A Quantitative Risk Assessment to Evaluate the Efficacy of Mitigation Strategies to Reduce Highly Pathogenic Avian Influenza (HPAI) Virus, Subtype H5N1 (HPAI H5N1) in the Menoufia Governorate, Egypt

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Abstract

Background

The poultry industry in Egypt has been suffering from endemic highly pathogenic avian influenza (HPAI) virus, subtype H5N1 since 2006. However, the emergence of H9N2, H5N8, and H5N2 in 2011, 2016, and 2019 respectively, has aggravated the situation. Our objective was to evaluate how effective are the mitigation strategies by a Quantitative Risk Assessment (QRA) model utilizing daily outbreak data of HPAI-H5N1 stratified by different epidemic waves from 2006 to 2016 are in Egypt.

Results

Utilizing the epidemiologic problem-oriented approach methodology, a conceptual scenario tree was drawn based on the knowledgebase. Monte Carlo simulations of QRA parameters were ran utilizing @Risk software. In poultry farms, the likelihood of poultry still having a high Prevalence Rate (PR) after failure of mitigation strategies such as vaccination, passive, and active surveillance, in 90% of the time, these mitigations will fail 48% of the time. Failure of efficacy of these mitigations will raise PR to 70% with missed vaccination, while failure in detection by surveillance will raise it to 99%. In backyard poultry, the likelihood of still having a high HPAI-H5N1 PR in three different poultry types due to failure of passive and active surveillance varies between domestic, mixed and reservoir. In mixed poultry, the probability of HPAI-H5N1 not detected by surveillance was higher with a mean and a SD of 16.8×10^{-3} and 3.26×10^{-01} respectively. The sensitivity analysis ranking for the likelihood of HPAI-H5N1 in poultry farms due to missed vaccination, failure to be detected by passive and active surveillance was examined. In poultry farms, increasing vaccination by 1 SD will decrease the PR by 14%, in active surveillance by 12% and in passive surveillance by 6%, respectively. while in backyard, the active surveillance had high impact in decreasing the PR by 16% in domestic poultry. Whereas the passive surveillance had less impact in decreasing PR by 14% in mixed poultry and 3% in domestic poultry.

Conclusion

It could be concluded that the applied strategies were not efficient in controlling the spread of the HPAI-H5N1 virus. Public health officials should take into consideration the evaluation of their control strategies in their response.

Introduction

The poultry industry in Egypt has been experiencing endemic highly pathogenic avian influenza (HPAI) virus, subtype H5N1 (HPAI-H5N1) since 2006 [1]. The situation has been aggravated by the emergence of H9N2, H5N8, and H5N2 in 2011, 2016, and 2019 respectively [2-4]. With continuous circulation and long term endemicity for more than a decade, H5N1 viruses have predictably undergone substantial genetic evolution [5], which resulted in increased binding ability of the virus to the human receptor [6, 7]. This resulted in Egypt reporting the highest number of human cases per country worldwide [5, 8, 9]. Along with the changed HPAI-H5N1 virus pathogenicity pattern in poultry, mortality increased (up to 100%) in poultry flocks in the first wave of 2006 then dropped to 20%–60% in 2008–2017 in the other five waves [5, 10].

Egyptian authorities constantly endeavor to mitigate the distress, the early control strategies after the HPAI-H5N1 virus introduction include; increasing awareness; stamping out infected birds (within 3 km of the initial outbreak); surveillance; quarantine by restriction of movement within a 7 km radius from the outbreak location; and emergency vaccination of parent flocks [1, 10]. Not all these, however, limited the spread of infection. Therefore, the decision was made to increase vaccination to cover all commercial flocks and backyard poultry [1]. From then on control strategy changed to mainly mass vaccination, surveillance, and preemptive culling of infected birds to combat the disease [11]. Despite these control efforts by the government, HPAI-H5N1 became endemic by 2008 with continuous and extensive circulation revealed by regular nationwide active, passive, and targeted surveillance [11-17].

Vaccination has become the main tool used to control the HPAI-H5N1 virus in Egypt, as other aspects of the control strategies became neglected. [18]. Using vaccination became a routine, Egypt was considered as the second country after China which accounted for over 99% of vaccination usage [19]. It is noticeable that mass vaccinations are implemented without extensive outbreak management, bio-security measures, and adequate coverage [20-22]. As a consequence, the efficiency of vaccination was reduced over time with vaccine failures that have occurred following the emergence of antigenic drift variants [23]. Therefore, inadequate vaccination policies could drive antigenic drift rather than control [5].

Egypt has become an epicenter for A(H5) virus evolution, outbreaks in poultry continued to occur with genetic drift in the hemagglutinin (HA) gene was observed each year [5, 9]. What constituted a challenge to effectively control virus spread and infection, besides poultry industry infrastructure itself is a great obstacle for control of the disease [23]. Before deciding on the continued use of one tool for controlling HPAI, the outcome must be compared with other available control measures, to best use the existing control resources [5, 18]. It is an urgent requirement for decision-makers to resolute a more concerted, controlled, and regulated strategy than what has been done to date. To the authors' knowledge, this is the first study to evaluate the mitigation strategies in Egypt using a Quantitative Risk Assessment (QRA) model utilizing daily outbreak data of HPAI-H5N1 stratified by different Epidemic waves from 2006 to 2016. This work presents a pilot study in Menoufia governorate, Egypt.

Materials And Methods

-The Epidemiologic Problem-Oriented Approach (EPOA):

Is a methodology that facilitates the development of systematic and structured knowledge bases in epidemiologic modeling was used to gather the fundamental information and data that are used in the variable and parameter estimations and analysis (biological, mathematical, statistical, and computer simulations) used for risk assessments and modeling. The methodology is very useful and essential in the collection and analysis of epidemiological information and data. The EPOA comprises two basic steps: problem identification and problem solving. Using the EPOA, a knowledgebase was developed after reviewing several different published literature, and the data was collected from different sources [24-26].

The QRA methods are extensions of standard statistical and epidemiological methods [27], which are expressed numerically and enable one to evaluate the likelihood and consequences of an adverse event occurring [28]. In a QRA, each parameter requires to be described and scientific evidence presented for the justification of the parameter estimates. A QRA was developed to examine the likelihood of poultry infected with the HPAI-H5N1 virus due to failure of mitigation strategies of vaccination, passive and active surveillance. This had been applied and stratified by six epidemic waves (**EW1-EW6**) from 2006 to 2016, in the Menoufia Governorate, Egypt. This QRA model relied on outbreaks daily data collected by national authorities stratified by six epidemic waves that occurred in this period. The quantified parameter input values were presented in terms of probability distributions: total number of poultry affected; non-infected poultry; and prevalence rates.

The risk pathway (Scenario Tree) presented in **Figure 1**, consists of a sequence of specific events and for each node or event a specific question related to the risk of transmission of HPAI-H5N1 is asked. Values for each parameter using the collected data for each node are tabulated. Using the appropriate @Risk function and simulation, a probability distribution is determined for that specific parameter. The product of these probability distributions of the answers to these questions will determine the final risk related to the likelihood of transmission of HPAI-H5N1 virus due to missed vaccination, failure to detect sickly poultry by passive or active surveillance. The variables are organized into five major parameter estimations or categories (**Figure 2**). These are the input parameters. Monte Carlo simulations with iterations set at 10,000 iterations for the QRA input parameters of HPAI-H5N1 infection transmission due to missed vaccination, failure to detect sickly poultry by passive or active surveillance were executed utilizing @Risk software version 5.7 (Palisade Corporation). Sensitivity analysis was used to show the aggregate effect of what each input variable has on the likelihood of missed vaccination, failure to detect sickly poultry by passive or active surveillance frequencies in HPAI-H5N1 infection transmission. At each of the nodes, probability distributions were assigned and @ Risk Bestfit distributions together with Monte Carlo simulation were used in determining the efficacy of vaccination, failure to detect sickly poultry by passive or active surveillance in reducing HPAI-H5N1 infection transmission in the poultry farms and the backyard poultry. To see the effect of various inputs on the output, a sensitivity analysis was performed using regression and correlation coefficients of tornado graphs.

-Assumptions

The following assumptions were taken into consideration while developing this QRA about the decision of determining the number of infected poultry with HPAI-H5N1 virus after mitigation strategies of vaccination and surveillance had been applied for six epidemic waves (EW(Ew1-EW6)) from 2006 to 2016, in the Menoufia Province, Egypt

1. In this study, the model is built on the poultry farms and the backyard poultry considering the two main divisions of the poultry industry in Egypt [11]. Most of the production takes place in sector 3 (small commercial farms) and sector 4 (village or backyard poultry) in Egypt according to the Food and Agriculture Organization (FAO) classification [5, 19].
2. According to [29] who defined an outbreak as 'the confirmed presence of disease, clinically expressed or not, in at least one bird in a defined location and during a specified period of time'. All poultry population in a given single village in Menoufia governorate, Egypt, was considered infected with HPAI-H5N1 virus even if there was only one reported outbreak within a certain circumscribed location in this village at a certain point in time.
3. A village is the smallest epidemiologic unit in Menoufia governorate, and it contains 62,316 poultry based on the total poultry population, from which the total number of cases is calculated for each outbreak event.
4. The total poultry population of each epidemic wave (EW) was calculated relative to the period in which the EW lasted, and it was from this that the prevalence rate was calculated per 100,000 poultry population.
5. Any poultry species raised in the backyard other than domestic ones are reservoir poultry, while domestic ones raised with any other species are considered mixed poultry.
6. Only domestic poultry raised in farms such as chickens is the most common type raised in the commercial sector [23]. All outbreaks data of farms were obtained after vaccination. This was because the commercial poultry producers apply their mass vaccination program, which is usually of highly variable standards (different vaccines, frequency, dose, route, age, etc.) and not monitored by the Egyptian general organization of veterinary services [1, 12].
7. In Egypt, vaccine failures have occurred following antigenic drift in field viruses [22]. The immune pressure exerted by the vaccines or natural infection accelerates virus evolution in poultry, reducing the efficacy of vaccination over time [23, 30-35]. Besides, improper administration, mishandling [36] and inappropriate storage of the vaccine [12] or suppression of the immune system (i.e.: due to chicken anemia virus infection or ingestion of mycotoxins) [37]. All these factors could be considered as missed vaccinated poultry.

8. There was no vaccination in the backyard poultry. Since there is no data indicating vaccination of those cases, (D Swayne, G Pavade, K Hamilton, B Vallat and K Miyagishima [19] highlighted that vaccination coverage of household poultry is lower than 20%. Therefore, vaccination of the backyard poultry is no longer provided nor supervised by the government. A previous study showed that village cumulative annual flock immunity (CAFI) from household vaccination by the Egyptian government is unlikely to be maintained at the levels required to significantly reduce the virus load and restrict transmission [18].
9. Notification and surveillance of poultry infected with the HPAI-H5N1 virus reported by owners were considered as passive surveillance. While targeted surveillance or preslaughter or live bird market (LBM) surveillance samples were considered as active surveillance. All surveillance data were considered under active and passive surveillance terms as stated by [13, 15].

-Evidence Gathering

The evidence underlying this QRA comes from published data, studies, routine reports, and other technical documents from public health organizations and agencies including the Food and Agriculture Organization of the United Nations (FAO), World Health Organization (WHO), and Centers for Disease Control and Prevention (CDC). This evidence was collected and documented for each node of the scenario tree. Appropriate probability distributions were assigned to the various nodes. These probability distributions capture the variability and uncertainties associated with each event occurring on the scenario tree. Appropriate probability distributions were also used to represent the prevalence rates of HPAI-H5N1 outbreak.

-Study area

Egypt is in the northeast corner of Africa, spanning approximately 1 million square kilometers. As per United Nations estimates, the human population of Egypt is 100 million, with most of them living in the Nile Delta [5], where there were recorded higher disease incidences as a reflection of high densities of poultry and human activities [38, 39]. This pilot study was carried out using the extent of one of the Nile Delta governorates (Menoufia, Egypt), where the highest number of outbreaks were recorded [5, 38]. In addition to that, Menoufia is considered the leading poultry producing governorate in Egypt [40], district level is the smallest administrative unit used for defining surveillance and control strategies related to HPAI (H5N1) among poultry [41].

-Data source

Domestic poultry HPAI-H5N1 outbreak data used in this study were extracted from the Egyptian ministry of agriculture (Egyptian Committee for Veterinary Services) official reports for national surveillance for the study period from January 2006 to December 2016.

-Parameter estimations:

Initiating event: IE Decision to determine the number of poultry infected with Highly Pathogenic Avian Influenza A subtype H5N1 (HPAIH5N1) virus after mitigation strategies of vaccination, passive and active surveillance has been applied after six epidemic waves ***EW (EW1-EW6)*** from 2006 to 2016, in the Menoufia, governorate, Egypt.

N - The total number of poultry in Menoufia, Province Egypt.

Description: The data that was collected is historical and not well organized to facilitate capture of the variability and uncertainty of the total number of poultry in six epidemic waves ***EW (EW1-EW6)*** whereby the available data were given in intervals. In a QRA using Monte Carlo simulation, uncertain inputs in a model are captured by using ranges of possible values known as probability distributions. Using probability distributions, input variables can be expressed as probability distributions for the different outcomes occurring. Probability distributions are a much more realistic way of describing uncertainty in variables of a risk analysis [42].

Probability distribution: The probability distributions of individual input variables at each node were determined by using the @Risk Bestfit distributions (See Table 1 and 2 for details). @Risk Bestfit distribution was used to pick the best distribution of the data whereby the variability and uncertainty of prevalence rate of HPAI-H5N1 virus infection would be best captured.

Node 1- P1: Prevalence rate (PR) of HPAI-H5N1 infection in poultry in each EW (EW1- EW6)

Prevalence Rate: As described previously in parameter ***N***, the data in nodes ***1-5*** is also historical and not well organized, to capture the variability and uncertainty of ***PR*** of influenza A subtype HPAI-H5N1 virus outbreak in birds in each epidemic wave ***EW (EW1- EW6)*** where the available data were given in intervals. @Risk Bestfit distributions were used to generate probability distributions. This specific variable is the prevalence rate (***PR***) of HPAI-H5N1 infection in poultry expressed as the probability distribution in each epidemic wave ***EW (EW1- EW6)*** stratified by ***P, C, and TP*** respectively (See Table 1 and 2 for details). Thus, both the numerator and denominator in ***PR*** were estimated using Monte Carlo simulations with @Risk software. The probability distribution values for this variable were determined by @RiskBestfit as described previously in parameter ***N***. The general mathematical formula used for calculating the ***PR*** of HPAI-H5N1 infection in poultry in each epidemic wave ***EW (EW1- EW6)*** were calculated using available data on disease cases from 2006 to 2016 in the Menoufia province, Egypt is as follows:

$$PR_{(EW(1-6))} = P_{(EW(1-6))} = \frac{C_{(EW(1-6))}}{TP_{(EW(1-6))}} \quad (1)$$

Whereby P is the probability distribution, C is outbreak cases of HPAI-H5N1 infection and TP is total poultry population, respectively.

Node 2-P2: Prevalence rate (PR) of HPAI-H5N1 infected poultry in each type of breeding (B 1-2) in each EW (EW (EW1-EW6))

This specific variable represents the prevalence rate (PR) of HPAI-H5N1 infection in the backyard poultry in each epidemic wave EW (EW ($EW1-EW6$)), stratified by type of breeding (B 1-2) and P , C , TP respectively. The variable input values for this parameter $P2$ are calculated by dividing the number of cases of HPAI-H5N1 by the total populations in different breeding categories. The probability distribution values for this variable were determined by @RiskBestfit as described previously in parameter N (See Table 1 and 2 for details). The general mathematical formula is as follows:

$$PR_{(B(1-2) EW(1-6))} = P_{(B(1-2) (EW(1-6)))} = \frac{C_{(B(1-2) EW(1-6))}}{TP_{(B(1-2) EW(1-6))}} \quad (2)$$

Whereby $B1$ is the poultry farms and $B2$ is the backyard poultry, respectively.

Node 3-P3: Prevalence rate (PR) of HPAI-H5N1 infected poultry in each type of breeding (B 1-2) different poultry types (T 1-3) in each EW (EW (EW1-EW6))

This specific variable represents the prevalence rates (PR) of HPAI-H5N1 infection in poultry in each epidemic wave (EW) stratified by type of breeding (B 1-2) and different poultry types (T 1-3) and P , C , TP . The variable input values for this parameter $P3$ are calculated by dividing the number of cases of HPAI-H5N1 by the total populations in different breeding categories and different poultry types to be expressed as probability distributions. The probability distribution values for this variable were determined by @RiskBestfit as described previously in parameter N (See Table 1 and 2 for details). The general mathematical formula is as follows:

$$PR_{(T(1-3) B(1-2) EW(1-6))} = P_{(T(1-3) B(1-2) (EW(1-6)))} = \frac{C_{(T(1-3) B(1-2) EW(1-6))}}{TP_{(T(1-3) B(1-2) EW(1-6))}} \quad (3)$$

Whereby $T1$ is domestic poultry, $T2$ is mixed poultry and $T3$ reservoir poultry, respectively.

Node 4-P4: Are there poultry still infected with HPAI-H5N1 due to failure in vaccination (V) and passive and active surveillance (S 1-2) in the farms in domestic poultry (T 1) in each EW (EW (EW1-EW6))?

This specific variable represents the prevalence rate (PR) of HPAI-H5N1 infection in vaccinated (V) poultry after passive and active surveillance (S 1-2) used in each epidemic wave EW (EW ($EW1-EW6$)) stratified by type of breeding (B 1) and P , C , TP . The variable input values for this parameter $P4$ are calculated by dividing the number of cases of HPAI-H5N1 by the total populations in the poultry farms, vaccination and surveillance types. The probability distribution values for this variable were determined by @RiskBestfit as described previously in parameter N (See Table 1 for details). In this study, it was assumed that only domestic poultry raised in farms were vaccinated. The general mathematical formula is as follows:

$$PR_{(V(1) S(1-2) B(1) EW(1-6))} = P_{(V(1) S(1-2) B(1) (EW(1-6)))} = \frac{C_{(V(1) S(1-2) B(1) EW(1-6))}}{TP_{(V(1) S(1-2) B(1) EW(1-6))}} \quad (4)$$

Whereby V is vaccinated poultry, $S1$ is passive surveillance and $S2$ is active surveillance, respectively.

Node 5-P5: Does passive and active Surveillance (S 1-2) detect HPAI-H5N1 infected poultry in the backyard (B 2) in different poultry types (T 1-3) in each EW (EW (EW1-EW6))?

This specific variable represents the prevalence rate (PR) of HPAI-H5N1 infection after passive and active surveillance (S 1-2) used in each epidemic wave EW (EW ($EW1-EW6$)) stratified by type of breeding (B 2) and different poultry types and different poultry types: domestic, mixed and reservoir (T 1-3) and P , C , TP respectively. The variable input values for this parameter $P5$ are calculated by dividing the number of cases of HPAI-H5N1 by the total populations in the backyard poultry, surveillance types, and different poultry types. The probability distribution values for this variable were determined by @RiskBestfit as described previously in parameter N (See Table 1 and 2 for details). Whereas, in this node (**Node 5**) it was assumed that in the backyard poultry no vaccination measures were taken except in a few cases. Therefore, in this study, it was assumed that vaccination has not been used in backyard poultry. The general mathematical formula is as follows:

$$PR_{(S(1-2) T(1-3) B(2) EW(1-6))} = P_{(S(1-2) T(1-3) B(2) EW(1-6))} = \frac{C_{(S(1-2) T(1-3) B(2) EW(1-6))}}{TP_{(S(1-2) T(1-3) B(2) EW(1-6))}} \quad (5)$$

Whereby $S1$ is passive surveillance and $S2$ is active surveillance, respectively.

Results

a. POULTRY FARMS

As represented by the sigmoid curve in **Figure 2**, the results show that in the poultry farms, the likelihood of poultry still having a high prevalence rate of HPAI-H5N1 after the failure of mitigation strategies such as vaccination, passive, and active surveillance in six epidemic waves (**EW (1-6)**) in the poultry farms (**B1**) in Menoufia, Egypt. In 90% of the time, these mitigations will fail about 48%. This value ranged from 0.00 to 6.40×10^{-01} with a mean and a standard deviation (SD) of 3.05×10^{-03} and 1.28×10^{-01} respectively. The efficacy of these mitigations is expected to decrease PR to 70% with missed vaccination, while in case of failure in detection by surveillance (passive and active), it will decrease up to 99%.

Sensitivity Analysis

The sensitivity analysis ranking of regression coefficients of tornado graph shows that the likelihood of HPAI-H5N1 prevalence rate has on six epidemic waves (**EW (1-6)**) in the poultry farms (**B1**) in Menoufia, Egypt due to missed vaccination, failure to detect of sickly poultry by passive or active surveillance was examined. In the poultry farms, increasing vaccination will decrease the likelihood of increasing prevalence rates by 14%, in active surveillance by 12%, and in passive surveillance by 6% (regression coefficients = -0.14, -0.12 and -0.06 respectively) (**Table 3 and Figure 3**). Therefore, vaccination, active, and passive surveillance were considered to be strong predictors of the likelihood of HPAI-H5N1 high outbreaks in poultry due to missed vaccination. In addition, failure to detect sickly poultry by passive or active surveillance in farms (**B1**).

In the sensitivity analysis, regression, and correlation coefficients both were used to indicate the direction of the relationship whether positive or negative. A positive means as parameter input increases, the output increases; and a negative means that as input increases, the output decreases. A regression coefficient shows the strength of the relationship, and a correlation coefficient shows the consistency of the relationship. The coefficient of determination (R^2) is utilized to decide whether to use correlation coefficients or regression coefficients. A low value of R^2 means that a linear regression model is not very good at predicting the output from the indicated inputs. In this case, the focus is more on correlation coefficients, because rank-order correlation does not depend on the two distributions having a similar shape or being linearly related. If R^2 is high, a linear regression model is a good fit mathematically [43].

As shown in **Figure 3**, concerning regression coefficients, the longer the bar or the larger the coefficient, the greater the impact that particular input has on the corresponding output that is being analyzed. A positive coefficient, with a bar extending to the right, indicates that this input has a positive impact: increasing this input will increase the output [43]. For example, in this study, it is the case of HPAI-H5N1 prevalence rates in infected poultry in Menoufia in each epidemic wave with the highest regression coefficient of 0.97. A negative coefficient, with a bar extending to the left, indicates that this input has a negative impact on the output: increasing this input will decrease the output [43]. For example, in this study, HPAI-H5N1 prevalence rates due to failure in detection by passive surveillance in farm poultry with the lowest regression coefficient of -0.06. The tornado graph (**Figure 3**) shows pictorial representations of sensitivity analyses of the simulation results of the probabilities of HPAI-H5N1 prevalence rates in poultry due to missed vaccination and failure to detect sickly poultry by passive or active surveillance. This was in six (**EW (1-6)**) in the poultry farms in Menoufia, Egypt.

Tornado graph shows how the outputs are ranked by the magnitude of input effects have had on the outputs. In addition, **Table 3** shows simulation ranking results in tabular form. The tornado graph shows the influence of how much each specific input distribution has on the change in the values of the corresponding specific output distribution [44].

In addition, **Figure 3** shows the likelihood of HPAI-H5N1 prevalence rates (**P**) were higher in poultry in each epidemic wave (**EW (1-6)**). Whereas HPAI-H5N1 prevalence rates likelihood in poultry were lower due to missed vaccination, failure to detect sickly poultry by passive or active surveillance in the farm (**P2, P4, and P3**), as the inputs were less likely affected the output. For instance, in this study, when the prevalence rate parameter (**p**) input is changed by one SD given that the other input parameters are held constant, the output will change by 97%. This is the influence that the input will have on the output. In the case of the mitigation inputs, by one SD while holding the other inputs the same the outputs will decrease by the indicated percentages [44]. In this case, increasing vaccination as a mitigation parameter by one SD will decrease the prevalence rates by 14%, while increasing active surveillance by one standard deviation SD, will decrease prevalence rates by 12%. These were followed by passive surveillance, which will affect in decreasing the prevalence rates by only 6% (regression coefficients = -0.14, -0.12, and -0.06 respectively).

b. BACKYARD POULTRY

Table 4 and Figure 4, illustrate and represent the results of comparison of cumulative probability distributions (as represented by sigmoid curves) of HPAI-H5N1 prevalence rates in different poultry types not detected by passive and/or active surveillance in six epidemic waves (**EW (1-6)**) in the backyard poultry (**B2**) in Menoufia, Egypt. The x-axis shows the three overlying graphs which represent the cumulative probability distributions of HPAI-H5N1 prevalence rates while the y-axis shows the probability confidences of the risk value equal to or less than the values on the x-axis [25]. In the backyard poultry, the likelihood of still having a high HPAI-H5N1 prevalence rate in three different poultry types (domestic, mixed, and reservoir) due to failure of passive and active surveillance varies between these three types. In mixed poultry, the likelihood of HPAI-H5N1 prevalence rates not detected by passive or active surveillance was higher, ranging from 0.00 to 1.06×10^{-3} with a mean and a SD of 16.8×10^{-3} and 3.26×10^{-01} respectively. This was followed by domestic poultry ranging from 0.0 to 7.08×10^{-01} with a mean and a SD of 1.48×10^{-3} and 3.69×10^{-01} respectively and in reservoir poultry ranging from 0.0 to 1.11×10^{-01} with a mean and a SD of 4.94×10^{-3} and 8.34×10^{-03} respectively. However, the likelihood of HPAI-H5N1 prevalence rates in mixed poultry in the backyard not detected by passive or active surveillance is 3.4 times higher than those of reservoir poultry and 113 times higher than those of domestic poultry.

Sensitivity Analysis

Likewise, in the poultry farms, the sensitivity analysis ranking of the tornado graph for the likelihood of decrease of HPAI-H5N1 prevalence rates in six epidemic waves (*EW (1-6)*) in the backyard poultry (*B2*) in Menoufia, Egypt due to detection of sickly poultry by passive and/or active surveillance was examined (**Table 5**). The effect of active and passive surveillance in the backyard poultry of three different types (domestic, mixed, and reservoir) were compared. In domestic poultry, the active surveillance had a high impact in decreasing the prevalence rates by 16%, and 1% in both mixed and reservoir poultry (correlation coefficients = -0.16, -0.01) respectively. Whereas the passive surveillance had less impact in decreasing prevalence rates by 14% in mixed poultry and 3% in domestic poultry (correlation coefficients = -0.14, and -0.03 respectively). Therefore, in this study, active and passive surveillance were considered to be strong predictors of the likelihood in decrease HPAI-H5N1 prevalence rates in different poultry types not detected by passive or active surveillance in the backyard poultry (*B2*).

Figure 5 shows the results of sensitivity analysis presented as the correlation coefficient of the overlaid tornado graphs, which provide a pictorial representation of HPAI-H5N1 prevalence rates in different poultry types not detected by passive and/or active surveillance in six epidemic waves (*EW (1-6)*) in backyard poultry (*B2*) in Menoufia, Egypt. The sensitivity analysis illustrates the degree to which the uncertainties of output variables are affected by the uncertainty of the individual variables within the input variable. The higher the degree of correlation between the input and output variables (calculated using rank-order correlation), the more the input variable is affecting the output variable. The final output is affected by the following parameters by the same mentioned sequence: HPAI-H5N1 prevalence rates in reservoir poultry (*P4*); prevalence rates in mixed poultry (*P3*); prevalence rates in domestic poultry (*P2*); prevalence rates of all infected poultry in the backyard (*P1*); and prevalence rates of infection in poultry in each *EW (P)*. The effect of active and passive surveillance as mitigation strategies in backyard poultry's different types (domestic, mixed and reservoir) was compared. In domestic poultry, the active surveillance had a high impact in decreasing the HPAI-H5N1 prevalence rates by 16%, and 1% in both mixed and reservoir poultry (correlation coefficients = -0.16, -0.01) respectively. Whereas the passive surveillance had less impact in decreasing prevalence rates by 14% in mixed poultry and 3% in domestic poultry (correlation coefficients = -0.14, and -0.03 respectively). (Table 5 and Figure 5).

Discussion

The results of this study demonstrate that the likelihood of poultry still having a high prevalence rate of HPAI-H5N1 after failure of mitigation strategies such as vaccination, passive and active surveillance in six epidemic waves (*EW (1-6)*) in the poultry farms (*B1*) in Menoufia, Egypt is still causing for alarm. In 90% of the time, these mitigations will fail about 48%. Obtained results are broadly consistent with E Abdelwhab and H Hafez [11].

Probability distributions of HPAI-H5N1 prevalence rates in the poultry farms imply that coverage by vaccination and surveillance is unexpectedly low. From the 37% of HPAI-H5N1 prevalence rates in poultry in each epidemic wave, the probability that infected poultry were vaccinated in farms is 3.6%. Although Egypt is considered the second country after China, accounted for over 99% of vaccination usage [19], surveys of vaccination coverage rates showed vaccination rates of less than 20% in sector 4 [45] with the suggestion that the average coverage rate would be much lower than the calculated coverage [19]. Inadequate coverage of vaccinations makes the control of the virus spread difficult [19] because reducing HPAI-H5N1 viral load and transmission requires maintenance of high levels of flock immunity [18]. The low vaccination coverage could be attributed to inherent logistical problems in applying any type of vaccine since there are more poultry within sectors 3 and 4 where most of the production in Egypt takes place which have more premises and independent management systems, there tends to be a lower coverage rate of vaccination [19].

The probability that active and passive surveillance can detect those vaccinated poultry on the farms if they get infected is 0.27% and 0.09% respectively. This is because the Egyptian General Organization of Veterinary Services monitors only <6.5% of vaccinated poultry in the commercial sectors [1, 12]. Field outbreaks have occurred in vaccinated countries, primarily because of inadequate coverage in the target species, besides in Egypt, vaccine failures have occurred following antigenic drift in field viruses [22]. The immune pressure exerted by the vaccines or natural infection accelerates virus evolution in poultry, reducing the efficacy of vaccination over time [23, 30-35]. Besides, improper administration, mishandling [36] and inappropriate storage of the vaccine [12] or suppression of the immune system (i.e.: due to chicken anemia virus infection or ingestion of mycotoxins) [37]. These could be considered as missed vaccinated poultry. In this study, the model predicts that HPAI-H5N1 prevalence rates in the poultry farms will increase to 70% in the case of missed vaccinated poultry (population still at risk after application of mass vaccination).

On the other hand, in the backyard poultry, the likelihood of still having a high HPAI-H5N1 prevalence rate in three different poultry types (domestic, mixed, and reservoir) due to failure of passive and active surveillance, varies between these three types. In mixed poultry, the likelihood of HPAI-H5N1 prevalence rates not detected by passive or active surveillance was higher with a mean of 16.8×10^{-3} . This was followed by domestic poultry with a mean of 1.48×10^{-3} and reservoir poultry with a mean of 4.94×10^{-3} . In case of failure in detection of HPAI-H5N1 by passive and active surveillance in both the farm and backyard poultry, the model predicts that the mean probability of prevalence rates of HPAI-H5N1 will increase to 99% due to an increase in the spread of infection. Despite the high prevalence rates of HPAI-H5N1, with more infected poultry, they were able to detect more, however, we found that the effect of surveillance gets lower with high prevalence. This finding was quite expected because the previous study reported that since the use of mass vaccination in Egypt, a decrease in disease incidence has been observed. This may be because of the result of lower outbreak detection and inadequate reporting rather than immunity conferred by vaccination (M Peyre, H Samaha, YJ Makonnen, A Saad, A Abd-Elnabi, S Galal, T Ettel, G Dauphin, J Lubroth and F Roger [1]).

Overall, this study demonstrated that an increase in the completeness of poultry vaccination, active and passive surveillance of HPAI-H5N1 in the farms and backyard poultry in Menoufia, Egypt would have a decrease in the infection rates and ultimately decrease in HPAI-H5N1 prevalence rates. Consequently, sensitivity analysis results of selected variables that were examined together with their sensitivity ranking with respect to the likelihood of HPAI-H5N1 prevalence rates not detected by passive or active surveillance to show the aggregate effect of each input variable has on a corresponding output variable. The tornado graphs, which provide a pictorial representation of a sensitivity analysis of simulation results, which demonstrate the significance of each input variable has on an output variable.

In the poultry farms, it was indicated that an increase in efficacy of vaccination would lead to decrease of the likelihood of infection with HPAI-H5N1 however, due to missed vaccination, not detected by passive and active surveillance more likelihood of increased infection will be observed. Since increasing vaccination as a mitigation strategy parameter by one standard deviation (SD) will decrease the prevalence rates by only 14%, which is a limited effect as a primary required control measure in the mitigation strategy revealing how much vaccination faces a lot of challenges and limitations. One of the facts that cannot be ignored is that vaccination cannot prevent infection, or its transmission [46-49]. Besides circulation of the virus within vaccinated poultry [48, 50] along with inadequate vaccination coverage [18] and acceleration of viral evolution due to inadequate vaccination [17], in addition to improper antigenic matching between vaccines' seed strain and circulating viruses [9].

Vaccination alone is not enough to reduce prevalence rates and infection spread. This should be integrated with other measures principally effective surveillance systems and outbreak management [1, 23]. Active to a more extent than passive surveillance is the second and third intervention strategies on the poultry farms. In this study, the effects of both active and passive surveillance as mitigation strategies in the backyard poultry's different types (domestic, mixed and reservoir) are compared. In domestic and mixed poultry, the active surveillance had a higher impact in decreasing the HPAI-H5N1 prevalence rates by 16% and 14% respectively. Whereas the active surveillance had less impact in a decrease in the disease prevalence rates by 3% in domestic poultry and 1% in both mixed and reservoir poultry.

It is not surprising that passive surveillance has less impact in detecting the likelihood of HPAI-H5N compared to active surveillance since farmers don't report outbreaks neither in backyard nor commercial farms [51]. Generally, adherence to control measures is low because of social norms, especially in rural areas, and declining public awareness in the community [5]. The results reflect the true situation because of the prevailing under-reporting in the commercial sector to protect their business interests and prevent the mass culling of their stocks [52]. As well as, surveillance activities' biases towards the household sector due to lack of incentive to report outbreaks as there is very limited or no compensation scheme for poultry owners [1, 10]. Besides, owners of the poultry farms are becoming reluctant to vaccinate their poultry or notify authorities if there is any infection after sudden deaths in poultry following vaccination campaigns "post-vaccination sudden death" [1]. In addition to that, local veterinary services consequently are reluctant to declare new outbreaks due to the fear of being unfairly blamed for failing to effectively perform their duties [1].

Nevertheless, some studies support the hypothesis that mass avian influenza vaccination of domestic poultry may negatively affect passive surveillance [1, 41], as it increases the viral load in the environment which leads to the possible presence of silent infection with masking clinical expression of the disease [53]. Not only vaccination could change the clinical features of the disease, but also concurrent infection by low-pathogenic avian influenza viruses can protect from disease signs and death if becoming infected with the HPAI-H5N1 [54], but still could shed HPAI-H5N1 virus in their feces and could be capable of infecting other poultry, and potentially humans [55, 56].

Unlike Passive surveillance, which has many limitations, active surveillance is better than passive surveillance in detecting the virus as it is performed by highly experienced persons and more advanced techniques to detect even silent infected poultry. Increases in the surveillance activities (active) in form of utilization of rapid antigen detection test nationwide at the public veterinary clinics and the implementation of participating disease search (Community-Based Animal Health And Outreach Program-CAHO) enhanced the surveillance programs (active) leading to observed increases in reported cases in the household poultry during 2010/2011 [38]. It allows monitoring the evolution and prevalence of endemic viruses, which provide an early alert for the incursion of emerging viruses [5].

The results of this study are comparable with A Arafa, I El-Masry, S Khoulouy, MK Hassan, M Soliman, OG Fasanmi, FO Fasina, G Dauphin, J Lubroth and YM Jobre [38] study which has shown that more than 52% incidence rate was reported in the mixing of different bird species in the household sector in comparison to any other sector. The virus was more prevalent in mixed waterfowls and chickens than turkeys and pigeons [11]. Surveillance also indicated the persistence of H5N1 in scavenging household ducks where the contact with feral birds is higher than other poultry [57]. Ducks were speculated to be a major source for infection as the emergence of the new 2.2.1.2 cluster in the recent 2014/2015 upsurge in poultry and humans in Egypt where the predecessor virus of this clade was probably of a duck-origin virus [58]. This clade was responsible for a majority of documented human infections in recent years [59, 60]. Besides, viruses isolated from ducks were more genetically diverse than those isolated from chickens [61], suggesting a role for ducks in perpetuating the endemicity of A/H5N1 in Egypt. In this study, the model in the backyard poultry, demonstrated that decreasing HPAI-H5N1 infection in reservoir and mixed poultry might directly decrease the overall prevalence rates. Therefore, targeted surveillance to elucidate the spread of the HPAI-H5N1 virus in ducks and household with mixed different poultry species should be considered.

Conclusion

It can be concluded from the quantitative risk assessment (QRA) model that the applied strategies were not efficient to control the spread of the HPAI-H5N1 virus, but data quality, state of the scientific knowledge, and values of the parameters used to fit the model are continuously evolving. This calls

for the need to periodically revise the QRA to update the estimates and improve the quality of the conclusions. The choice of an effective strategy will vary depending on an evaluation of the chosen mitigations for combating outbreaks in the whole of Egypt. This QRA model dynamics are to be applied with other data if it becomes available. Although, this is a model for avian influenza HPAI-H5N1 strain, the nature of the next epidemic virus strain is uncertain. The model could also apply to most infectious diseases especially those of viral nature. The effectiveness of any strategy depends very much on rapid implementation with strong political commitment and determined implementation along with strict public compliance with any or all interventions. Using the HPAI-H5N1 virus QRA model can also help public health officials to take into consideration the evaluation of the mitigations and control strategies in their response to this disease of great public health importance. Although this QRA is developed for the Menoufia, governorate, Egypt, it is generic in nature and it can be utilized in similar areas with similar prevailing problem.

Declarations

- **Ethics approval and consent to participate:** Not applicable
- **Consent for publication:** Not applicable
- **Availability of data and materials:** All data generated or analyzed during this study are included in this published article [and its supplementary information files].
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- **Authors' contributions:** YE design the manuscript, data collection and processing, was a major contributor in cleaning, analysis, interpretation and writing of the manuscript. EA has given significant intellectual inputs and supervised the work, participated in the conceiving and designing of the manuscript. Made significant contributions to cleaning, analysis, interpretation of the data, and writing the manuscript. DN participated in designing, cleaning, writing the manuscript. GE supervised the work, participated in interpretation and writing. AB participated in data collection, processing, and writing. GR made substantial contributions in collection and cleaning of the data. All authors critically reviewed manuscript and approved the final manuscript.
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Tables

Table 1. Parameter estimates for a quantitative risk assessment of HPAI-H5N1 in poultry farms (B1) in Menoufia, Egypt. For all the parameter estimates, we used the best-fit probability distributions.

Parameter notation	Parameter description	Best-fit probability distributions	Minimum	Maximum	Mean	Std Dev	5%	95%
N	Total number of poultry in Menoufia, Egypt	<i>RiskPareto</i> (0.72898,3749375.0)	3,749,375	52,857,042	23,511,705	22,775,444	3,749,374	52,857,042
P	The probability of HPAI-H5N1 prevalence rates in poultry in each epidemic wave	<i>RiskExtValueMin</i> (0.44313,0.11949)	0.08253	0.55095	0.36933	0.17576	0.08253	0.55095
P1	The probability of HPAI-H5N1 prevalence rates in poultry that were vaccinated in farms	<i>RiskLaplace</i> (0.10269,0.053750)	0.01651	0.1791	0.0988	0.05487	0.01651	0.1791
P2 (1-P1)	The probability of HPAI H5N1 prevalence rates in birds that missed vaccination in farm							
P3a	The probability of HPAI-H5N1 prevalence rates in poultry due to detection by passive surveillance in farms	<i>RiskExpon</i> (0.024769, <i>RiskShift</i> (-0.0041281))	0	0.066481	0.024769	0.026972	0	0.066481
P3 (1-P3a)	The probability of HPAI H5N1 prevalence rates in birds due to failure in detection by passive surveillance in farm							
P4a	The probability of HPAI-H5N1 prevalence rates in poultry due to detection by active surveillance in farms	<i>RiskUniform</i> (-0.0077277,0.15365)	0.01533	0.1306	0.07403	0.04811	0.01533	0.1306
P4 (1-P4a)	The probability of HPAI H5N1 prevalence rates in birds due to failure in detection by active surveillance in farm							

Table 2. Parameter estimates for a quantitative risk assessment of (HPAI-H5N1) in backyard poultry (B2). For all the parameter estimates, we used the best-fit probability distributions.								
Parameter notation	Parameter description	Best-fit probability distributions						
		Function	Minimum	Maximum	Mean	Std Dev	5%	95%
N	Total number of poultry in Menoufia, Egypt	<i>RiskPareto</i> (0.72898,3749375.0)	3,749,375	52,857,042	23,511,705	22,775,444	3,749,374	52,857,042
P	The probability of HPAI-H5N1 prevalence rates in poultry in each epidemic wave	<i>RiskExtValueMin</i> (0.44313,0.11949)	0.08253	0.55095	0.36933	0.17576	0.08253	0.55095
P1	The probability of HPAI-H5N1 Prevalence rates in Backyard poultry (B2) in each EW	<i>RiskUniform</i> (-0.0058329,0.49715)	0.06602	0.42529	0.26682	0.1612	0.06602	0.42529
P2	The probability of HPAI-H5N1 Prevalence rates in domestic poultry in backyard	<i>RiskUniform</i> (-0.023407,0.25598)	0.01651	0.21606	0.10608	0.08142	0.01651	0.21606
P3	The probability of HPAI-H5N1 Prevalence rates in mixed poultry in backyard	<i>RiskUniform</i> (-0.032087,0.21864)	0.00373	0.18282	0.09288	0.08264	0.00373	0.18282
P4	The probability of HPAI-H5N1 Prevalence rates in reservoir poultry in backyard	<i>RiskExpon</i> (0.067856, Risk Shift (-0.011309))	0	0.21171	0.06786	0.08028	0	0.21171
P5a	The probability of H5N1 Prevalence rates in domestic poultry due to detection by passive surveillance in backyard	<i>RiskUniform</i> (-0.010885,0.090071)	0.003537	0.075648	0.036997	0.031555	0.003537	0.075648
P5 (1-P5a)	The probability of H5N1 Prevalence rates in domestic chicken due to failure in detection by passive surveillance in backyard							
P6a	The probability of H5N1 Prevalence rates in domestic poultry due to detection by active surveillance in backyard	<i>RiskPareto</i> (0.76486,0.012968)	0.01297	0.1662	0.06909	0.0619	0.01297	0.1662
P6 (1-P6a)	The probability of H5N1 Prevalence rates in domestic chicken due to failure in detection by active surveillance in backyard							
P7a	The probability of H5N1 Prevalence rates in mixed poultry due to detection by passive surveillance in backyard	<i>RiskPareto</i> (0.51481,0.0023579)	0.002358	0.099722	0.03821	0.040182	0.002358	0.099722
P7 (1-P7a)	The probability of H5N1 Prevalence rates in mixed poultry due to failure in detection by passive surveillance in backyard							
P8a	The probability of	<i>RiskUniform</i>	0	0.11599	0.05467	0.04632	0	0.11599

	<i>H5N1 Prevalence rates in mixed poultry due to detection by active surveillance in backyard</i>	(-0.023198,0.13919)						
P8 (1-P8a)	<i>The probability of H5N1 Prevalence rates in mixed poultry due to failure in detection by active surveillance in backyard</i>							
P9a	<i>The probability of H5N1 Prevalence rates in reservoir poultry due to detection by passive surveillance in backyard</i>	RiskExpon (0.0080041, RiskShift (-0.0013340))	0	0.034822	0.008004	0.013668	0	0.034822
P9 (1-P9a)	<i>The probability of H5N1 Prevalence rates in reservoir poultry due to failure in detection by passive surveillance in backyard</i>							
P10a	<i>The probability of H5N1 Prevalence rates in reservoir poultry due to detection by active surveillance in backyard</i>	RiskExpon (0.059852, RiskShift (-0.0099753))	0	0.21171	0.05985	0.07899	0	0.21171
P10 (1-P10a)	<i>The probability of H5N1 Prevalence rates in reservoir poultry due to failure in detection by active surveillance in backyard</i>							

Table 3. Sensitivity ranking for the likelihood of HPAI-H5N1 prevalence rate in poultry due to missed vaccination, not detected by surveillance in six epidemic waves in the poultry farms (B1).		
Sensitivity Ranking	Variables	Regression coefficient values
1	<i>HPAI-H5N1 prevalence rates in poultry in each epidemic wave</i>	0.97
2	<i>HPAI-H5N1 Prevalence rates in poultry that missed vaccination in farm</i>	-0.14
3	<i>HPAI-H5N1 prevalence rates in poultry due to failure in detection by active surveillance in farm</i>	-0.12
4	<i>HPAI-H5N1 prevalence rates in poultry due to failure in detection by passive surveillance in farm</i>	-0.06

Table 4. Output summary statistics for the likelihood of HPAI-H5N1 prevalence rate in different poultry types not detected by surveillance in six epidemic waves in Backyard poultry (B2).			
@RISK Output statistics	Probability of HPAI-H5N1 prevalence rate in domestic poultry not detected by passive or active surveillance in six epidemic waves (EW (1-6)) in Backyard poultry (B2)	Probability of HPAI-H5N1 prevalence rate in mixed poultry not detected by passive or active surveillance in six epidemic waves (EW (1-6)) in Backyard poultry (B2)	Probability of HPAI-H5N1 prevalence rate in reservoir poultry not detected by passive or active surveillance in six epidemic waves (EW (1-6)) in Backyard birds poultry (B2)
Minimum	0.00	0.00	0.00
Maximum	7.08×10^{-01}	1.06×10^{-03}	1.11×10^{-01}
Mean	1.48×10^{-3}	16.8×10^{-3}	4.94×10^{-3}
SD	3.69×10^{-01}	3.26×10^{-01}	8.34×10^{-03}
5%	0.00	0.00	0.00
95%	3.29×10^{-3}	2.83×10^{-3}	2.08×10^{-3}

Table 5. Sensitivity ranking for the likelihood of HPAI-H5N1 prevalence rate in different poultry types not detected by surveillance in six epidemic waves in the backyard poultry (B2).		
Sensitivity Ranking	Variables	Correlation coefficient values
1	<i>The probability of HPAI-H5N1 Prevalence rates in reservoir poultry in backyard</i>	0.80
2	<i>The probability of HPAI-H5N1 Prevalence rates in mixed poultry in backyard</i>	0.63
3	<i>The probability of HPAI-H5N1 Prevalence rates in domestic poultry in backyard</i>	0.60
4	<i>The probability of HPAI-H5N1 Prevalence rates in Backyard (B2) in each EW (Domestic poultry)</i>	0.46
	<i>The probability of HPAI-H5N1 Prevalence rates in Backyard (B2) in each EW (Mixed poultry)</i>	0.40
	<i>The probability of HPAI-H5N1 Prevalence rates in Backyard (B2) in each EW (Reservoir poultry)</i>	0.37
5	<i>The probability of HPAI-H5N1 prevalence rates in poultry in each epidemic wave (Domestic poultry)</i>	0.28
	<i>The probability of HPAI-H5N1 prevalence rates in poultry in each epidemic wave (Mixed poultry)</i>	0.25
	<i>The probability of HPAI-H5N1 prevalence rates in poultry in each epidemic wave (Reservoir poultry)</i>	0.22
6	<i>The probability of H5N1 Prevalence rates in domestic poultry due to failure in detection by active surveillance in backyard</i>	-0.16
7	<i>The probability of H5N1 Prevalence rates in mixed poultry due to failure in detection by passive surveillance in backyard</i>	-0.14
8	<i>The probability of H5N1 Prevalence rates in domestic poultry due to failure in detection by passive surveillance in backyard</i>	-0.03
9	<i>The probability of H5N1 Prevalence rates in mixed poultry due to failure in detection by active surveillance in backyard</i>	-0.01
10	<i>The probability of H5N1 Prevalence rates in reservoir poultry due to failure in detection by active surveillance in backyard</i>	-0.01
11	<i>The probability of H5N1 Prevalence rates in reservoir poultry due to failure in detection by passive surveillance in backyard</i>	0.00

Figures

Figure 1

Risk pathway (Scenario tree) for the likelihood of HPAI-H5N1 prevalence rate in poultry due to missed vaccination, not detected by surveillance in six epidemic waves.

Figure 2

Figure 3

Figure 4

Comparison of cumulative probability distributions of HPAI-H5N1 prevalence rate in different poultry types not detected by surveillance in six epidemic waves in Backyard birds (B2).

Figure 5

Tornado graph showing the likelihood of HPAI-H5N1 prevalence rate in different poultry types not detected by surveillance in six epidemic waves in the backyard poultry (B2)

Supplementary Files

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- [scenariotreesimulation.xlsx](#)
- [supplementarydata.xlsx](#)