12th–May 2nd	24	22 last case onset (Zhejiang/Jiangsu): April 17th, 2013.	
		Jiangsu province (Nanjing, Suzhou, Wuxi and Zhenjiang)	Between April 8th and 10th , 2013	*Before*: March 8th–April 8th *After*: April 9th–May 1st	21	4	
Han et al. (2013)	Sequential closure of 139 LPMs	Huzhou	Between April 11th and April 21st, 2013	*Before*: March 5th–April 11th *After*: April 22st–May 13th	7 during closing period: 5	0 last case: May 15th	Laboratory-confirmed H7N9-cases according to the definition in the Chinese MoH guidelines
He et al. (2014)	Temporary closure of 464 LPMs, C/D, ban on poultry import	Shanghai	On April 6th, 2013	*Before*: February 12th–April 6th, 2013 *After*: April 7th–May 10th, 2013	29 *Control provinces*: 34	1st incubation period: 4 2nd incubation period: 0 *Control provinces:* 1st incubation period: 31 2nd incubation period: 13	Confirmed H7N9-cases; source not reported
	Second LPM closure		On January 31st, 2014	*Before*: early January–January 31st, 2014 *After*: February 1st–September 2014	8	0	
Xiang et al. (2013)	LPM closure	Shanghai	On April 6th, 2013	*Before*: 1–7 days before LPM closure *After*: 1–7 or 8–14 days after LPM closure	11 (14% of all PUE-cases)	*1–7 days after:* 4 (2% of all PUE-cases) *8–14 days after:* 1 (1% of all PUE-cases)	National PUE surveillance system
		Nanjing	On April 8th, 2013		5 (71% of all PUE-cases)	*1–7 days after:* 0 (0% of all PUE-cases) *8–14 days after:* 1 (100% of all PUE-cases)	
		Hangzhou	on April 15th, 2013		15 (25% of all PUE-cases)	*1–7 days after:* 4 (12% of all PUE-cases) *8–14 days after:* 0 (0% of all PUE-cases)	
		Provinces combined			31 (21% of all PUE-cases)	*1–7 days after:* 8 (4% of all PUE-cases) *8–14 days after:* 2 (2% of all PUE-cases)	

n_{pre} = number of H7N9-cases during the time period before the intervention.
n_{post} = number of H7N9-cases during the time period after the intervention.
LPM = live poultry market.
wLPM = wholesale live poultry market.
C/D = cleaning and disinfection.
MoH = Ministry of Health.
PUE = pneumonia of unknown etiology

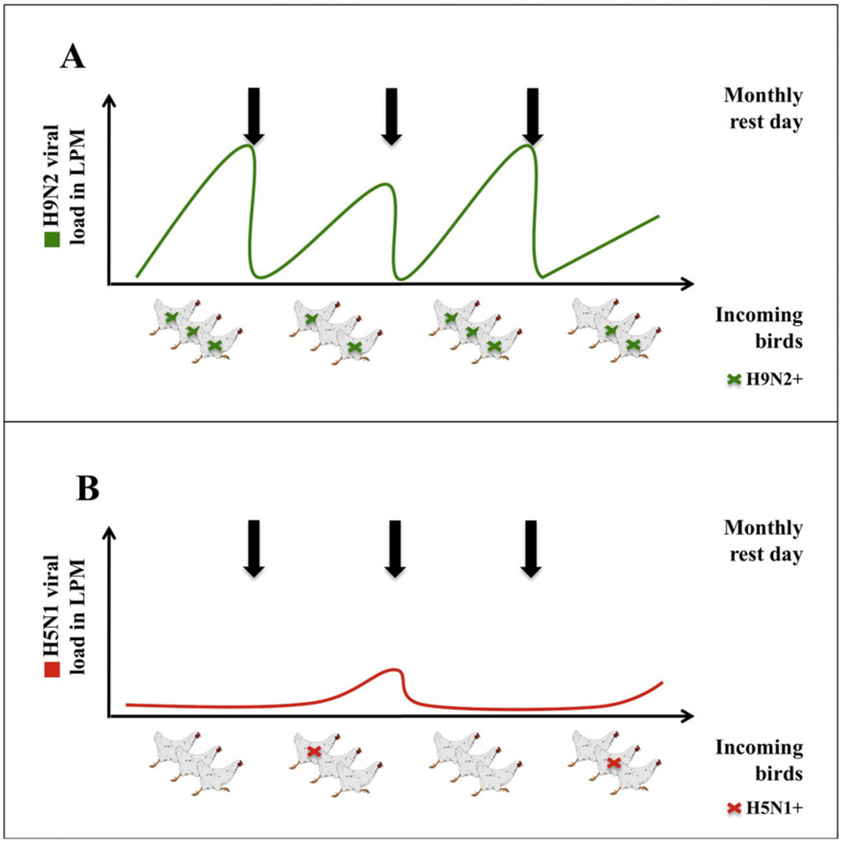

Fig. 2. Impact of incoming poultry prevalence on the effectiveness of rest days in LPMs. (A) Effectiveness of regular rest days in LPMs in reducing isolation rates of the H9N2 subtype. Because of the high endemicity of H9N2 in incoming poultry, viral amplification within the LPM is a less significant factor in determining overall zoonotic exposure. In this scenario, even frequent depopulation interventions might fail to substantially reduce human exposure. (B) Effectiveness of regular rest days in LPMs in reducing isolation rates of H5N1. If the AIV-prevalence among incoming birds is relatively low, regular rest days might substantially reduce the risk of human exposure to zoonotic infection.

into the market the next day. Considering the poor knowledge about AIVs [38] and low perceived self-infection risk [39] among LPM workers, it is not unreasonable to suspect that the motivation to adhere to a rigorous implementation of these interventions and to carry out effective disinfection of the premises may decline over time. To date, the relative contribution of the disinfection of the market to the observed impact of rest days or overnight bans is not elucidated. Emptying of the facilities may already be sufficient to reduce residual viral load through thermal inactivation of the virus infectivity. Additional studies using virus isolation (rather than RT-PCR,

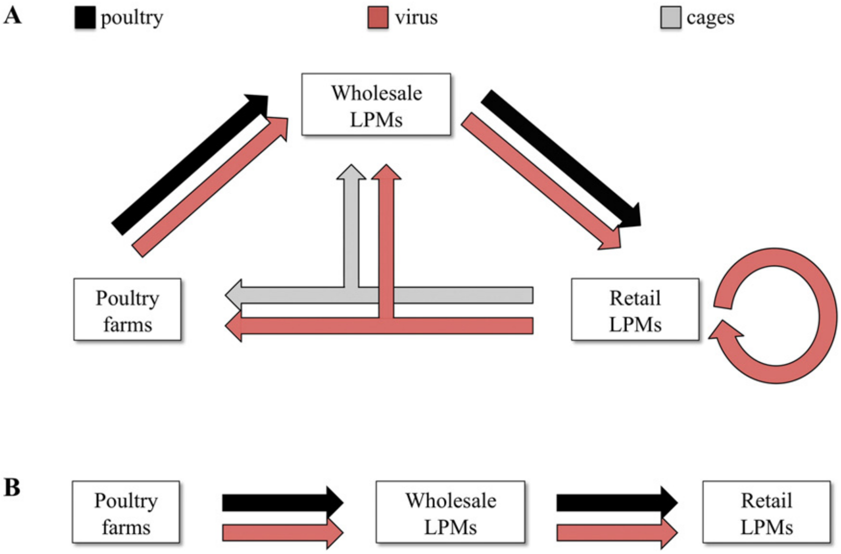

Fig. 3. One health approach to eliminate the risk of human and animal influenza (A) AIVs may be introduced into retail LPMs (rLPMs) through infected birds from farms or wholesale markets. The amplification of AIVs in rLPMs contributes to dissemination of viruses back to wholesale LPMs and poultry farms via contaminated cages and trucks. (B) Interventions reducing AIV circulation in LPMs may also reduce the spread of viruses to the upstream poultry production sector.

which does not discriminate between live and dead virus) are needed to address these questions.

Finally, it is relevant to note that the amplification of avian influenza in live poultry markets also contributes to dissemination of viruses back to poultry farms via contaminated cages and trucks (Fig. 3) [8,11]. Evidently, measures to reduce AIV amplification in LPMs may reduce the spread of avian influenza to both the upstream poultry production sector and to humans, thus truly exemplifying the implementation of the "one health" concept.

Although RRRs represent relatively comparable outcome measures of the intervention effects across publications, these values should be interpreted with care. Aside from the very different sampling schedules, with time windows ranging from <14 days [19,23,27] to year-long surveillance [20,21,26], the studies actually assessed very distinct scenarios: the duration and frequency of interventions ranged between one weekly rest day [26] and a one-time two-week LPM closure [27] in different LPM systems. In addition, sample sizes were very variable [21,26,27]. Importantly, samples were usually collected from different markets, distinct market areas and from several bird species, but pre- and post-intervention data was not unequivocally matched [19–21,23,26,27]. Moreover, some investigations assessed AIV-prevalence by virus isolation [19–21,23,27], while others used RT-PCR [26,27]. Positive RT-PCR results do not discriminate between viable infectious virus and inactivated virus and thus does not have the same biological implications as virus isolation does. Finally, some interventions had different impacts on AIV circulation in different bird species [20,21]. This suggests distinct AIV-transmission dynamics across species or varying market practises, highlighting the importance to investigate different species separately.

4.2. Studies with avian influenza infections in humans as outcome

The existing literature convincingly points at LPMs as the source of the majority of confirmed H7N9-cases in China [18,28–35,40]. A significant deceleration of H7N9-incidence following LPM closure was consistently detected in all investigations assessed in this review, confirming a significant association of LPM closure with a reduction in bird-to-human transmission.

In some instances, the prolonged emergence of cases in adjacent provinces, where LPM trade was not arrested, served as negative control [18,29]. Similarly, the fluctuations in H7N9-incidence rates closely following the time course of closing, re-opening and re-closing of the markets in Shanghai [18], supported the reliability of the causal inferences.

However, all included studies remain of ecologic nature and, although one investigation ascertained the geographical and temporal coincidence of the reported incidence drops with specific LPM closure dates [29], an estimation of area-specific effectiveness was often not possible. Thus, most of these studies are prone to confounding and bias, especially when no causal inferential framework was used [18,33–35]. For instance, the impact of contemporaneous interventions outside LPMs or behavioural changes was never incorporated. Although some studies accounted for climatic factors, e.g. humidity [29,31], it cannot be ruled out that unmeasured or unknown seasonal factors influencing influenza virus transmission in birds or humans [41–43] might have affected the incidence of H7N9.

Moreover, the source of human incidence data was not always reported [18,31–33], although estimates of LPM closure effectiveness might be strongly dependent on case reporting patterns. The findings are to be regarded as valid only if reporting through each specific data source had closely tracked the outbreak patterns [28].

5. Conclusions

The risk of zoonotic AIV-transmission from LPMs continues to pose an important threat to human health [44,45]. Besides the current efforts of pre-emptive vaccine manufacture [46] and systematic risk assessment [47], efficient pandemic preparedness requires interventions that prevent viral emergence at the source.

The proactive substitution of live poultry trade with a central slaughtering system would probably reduce the zoonotic risk to a minimum, although it should be noted that AIV-contamination of chicken carcasses may conceivably continue to pose a threat through freshly slaughtered, chilled poultry. Moreover, such a dramatic intervention would imply a major re-structuring of the current poultry industry in many parts of Asia [29,48], the annihilation of a long-standing culture of live bird trading and the potential amplification of illegal poultry trafficking [49]. It is also relevant to note that, while the majority of zoonotic H7N9-cases have a history of exposure to poultry or LPM, a minority of them do not [50–52].

Based on the evidence collected in this review, the interplay between the poultry's length of stay in the markets and the AIV-incubation period is a crucial control point to curb AIV-circulation in LPMs. In addition to accompanying precautions, e.g. vaccination of incoming poultry, the magnitude of the detected effects advocates for the prioritization of periodic rest days, overnight storage bans and the separation of poultry species as highly effective and applicable interventions worldwide.

Conflicts of interest

No conflicts of interest declared.

Acknowledgments

The project was funded in part by the Research Grants Council of the Hong Kong Special Administrative Region, China (Project No. T11-705/14 N) and the National Institutes of Health (NIAID contract HHSN272201400006C).

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.onehlt.2016.03.002.

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