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COST-EFFECTIVENESS ANALYSIS OF
H5N1 CLADE 1 PREPANDEMIC VACCINATION AMONG
COMMERCIAL BROILER OPERATION EMPLOYEES

BY

Sheila Bashirian
Degree to be awarded: M.P.H.
Career MPH

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An abstract of
A Thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements of the degree of
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Abstract

COST-EFFECTIVENESS ANALYSIS OF
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Objectives: Economic evaluation of a prepandemic H5N1 clade 1 vaccination policy among commercial broiler operation (CBO) employees

Methods: Cost-effectiveness analysis (CEA) of a decision tree model considering the societal perspective. Model inputs primarily were from published sources. The probabilistic model, adjusted for various case-fatality scenarios, was evaluated at varying levels of immunization coverage, vaccine efficacy and infection levels.

Results: The CE ratio (Cost per QALY) decreased as the immunization coverage of prepandemic H5N1 clade 1 increased among commercial broiler operation (CBO) employees. The 100% vaccination coverage dominated the alternative policies (0%, 25%, 50% and 75% vaccination coverage) at vaccine efficacy and infection levels in low (0.02%), moderate (1.08%) and high (59%) case-fatality scenarios.

Conclusion: Prepandemic H5N1 clade 1 vaccination is a viable option for CBO employees even when allowing for the lowest infection level and lowest vaccine efficacy in low, moderate and high case-fatality scenarios.

Keywords: cost-effectiveness analysis, H5N1, vaccines

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Introduction

H5N1 is an Influenza A subtype that causes a respiratory infection with a case fatality of 59% among humans (1-4). Commonly known as “avian flu” or bird flu”, H5N1 is a zoonotic infection with the majority of human cases having had exposure to infected poultry (1, 4). H5N1 persists among wild waterfowl who inhabit wetlands (5-6). H5N1 is transmitted from infected waterfowl via fecal-oral route to naïve domesticated poultry which in turn expose humans to H5N1 especially in the industrial mass food production setting of the commercial broiler operation (CBO) (6-8). CBO supply broilers, raised for chicken meat consumption, to meet demand by utilizing high density production (6, 9-10). Waterfowl habitat has undergone alteration and destruction because of human population growth, land use and climate change. As a result, wild waterfowl have moved closer to human settlements including domesticated poultry in CBO (5-8, 11-12). In addition, the biosolid waste distributed on the CBO property contains spilled feed and attracts displaced wild waterfowl (7-8). Since transmission among birds is fecal-oral, H5N1 is sustained in new broilers when biosolid waste of previously culled broilers remain in the CBO premises and attract wild waterfowl. The CBO with concentrated, confined naïve poultry in close proximity to biosolid waste has resulted in an environment conducive to H5N1 infection among poultry and poultry workers making CBO employees at high-risk for H5N1 exposure and infection. At present, human cases have been detected in 15 countries (3). In addition to the reporting of human cases to the WHO, H5N1 surveillance is ongoing in wild birds and domestic poultry both internationally and nationally (13-14). Cases have been detected among domestic poultry in 51 countries (15). In two countries, Egypt and Indonesia, H5N1 is endemic among domestic poultry (16). H5N1 pandemic preparation includes manufacturing of prepandemic vaccines that have either been approved for use, ordered in advance and/or stockpiled (2, 17-21).

The current United States policy towards H5N1 pandemic preparation is stockpiling clade 1 and 2 prepandemic vaccines at an amount needed to inoculate 20 million “front-line” people during a pandemic onset before the pandemic vaccine is produced and available to the general population (22). Among the United States stockpiled prepandemic vaccines, the clade 1 vaccine is solely manufactured by Sanofi Pasteur (22). Clade 2 vaccines consist of 2.1, 2.2 and 2.3 from Sanofi Pasteur, GlaxoSmithKline and Novartis (23). As of 2008, more than $1.1 billion has been spent on stockpiling prepandemic vaccines

(22-23). The annual cost of maintaining the stockpile is estimated between $300 million to $1.1 billion depending on when the vaccine expires and how much antigen is used per dose. Though the antigen amount per dose can vary, a vaccine typically expires after two years. In the absence of a H5N1 pandemic, vaccines expire and are disposed of (22). Currently, there is a gap in knowledge on the cost-effectiveness of various options on utilizing H5N1 prepandemic vaccines prior to expiration in non-H5N1 pandemic years.

Stockpiling may not be sustainable spending for "just in case" in times of national economic hardship particularly in the current budgetary environment. Utilization of stockpiled vaccines even in non-pandemic years can generate pre-existing immunity against H5N1 via vaccination. Utilizing H5N1 prepandemic vaccines within a month of expiration on immunizing high risk groups instead of "throwing away" vaccines on non-H5N1 pandemic years due to vaccine expiration, assuming cost of administering vaccine is comparable to the cost of disposing vaccine, could be a more cost-effective alternative. Due to financial scarcity stockpiling may not be a sustainable policy and due to vaccine scarcity vaccinating everyone is not a feasible or economic option however, as this study will address, vaccinating a high-risk group will increase pre-existing H5N1 antibodies and decrease the likelihood of establishing a H5N1 chain-of-transmission.

The study's objective was to conduct a cost-effectiveness analysis from the societal perspective regarding the marginal cost and benefit of vaccinating a high risk group of H5N1 to find the optimal rate of vaccination. Assuming there is a human case association with exposure to infected poultry, the first pandemic index case would more likely be due to exposure to infected poultry. A high-risk group for H5N1 exposure, if related to H5N1 infected poultry, would be people whose occupation involve poultry such as employees of commercial broiler operations (CBO) (Figure 1). Immunization of this high-risk group with stockpiled H5N1 prepandemic vaccines can reduce the likelihood of H5N1 transmission to general population because pre-existing H5N1 immunity can be generated via vaccination. Reduction in H5N1 transmission to the general population will be reflected in lower H5N1 cases and medical costs.

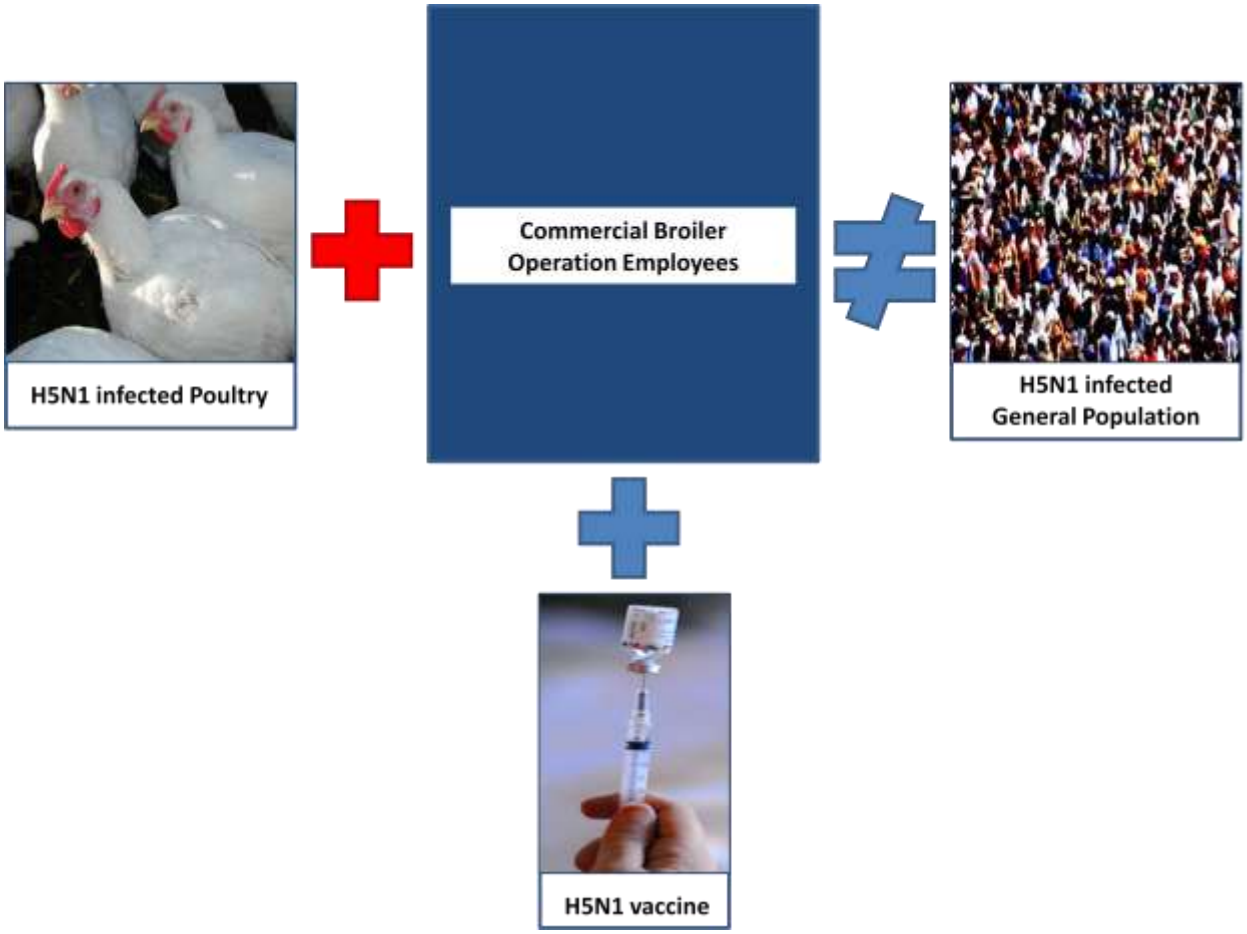

Figure 1. Conceptual Model

Methods

Decision tree models were constructed using TreeAge Pro 2011 (TreeAge Software, Inc). The decision tree models accessed varying vaccination coverage options (0%, 25%, 50%, 75%, 100%) to determine the cost-effectiveness of vaccinating commercial broiler operation employees (CBOE). The model outlines potential paths from infection to cost and outcome in a time frame of one year (Figure 2).

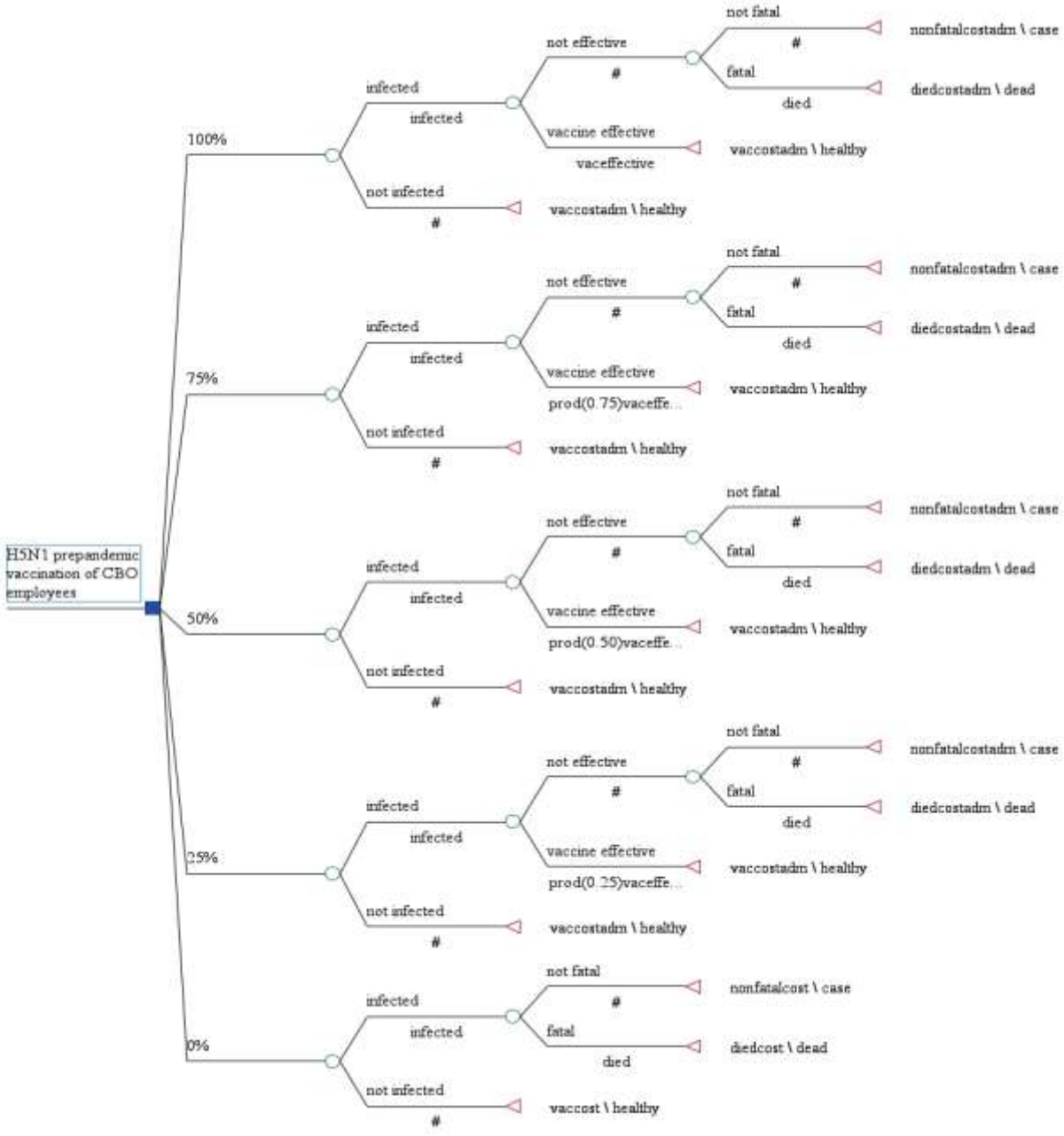

Figure 2. Structure of Decision Tree models

The protection for each vaccination coverage, number of people vaccinated, was reflected in the value of the vaccine effective branch. For example at the vaccine effective branch, 75% vaccination coverage is calculated as 75% of vaccinees mounting an adequate and protective immune response to the vaccine (44%, vaceffective variable value) and results in 33% protected among vaccinees. The outcomes are represented by the variables healthy, case and dead which are estimated to be valued at 1, 0.5 and 0 quality adjusted life years (QALYs). Most of the model variables included lower and upper bound values based on assumptions, calculated or estimated (Table 1, 2).

In addition to evaluating vaccination coverage options, the models accessed the potential paths from infection to outcome in the context of three scenarios: H5N1, 1918 H1N1 and 2009 H1N1 (Table I). The H5N1 model utilizes data from sporadic cases with high case fatality (59%) which is highly specific but has low sensitivity since the WHO surveillance case definition of the data only includes laboratory confirmed cases (3). On the other hand, the 1918 H1N1 model utilizes a combination of not specific but sensitive data generated by symptom-based mortality statistics and house-to-house surveys for a moderate case fatality pandemic (0.25%-2.33%) (31-33). The 2009 H1N1 model is derived from moderately specific and sensitive data that is a combination of laboratory confirmation, mortality statistics, hospital and community studies for a low case fatality pandemic (0.011%-0.066%) (34-35).

Table 1. Decision Tree Model Variables

Name	Description	Root	Low	High	Source
Variables Common to All Models					
infected	infection resulting from an exposure-related activity	0.50	0.10	0.90	(24)
vaceffective	antibody titer > 1:40 measured 28 days after second dose via HI assay	0.44	0.34	0.55	(17)
vaccost	cost of vaccine only + 2011 inflation adjustment	83.80	-	-	calculated (22, 25)
vaccostadm	[vaccine administration (20 min of nurse time for 2 doses) + cost-of-living adjustment estimation] + *vaccost*	94.92	-	-	calculated (22, 25-27)
diedcost	[treatment + 2011 inflation adjustment] + *vaccost*	16077.73	11678.5	16077.73	(22, 25, 28)
diedcostadm	[treatment + 2011 inflation adjustment] + *vaccostadm*	16088.85	11689.62	16088.85	(22, 25, 27-28)
nonfatalcost	[treatment + 2011 inflation adjustment] + *vaccost*	8657.17	331.84	11678.5	(22, 25, 28-29)
nonfatalcostadm	[treatment + 2011 inflation adjustment] + *vaccostadm*	8668.29	342.96	11689.62	(22, 25-29)
healthy	QALYs for being healthy	1.00	-	-	estimated
case	QALYs for having flu	0.50	-	-	estimated
dead	QALYs for fatal case	0.00	-	-	estimated
Variables Specific to a Model					
died	H5N1 model case fatality	0.59	0.34	0.82	(3-4)
died	1918 H1N1 model case fatality	0.0108	0.0025	0.0233	(30-33)
died	2009 H1N1 model case fatality	0.0002	0.00011	0.00066	(34-35)

QALYs, quality adjusted life years

Table 2. Decision Tree Model Variable Assumptions and Limitations

Variable	Assumptions	Limitations
vaccost	Each vaccine dose equivalent in cost	Total cost and number of doses in stockpile published but cost per dose not stratified by H5N1 clade (22)
vaccostadm	Administration time for two doses = 20 min If disposal off-site, transport from stockpile to administration site = transport from stockpile to disposal site Disposal cost from use = disposal cost when unused	If disposal on-site, possible additional costs such as vaccine transport from stockpile to administration site were not included. Disposal cost to vaccinate one person < full vaccine vial disposal thus model overestimating cost associated from vaccine use
infected	Backyard poultry farming is minimal Easier to regulate commercial broiler operations versus private backyard poultry farming	Generalizable to Georgia (24) Decreased generalizability in other settings
vaceffective	Vaccine study participants results applicable to CBO population (17)	Vaccine efficacy reduced when mismatched to circulating strain

Results

The 100% vaccination coverage dominated alternative vaccination coverage options (0%, 25%, 50% and 75%) in all three case-fatality (low, moderate and high) scenarios when vaccine efficacy and infection levels were varied (Figure 3, 4). The trend of lower cost per QALY as vaccination coverage increased, whether the case fatality was low (0.02%, 2009 H1N1 scenario), moderate (1.08%, 1918 H1N1 scenario) or high (59%, H5N1 scenario), was reflected with varying vaccine efficacy and infection levels (Figure 3, 4). The difference in case fatality among the scenarios, in both varying vaccine efficacy and infection level conditions, at the 100% vaccination coverage was reflected in a higher CE ratio for the high case fatality scenario of H5N1 model versus the 1918 H1N1 model and the 2009 H1N1 model (Figure 3, 4). The case fatality was 59-fold higher in the H5N1 scenario (59%) as compared to the 1918 H1N1 scenario (1.08%). The CE ratio was higher for the H5N1 versus the 1918 H1N1 scenario (Figure 3, 4). Though the case fatality was 54-fold higher in the 1918 H1N1 scenario (1.08%) as compared to the 2009 H1N1 scenario (0.02%), there was only a slight difference in the CE ratio (Figure 3,4).

The 100% vaccination coverage had the lowest CE ratio (cost per QALY) when compared to the other coverage alternatives (0%, 25%, 50% and 75%) when varying infection level from 10%, 50% and 90% (Figure 3). The CE ratio, at each infection level, increased with decreasing vaccination coverage (Figure 3). Likewise, the CE ratio increased with increasing infection level (Figure 3). For example, the CE ratio for vaccination coverage at an infection level of 90% was higher than the corresponding CE ratios associated with 50% or 10% infection levels (Figure 3). The CE ratio was higher in the H5N1 model for all values of infection levels (10%-90%) and vaccination coverage (0%-100%) when compared to the 1918 H1N1 and 2009 H1N1 models. The magnitude of incremental CE ratio savings between vaccination coverage increased as infection level increased (Table 3). For example, in the H5N1 model the incremental CE ratio saved as vaccination goes from 75% to 100% coverage is $158.41 (10% infection level), $1256.20 (50% infection level) and $4133.36 (90% infection level).

The 100% vaccination coverage had the lowest CE ratio (Cost per QALY) when compared to the other coverage alternatives (0%, 25%, 50% and 75%) when varying vaccine efficacy between the lower bound confidence level (34%) and the upper bound confidence level (55%) for the published vaccine efficacy (44%) for the Sanofi Pasteur H5N1 clade 1 prepandemic vaccine (Figure 4). The CE ratio, at

each vaccine efficacy, increased with decreasing vaccination coverage (Figure 4). The 0% vaccination coverage CE ratio did not change as the vaccine efficacy was varied (Figure 4). Otherwise the CE ratio, in vaccination coverage 25%-100%, decreased with increasing vaccine efficacy (Figure 4). For example, the CE ratio for a vaccination coverage using a vaccine with a 55% efficacy was lower than the corresponding CE ratios associated with 44% or 34% vaccine efficacy (Figure 4). The CE ratio was higher in the H5N1 model for all values of vaccine efficacy (34%-55%) and vaccination coverage (0%-100%) when compared to the 1918 H1N1 and 2009 H1N1 models. The magnitude of incremental CE ratio savings between vaccination coverage increased as the vaccine efficacy increased (Table 4). For example, in the H5N1 model the incremental CE ratio saved as vaccination goes from 75% to 100% coverage is $1066.34 (34% vaccine efficacy), $1256.20 (44% vaccine efficacy) and $1423.02 (55% vaccine efficacy).

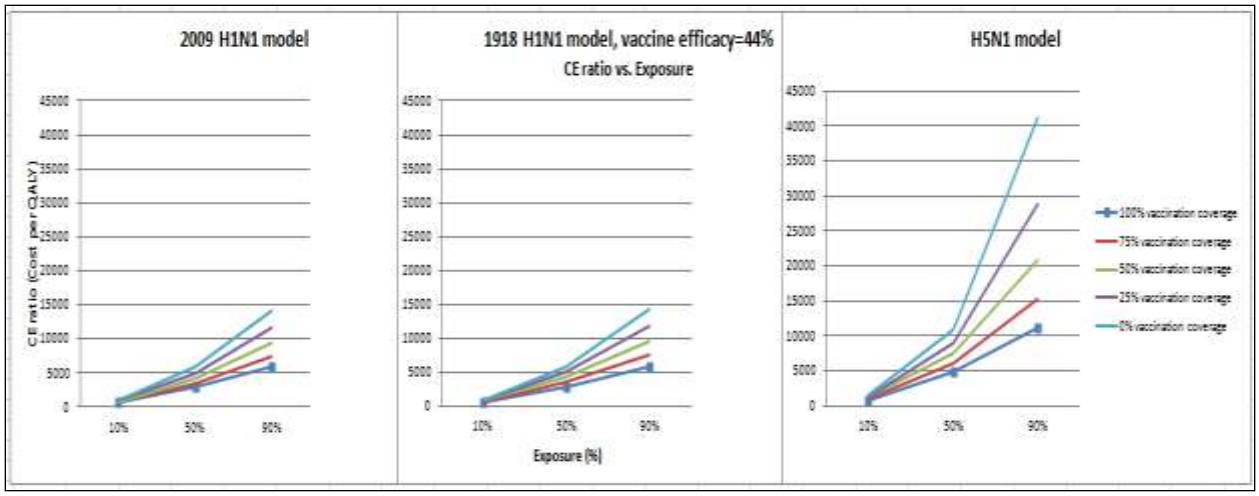

Figure 3. CE ratio with varying infection level (10%-90%) in vaccination coverage (0-100%) and case-fatality models (2009 H1N1 model- H5N1 model) assuming vaccine efficacy is at 44%

Table 3. Incremental CE ratio (Cost per QALY) for CE ratio vs. Infection with 100% vaccination coverage CE ratio as index

	2009 H1N1 Model Infection level			1918 H1N1 Model Infection level			H5N1 Model Infection level		
Coverage	**10%**	**50%**	**90%**	**10%**	**50%**	**90%**	**10%**	**50%**	**90%**
100%	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
75%	100.96	662.42	1634.02	101.96	671.09	1662.54	158.41	1256.20	4133.36
50%	203.08	1370.12	3517.38	205.09	1388.65	3582.94	319.78	2671.61	9739.03
25%	306.37	2127.89	5711.86	309.43	2157.68	5826.22	484.18	4278.57	17774.16
0%	399.15	2926.41	8281.26	403.28	2969.04	8460.89	639.62	6100.32	30215.92

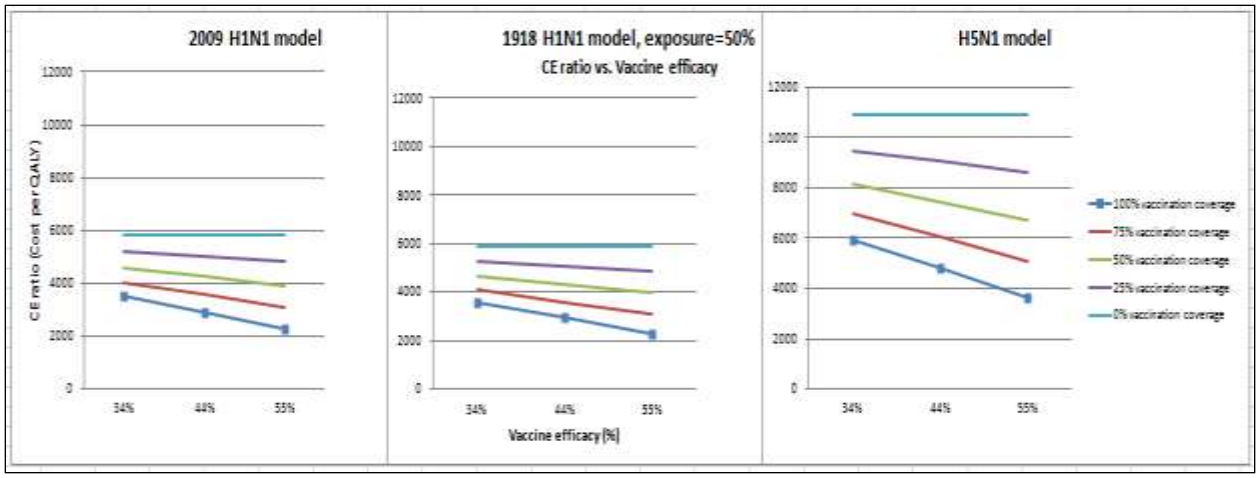

Figure 4. CE ratio with varying vaccine efficacy (34%-55%) in vaccination coverage (0-100%) and case-fatality models (2009 H1N1 model- H5N1 model) assuming infection level is at 50%

Table 4. Incremental CE ratio (Cost per QALY) for CE ratio vs. Vaccine efficacy with 100% vaccination coverage CE ratio as index

	2009 H1N1 model Vaccine efficacy			1918 H1N1 model Vaccine efficacy			H5N1 model Vaccine efficacy		
Coverage	**34%**	**44%**	**55%**	**34%**	**44%**	**55%**	**34%**	**44%**	**55%**
100%	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
75%	539.35	662.42	782.96	546.77	671.09	792.66	1066.34	1256.20	1423.02
50%	1107.64	1370.12	1631.69	1123.27	1388.65	1652.76	2240.21	2671.61	3064.58
25%	1707.24	2127.89	2554.82	1731.98	2157.68	2589.29	3538.75	4278.57	4979.20
0%	2326.01	2926.41	3547.77	2360.80	2969.04	3598.03	4964.47	6100.32	7222.73

Discussion

The 100% vaccination coverage dominated the alternative policies (0%, 25%, 50% and 75% vaccination coverage) when considering cost per QALY at varying vaccine efficacy and infection levels with low (0.02%), moderate (1.08%) and high (59%) case-fatality scenarios. Prepandemic H5N1 clade 1 vaccination is a viable option for CBO employees even when considering the lowest infection level (10%), vaccine efficacy (34%) and case-fatality scenario (0.02%). Being a high H5N1-risk group, CBO poultry employees have at least an estimated 20% infection level, which is an infection level twice more than the lowest infection level in the model (10%), if H5N1 is detected among the broiler flock (24). Additionally, H5 antibodies among poultry workers increase proportionally with poultry contact (7, 36). Currently, personal protective equipment and decontamination are not typical options for CBO poultry employees (7-8). An immunoprophylaxis, such as the currently thrown away prepandemic H5N1 vaccine, would provide protection due to an occupational risk arising from working in a CBO.

Every two years in the event of no H5N1 pandemic, stockpiled prepandemic H5N1 vaccines expire and are thrown away (22). The biggest expense has been paid since the prepandemic H5N1 vaccines have been purchased. This cost-effectiveness analysis model addresses the use of vaccines that would otherwise be thrown away. The additional cost factored in the model to use the vaccines is the cost for 20 minutes for a nurse to administer 2 doses of the vaccine (Table 1, 2). The model assumptions are that vaccine transport from stockpile facility to administration site is equivalent to the vaccine transport from the stockpile facility to a disposal site. Additionally, it is assumed that the disposal cost of used medical supplies and vaccine vials is equivalent to the disposal cost of unused vaccine. The total cost of administering the vaccine maybe less than the total cost of disposing unused vaccine since autoclaving of materials used to administer the vaccine to one person is less than autoclaving a full vial vaccine. Thus, the model maybe overestimating the cost associated with vaccine utilization.

The cost-effectiveness analysis has limitations. Other potential routes to H5N1-infected poultry exposure such as rural backyard poultry farming were not considered since it was determined to be of minimal impact in the potential spread of H5N1. Secondly, the analysis was done using a static model and did not incorporate the reproductive number which would address the potential number of community cases arising from the infection of one poultry employee (Figure 2). Lastly, vaccine efficacy decreases

when the vaccine does not match the circulating strain and thus a H5N1 clade 1 prepandemic vaccine will have a lower efficacy if the circulating strain is a H5N1 clade 2.

The cost associated as well as vaccine stockpile in this analysis is limited to the United States, but the analysis would be useful to the CBO located in H5N1-affected countries including the H5N1-endemic countries of Egypt and Indonesia. Though the biomedical literature has several publications on vaccination of poultry especially in Southeast Asia, similar to the United States, there is a lack in the biomedical literature of cost-effectiveness analysis on prepandemic vaccination among poultry workers especially in Egypt and Indonesia.

Conclusion

Prepandemic H5N1 clade 1 vaccination of CBO employees is a cost-effective option, optimally at 100% coverage but cost-savings result also from lower vaccination coverage, in preventing H5N1 chain-of-transmission establishment, H5N1-related infections and treatment costs especially associated with the worst high case-fatality scenario. Prepandemic vaccination remains cost-effective even at the lowest infection level and lowest vaccine efficacy during the best low case-fatality scenario. The biggest expense has been paid and prepandemic H5N1 vaccines have been purchased for stockpile. Administration on non-pandemic years is cost-effective because it salvages otherwise unused vaccines that expire and are thrown away. In this case, use is more cost-effective than disposal.

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Appendix A: Literature Review

Influenza A viruses

Influenzavirus A, B and C are genera within the Orthomyxoviridae family of negative-sense single-stranded RNA, (-)ssRNA, viruses (37). Influenzavirus C causes mild, asymptomatic cases. Influenzavirus B causes more severe cases than Influenzavirus C and typically occurs in children. Influenzavirus A with its one species, Influenza A virus, causes the most cases among humans and is responsible for influenza pandemics. Influenza A viruses are classified by hemagglutinin (HA) and neuraminidase (NA) with the general formula being HxNy (x represents the HA subtype and y represents the NA subtype) (38). There are known 16 HA (H1-H16) and 9 NA subtypes (N1-N9) (38).

While the genome of Influenzavirus C consists of 7 viral RNA segments, vRNA (missing NA), both Influenzavirus A and B consists of 8 vRNA segments. The 8 vRNA segments encode for 11 viral proteins: the polymerase proteins (PB2, PB1, PB1-F2, PA), surface proteins (HA, NA, M2), the matrix protein (M1), the nucleoprotein (NP) and the nuclear proteins (NS1, NS2) (39). Each vRNA segment binds to an NP scaffold with ends complexed to a set polymerase proteins (PB2, PB1, PA) to create the viral ribonucleoprotein (vRNP) (40-41).

The surface proteins that stud the viral phospholipid bilayer coat consist of two glycoproteins (HA, NA) and an ion channel protein (M2). HA predominates protein composition on the surface at ~80% followed by NA at ~17% and lastly M2 at ~3% (37). The HA impacts viral infectivity by interacting with sialic acid receptors of target epithelial cells that line the lumen of the upper and lower respiratory tract allowing for receptor mediated endocytosis and entry into the host cell within an endosome (37-38). Influenza viruses adapted to the human host have an HA that recognizes the sialic acid α(2,6) glycosidic linkage while influenza viruses adapted to either avian or swine hosts have an HA that recognizes the sialic acid α(2,3) glycosidic linkage (37). The M2 pumps in hydronium ions (H+) that acidifies the endosomal environment facilitating the HA-mediated viral and endosomal membrane fusion and release of vRNPs into the host cell cytosol. The NA, as a sialidase, impacts viral dispersion by interacting and cleaving sialic acids that bind the virus to the cell allowing for virions to be released from the host cell (37-38, 42). HA and NA elicit the host immune response via antibody production and thus impact the antigenicity of the virus.

Influenza A viruses cause influenza, a disease with such symptoms as a high fever, dry cough, headache, achy muscles and joints, fatigue, sore throat and runny nose (43). The seasonal epidemics result in 3 to 5 million cases and cause 250,000 to 500,000 deaths annually (43). In temperate regions, influenza epidemics occur annually during the colder seasons of autumn and winter (43). While in subtropical and tropical regions, influenza viruses are endemic but often peak during the rainy seasons (43). Seasonal epidemics reflect genomic drift of Influenza A viruses either due to the high error rate of viral replication or due to immune pressure from anti-HA and anti-NA antibodies (44).

Higher mortality among humans due to Influenza A pandemics occur with the appearance of new subtypes that displace a previously circulating subtype (39). New subtypes are thought to occur by reassortment and reintroduction (39). Four pandemic influenza viruses (1918 H1N1, 1957 H2N2, 1968 H3N2, 2009 H1N1) are believed to be composed of both human and either avian or swine derived segments (39, 44-45). One pandemic influenza virus (1977 H1N1 Russian influenza) is believed to have been reintroduced to humans from a frozen source possibly the subarctic water bodies (39, 46).

H5N1: an Influenza A Subtype

The first documented case, of H5N1 isolation in humans, occurred in a 3 year old from Hong Kong who died during hospitalization on May 21, 1997 (47). As a result of human fatalities in Hong Kong, the surveillance of the virus was initiated in 1997 (48). In a BALB/c mouse model, H5N1 viruses were classified as low pathogenic when the LD50 was greater than 106.5 and high pathogenic when the LD50 was greater than 103.0, meaning that a lower titer of a highly pathogenic virus is required to be lethal to 50% of the mice (49). These experimental designations do not consistently translate to disease in humans. For example, a virus classified as highly pathogenic in mice may cause mild disease in children, 4 years or older, while a virus classified as low pathogenic in mice may result in a fatality to a woman 34 years old (49). In addition to viral factors that determine H5N1 virulence, host factors such as age, co-morbidities may contribute to disease severity (49).

As of 2008, highly pathogenic avian influenza (HPAI) virus of H5N1 has appeared in more than 60 countries. In this short time, it has evolved extensively and its evolutionary tree is characterized by an extended trunk with short branches (48). The earliest H5N1 ancestral virus has the strain designation of A/goose/Guangdong/96 (Gs/GD) meaning the Influenza A virus was isolated in 1996 from a goose in

Guangdong, China (48). Most H5N1 genomes have undergone reassortment, replacing most of the gene segments, with lineages distinct from Gs/GD with exception to the hemagglutinin (HA) gene (48). To standardize the nomenclature system, clade classification is based on deviation in the HA gene and so far there are 10 first-order distinct clades (48). A clade is considered distinct by first-order, such as clades 0-9, when the average nucleotide distance (sequence deviation) is greater than 1.5% (48). There are also second-order clades (clades 2.1-2.5) and third-order clades (clades 2.1.1-2.1.3) where the average nucleotide distance is less than 1.5% (48). The first-order clades are related spatio-temporally, grouping by proximity in geography or time (48). An exception is clade 2.2 which has a wider geographic net extending 3 continents potentially as a consequence of viral movement with wild bird migration or poultry trade (48).

H5N1 and Commercial Broiler Operations (CBO)

H5N1, known as “avian or bird flu”, causes a respiratory infection among humans with a case fatality of 59%, unlike wild waterfowl and poultry where it causes a predominately intestinal infection (50-53). It is a zoonotic infection with the majority of human cases having had exposure to H5N1-infected poultry (50, 53). High risk groups for H5N1 infection include poultry workers, live bird market sellers and buyers, farmers, bird hunters and their families (7-8, 50, 53-54). Human cases have been detected in 15 countries as well as among domestic poultry in 51 countries including two countries, Egypt and Indonesia, where H5N1 is endemic (52, 55-56).

H5N1 persists among wild waterfowl who inhabit wetlands (5-6). Avian influenza viruses (AIV) such as H5N1 is transmitted from infected waterfowl via fecal-oral route to naïve domesticated poultry which in turn expose humans to H5N1 in the industrial mass food production setting of the commercial broiler operation (CBO) (6-8). Waterfowl habitat has undergone alteration and destruction because of human population growth, land use and climate change. As a result, wild waterfowl have moved closer to human settlements including domesticated poultry in CBO (5-8, 11-12). CBO supply broilers,raised for chicken meat consumption, to meet demand by utilizing high density production (6, 9-10). For example in 2006, the average American consumed 86 pounds of chicken which is triple the amount consumed in 1960 (10). High density production translates to each chicken house containing >100,000 broilers and each CBO containing between 1 to 18 houses (10). Additionally, CBO along with biosolid waste are

concentrated geographically (7, 57-58). In the United States, CBO are concentrated in the southeast (10, 57). For 2006, CBO in 17 states produced 95% of total production with 8.44 billion broilers (10). In parallel, CBOs are concentrated in Asia as in the case of China where CBOs are mostly found in the central and northeast regions (7, 58). Used poultry litter is the biosolid waste from CBO that consists of manure mixed with spilled feed and bedding material (wood shaving, sawdust or straw) (7-8, 10). The global 2003 estimate for used poultry litter was 140 million metric tons (7). In 2006, an estimated 40% of litter were applied to CBO fields (10). The spilled feed containing biosolid waste attracts displaced wild waterfowl which in turn expose naïve poultry to H5N1 (7-8). Since transmission among birds is fecal-oral, H5N1 is sustained in new broilers when biosolid waste of previously culled broilers remain in the CBO premises. In addition, poultry workers are not provided with protective clothing or decontamination options and instead most take work clothes home for washing (7-8). The CBO with concentrated, confined naïve poultry in close proximity to biosolid waste has resulted in an environment conducive to H5N1 infection among poultry and poultry workers.

H5N1 Policies

USA and global H5N1 policies have four categories: bioexclusion, biocontainment, trade restriction and pandemic preparation (59-60). Bioexclusion and biosecurity policies focus on poultry H5N1 infection prevention for example by vaccination (59). Biocontainment policies focus on controlling localized spread once H5N1 has caused infections among a poultry flock such as the “stamping out” strategy that involves culling suspect poultry and birds (59). The United States has trade restrictions on poultry and bird-product imports from H5N1-affected countries (60). United States H5N1 pandemic preparation include stockpiling antivirals and H5N1 prepandemic vaccines at an amount needed to inoculate 20 million “front-line” people at the onset before the pandemic vaccine is produced and available to the general population (17-18, 51, 61-64). Voluntary interventions during international travel include being aware of H5N1-affected countries and when traveling to a H5N1-affected country avoiding contact with birds and poultry, eating properly handled and cooked poultry, washing hands frequently with soap and water, declaring poultry-related items at customs, self-monitoring for flu-like symptoms and seeking medical attention if needed (65-66). Short-term solutions are the enforcement of current H5N1 policies from bioexclusion to pandemic preparation. Mid-term solutions should include personal

protective equipment and vaccination of CBO poultry workers to reduce H5N1 exposure. Long-term solutions are controlling CBO poultry density, geographic CBO density and biosolid waste disposal regulation.

H5N1 Vaccines

Influenza A interventions include both pharmaceutical and non-pharmaceuticals. Pharmaceutical interventions include antivirals and vaccines while non-pharmaceuticals interventions include hand-washing, school closures and restricting international air travel. Antiviral drugs typically are utilized in the treatment of influenza and fall into two classes: virus-uncoating and viral neuraminidase inhibitors (43, 67). Virus-uncoating inhibitors such as amantadine and rimantadine target the ion channel protein (M2) (67). Viral neuraminidase inhibitors include zanamivir and oseltamivir (67).

Vaccines are utilized in the prevention of influenza. Annually, there is vaccine strain selection for the southern and northern hemispheres to determine the three most representative influenza strains that will compose the seasonal vaccine (43). During most of the year with exception to approximately 3 months, seasonal vaccines are being manufactured (22). In the event of a pandemic, there is a shock to the supply which is reflected in the lag and shortage of needed vaccines (22, 68). United States governmental involvement to increase and stabilize vaccine supply include both supply-side and demand-side policies (69). In order to prepare for a potential H5N1 pandemic, the USA government has implemented a demand-side policy of stockpiling prepandemic H5N1 vaccines and a supply-side policy of mandating stockpiled vaccines to be manufactured domestically in order to expand vaccine manufacturing operations in the United States (69). At least $300 million has been spent annually on stockpiling H5N1 prepandemic vaccines since 2004. As of 2008, more than $1.1 billion has been spent on stockpiling prepandemic vaccines (22-23). The annual cost of maintaining the stockpile is estimated between $300 million to $1.1 billion depending on vaccine expiration and amount of antigen used per dose. The current policy is to dispose of unused and expired vaccines. A vaccine typically expires after two years. In the absence of a H5N1 pandemic, vaccines expire and are disposed of (22).

Abbreviations:
PB2: polymerase basic protein 2, PB1: polymerase basic protein 1, PB1-F2: polymerase basic protein 1 - F2, PA: polymerase acidic protein, HA: hemagglutinin, NA: neuraminindase, M2: matrix 2/ ion channel protein, M1: matrix protein, NP: nucleoprotein, NS1: non-structural protein 1, NS2: non-structural protein 2/ nuclear export protein