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ABSTRACT

France recently faced two epizootic waves of highly pathogenic avian influenza (HPAI) in poultry (H5N6 in 2015–2016 and H5N8 in 2016–2017), mainly in the fattening duck production sector. Vaccination against avian influenza (AI) is currently not authorised in France even though its potential benefits were discussed during these epizootic events. The objective of this work was to evaluate the potential efficiency of different vaccination strategies that could be applied against AI in France.

The EVACS tool, which is a decision support tool developed to evaluate vaccination strategies, was applied in several French poultry production sectors: broiler, layer, turkey, duck and guinea fowl. EVACS was used to simulate the performance of vaccination strategies in terms of vaccination coverage, immunity levels and spatial distribution of the immunity level. A cost-benefit analysis was then applied based on EVACS results to identify the most efficient strategy. For each sector, vaccination protocols were tested according to the production type (breeders/production, indoor/outdoor), the integration level (integrated/independent) and the type of vaccine (hatchery vaccination using a recombinant vaccine/farm vaccination using an inactivated vaccine). The most efficient protocols for each sector were then combined to test different overall vaccination strategies at the national level. Even if it was not possible to compare vaccination protocols with the two vaccines types in "foie gras" duck, meat duck and guinea fowl production sectors as no hatchery vaccine currently exist for these species, these production sectors were also described and included in this simulation.

Both types of vaccination (at hatchery and farm level) enabled protective immunity levels for the control of AI, but higher poultry population immunity level was reached (including independent farms) using hatchery vaccination. We also showed that hatchery vaccination was more efficient (higher benefit-cost ratio) than farm vaccination. Sufficient and homogeneously spatially distributed protective levels were reached in the overall poultry population with vaccination strategies targeting breeders, chicken layers and broilers and turkeys, without the need to include ducks and guinea fowls. However, vaccination strategies involving the highest number of species and production types were the most efficient in terms of cost-benefit.

This study provides critical information on the efficiency of different vaccination strategies to support future decision making in case vaccination was applied to prevent and control HPAI in France.

1. Introduction

France was hit with two epizootic waves of highly pathogenic avian influenza (HPAI) during the winters 2015−16 and 2016−17 (Briand et al., 2017; Napp et al., 2018). In both outbreaks, the viruses mainly circulated within the duck production network, the majority producing "foie gras" - a delicacy made from duck liver (Bronner et al., 2017; Le Bouquin et al., 2016). The duck production processes were identified as the main reason for the spread of HPAI viruses in the south-eastern region of France (Guinat et al., 2019). To control the spread of the disease, surveillance was increased and birds in infected farms were systematically culled. During the second outbreak, given the rapid and extensive spread of the disease, preventive culling was also performed in areas around confirmed outbreaks. In 2016–17, about 6.8 million birds were

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culled (Guinat et al., 2018). Culling caused huge economic losses not only for farmers but also for the whole French poultry industry. Total French and European compensation reached 137 million euro in 2015−16 and 123 million euros in 2016−17 (partial estimation) (Lalaurette and Hercule, 2019). The psychological impact on the farmers due to the suspension of their activity, the massive culling of their birds and the intense media focus on the epizootic was also very high (CIFOG, 2017). Even if vaccination was applied in the duck production sector in 2006 during the H5N1 epizootic (Capua et al., 2009), no vaccination was conducted during the both 2015–2016 and 2016–2017 waves. Vaccination against AI is currently not authorised in France, mainly due to the trade restrictions on exports. During the second outbreak (2016−17), because of the very large number of birds culled, some farmers and the media raised the issue of the use of vaccination if there was to be a similar event in the future.

Two main types of avian influenza (AI) vaccines exist: inactivated whole AI virus vaccine and live vector vaccines (Peyre et al., 2009). Sub-unit and virus-likes particle vaccines have been commercialised more recently (Beato et al., 2013) but less widely used. Inactivated vaccines can be homologous (based on strains with the same haemagglutinin (HA) and neuraminidase (NA) as the circulating field virus) or heterologous (based on strains with the same HA but different NA from the circulating field virus). In the case of HPAI strains, reverse genetics is often applied to the HA gene to make the virus strain low pathogenic for vaccine production. Vector vaccines are based on the insertion of an AI gene of interest (HA) into a carrier vector (non-pathogenic virus). Different types of recombinant vector vaccines exist for poultry: fowlpox recombinant vaccine (Swayne et al., 2000), Newcastle disease recombinant vaccine (Veits et al., 2006) and Herpes virus of turkey's (HVT) recombinant vaccine (Kapczynski et al., 2015). Inactivated vaccines require several applications (boosters) to maintain protection in the long run while recombinant vaccines provide long term protection with a single application, mostly at the hatchery (Peyre et al., 2009). As of today, the HVT vaccine is the main vector vaccine used for HPAI vaccination. It is currently applied in routine in Mexico, Bangladesh, Egypt and Viet Nam. To date no study has compared the efficiency of vaccination strategies using these two different types of vaccines in the French poultry production sector.

EVACS (Evaluation tool of VACcination Strategies) is one of the few existing decision support tools that has been developed to compare vaccination strategies (Peyre et al., 2016). The objective of this study was to apply the EVACs tool to identify the most effective and economically efficient vaccination strategy, using different types of vaccines (inactivated farm vaccines and/or recombinant hatchery vaccines) and risk-based approach to protect each French poultry production sector and the whole poultry production from a new HPAI epizootic wave. These results will support future decision making on the use of vaccination to prevent and control HPAI in France.

2. Materials and methods

2.1. Description of the EVACS tool

The EVACS tool was used to evaluate the performances of different AI vaccination strategies in France in different poultry production networks. This tool has been previously described as part of its application in Egypt (Peyre et al., 2016). The tool allows to evaluate the effectiveness and efficiency of different vaccination strategies within poultry production networks by estimating for each production type: i) the vaccination coverage (percentage of vaccinated birds versus total bird population), ii) the immunity level (percentage of birds with seroconversion, i.e. hemagglutinin inhibition level >4Log2); iii) the duration of immunity (proportion of weeks where more than 70 % of birds had a protective seroconversion level)); iv) the spatial distribution of the immunity level (the density of sero-positive birds) and v) the cost-benefit analysis of each strategy (efficiency) (Fig. 1). Only vaccination strategies and no other type of control strategies (i.e. culling, biosecurity, movement restriction, etc.) are compared. The implementation of the tool requires five steps: 1) modelling of the poultry production networks, 2) definition of vaccination strategies to be tested based on the poultry production networks; 3) simulation of vaccination strategies within the networks to generate the outputs in terms of vaccination coverage, immunity levels and duration of immunity; 4) spatial analysis of the immunity level distribution and 5) comparative cost-benefit analysis of the different strategies. Steps 1–4 are performed using specific scripts built in the EVACS "RStudio" project previously developed using the "RStudio" software version 1.1 ("R" version 3.5.1); step 5 is performed using the EVACs "cost-benefit analysis" Excel spread sheet (Microsoft Excel 2007). A description on how the tool applied to the evaluation of AI vaccination strategies in France is presented here.

2.2. Data requirement and collection

In order to model the poultry production networks in France, data on the poultry production organisation and census were collected for each production sector (layers or meat) and species (chicken, ducks ….) including: the number of birds and farm per type of production (grandparents, breeders, free-range production, indoor production); the level of integration (integrated with or without hatchery or independent); the type and volume of movements of birds, eggs or day-old birds between production types. Data were collected both from a public database for the national poultry census per production sector and production type (Agreste, 2018) and from a private database for day-old bird flows from hatcheries (Ceva Poultry database). In addition, interviews with representatives of most French poultry production sectors were performed. After this data collection and collation phase, a participatory workshop was organised with these representatives to

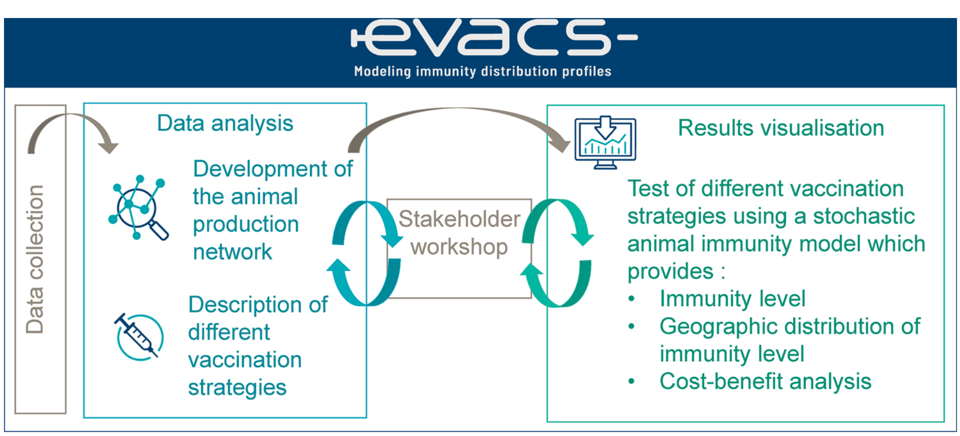

Fig. 1. Schematic representation on how the EVACS tool works.

validate the modelled networks.

To model the immunity within the poultry production networks, data were collected on: the type of vaccines used, the vaccination coverage per production type, the efficacy of the vaccine used (in terms of seroconversion and duration of protection), the number of vaccine doses administered and vaccination schedule (time interval between doses). To perform the spatial analysis the number of heads of the different poultry production types and sectors (grandparents, breeders, indoor production, free-range production) per region were collected (Agreste, 2018). To perform the cost-benefit analysis, data on the vaccination cost (i.e. cost of vaccine dose, vaccination implementation costs) and on the production values (i.e. sale price of eggs, meat birds, day-old birds, adult breeders and grand-parents) were collected.

2.3. Data analysis

All the data collected were entered in a database developed with Excel software (Microsoft Excel 2007).The EVACs tool was applied using “RStudio” software version 1.1 (“R” version 3.5.1). The network script is using “igraph” and “sna” packages (Butts, 2016). The immunity modelling script is a stochastic simulation model using gamma distribution and sensitivity analysis, and “igraph” and “MASS” packages (Gábor, 2018; Ripley et al., 2018). The spatial analysis script also uses “raster” and “rgeos” packages to generate maps (Bivand et al., 2018; Hijmans et al., 2017). The cost-benefit analysis uses an Excel spreadsheet (Microsoft Excel 2007).

2.4. Step 1: poultry production network modelling

The “network modelling” R script of the EVACs tool was used to conduct the network analysis (Peyre et al., 2016). The aim of the network modelling step is to characterise the poultry production networks and to identify the main type of farms (i.e. nodes of the social network analysis) and bird flow between the farms (e.g. day-old birds). Production network models were developed for each of the major French poultry production sectors in France (i.e. broiler, layer, fattening duck, meat duck, turkey and guinea fowl). Attribute tables were used to generate networks based on: the type of production (grandparents, breeders, free-range production, indoor production) for farms and hatcheries, the integration level (integrated with or without hatchery or independent), and the number of birds (heads) on the farms. Backyard flocks (i.e. flocks under 250 birds) were not included in this description as they had a limited role in the spread of H5N8 HPAI during the 2016–2017 epizootic (Souvestre et al., 2019). The different types of poultry production and integration levels were represented by the different nodes in the network. The movement of hatching eggs (between breeder farms and hatcheries) or of day-old birds (chicks, turkeys, ducklings or guinea fowls) between hatcheries and farms were represented by the directed links in the network, i.e. showing the direction of movements between the nodes. The volume of exchange of day-old birds between nodes was considered using directed-weighted matrices.

2.5. Step 2: vaccination strategies identification

Vaccination strategies were defined and tested at both sector and total poultry population level.

2.5.1. Vaccination protocols per sector

Vaccination protocols were defined following the network organisation for each production type and sector (Table 1 and Supplementary file 1). The first vaccination protocols focused on the bird population at higher risk (i.e. free-range) when the following protocols progressively include other production types (indoor, integrated and independent) while combining inactivated farm vaccine and recombinant hatchery vaccine. All protocols were tested in broiler and turkey production sector. The same protocols were tested in layer sector except protocol 3, as there is no hatchery integrated with production farms in this sector. Only protocols using inactivated vaccines were tested for duck and guinea fowl sectors (Table 1 P1, P5 and P6), as no recombinant vaccines are commercially available for these species yet. For all protocols, all grandparent and breeder farms of the concerned sector are vaccinated with inactivated farm vaccines.

2.5.2. Vaccination strategies for the total poultry population

The most efficient vaccination protocol per sector (i.e. resulting in the highest benefit cost ratio above 1) was selected to define the vaccination strategies at the total poultry population level, using a risk-based approach i.e. targeting the higher risk production type to start with i.e. layers and free-range production and then adding on more production types (Table 2). The risk level categorisation was retrieved from previous studies (Barnes et al., 2019; Elbers and Gonzales, 2019; Singh et al., 2018).

2.6. Step 3: Estimation of the efficacy of the vaccination strategies

The “immunity modelling” R script of the EVACs tool was used to estimate the efficacy of the different vaccination strategies for each type of production (network nodes) in terms of: vaccination coverage (proportion of birds in the entire poultry population which have been vaccinated); immunity level (proportion of birds with a protective seroconversion level) and duration of the immunity (proportion of weeks where more than 70 % of birds had a protective seroconversion level) (Peyre et al., 2016).

The parameters used for the model are described in Table 3. As the vaccination would be mandatory if applied in France, the vaccination coverage at farm level (% of vaccinated farms) was considered maximum (100 %). Due to practical aspects, the vaccination coverage at bird level (% of vaccinated birds in a vaccinated farm) was considered better with hatchery vaccination (mean = 98 %, IC 95 %=[95, 99]%) as compared with farm vaccination (mean = 95 %, IC 95 %=[90, 98]%)

Table 1
Vaccination protocols tested.

Vaccination protocol [a]	Production type				
	Grandparents and breeders	Free-range		Indoor	
Farm integration level	Not applicable	Integrated	Independent	Integrated	Independent
P 1	I[b]	I	–	–	–
P 2	I	R	R	–	–
P 3	I	R	R	R Int H	R Int H
P 4	I	R	R	I	–
P 5	I	I	–	I	–
P 6	I	I	I	I	I
P 7	I	R	R	R	R

[a] P: Protocol.
[b] I: Inactivated farm vaccine, R: Recombinant hatchery vaccine, R Int H: Recombinant hatchery vaccine in integrated hatcheries, - : No vaccination.

Table 2
Vaccination strategies tested at the total poultry production level.

Vaccination strategy[a]	Sectors					
	Grandparents and breeders (all sectors)	Broiler	Layer	Turkey	Duck (meat and fattening)	Guinea fowl
S 1	I All (as for all protocols)[b]	R FR (P2)	R All (P7)	R FR (P2)	I Int FR (P2)	I Int FR (P2)
S 2	I All (as for all protocols)	R FR (P2)	R All (P7)	R All (P7)	I Int (P5)	I Int (P5)
S 3	I All (as for all protocols)	R Indoor (P7 only for indoor)	–	–	–	–
S 4	I All (as for all protocols)	R All (P7)	R All (P7)	R All (P7)	–	–
S 5	I All (as for all protocols)	R All (P7)	R All (P7)	R All (P7)	I Int (P5)	–
S 6	I All (as for all protocols)	R All (P7)	R All (P7)	R All (P7)	I Int (P5)	I Int (P5)
S 7	I All (as for all protocols)	R All (P7)	R All (P7)	R All (P7)	I All (P6)	I All (P6)

[a] S: Strategy.
[b] I All: Inactivated farm vaccine in all farms; I Int FR: Inactivated farm vaccine in integrated free-range farms; I Int: Inactivated farm vaccine in all integrated farms; R All: Recombinant hatchery vaccine in all day-old birds; R FR: Recombinant hatchery vaccine in all free-range day-old birds; R Indoor: Recombinant hatchery vaccine of all indoor day-old birds; - : No vaccination; P2−7: Vaccination protocol at the sector level.

Table 3
Inputs parameters for the immunity modelling.

Vaccine type	Production type	% of vaccination coverage		Vaccine efficacy (% of seroconversion)
		% of farms vaccinated	% of birds vaccinated	
Inactivated vaccines (farm)	Grandparents and breeders	100 %	98 % [95−99]	92 % [90–95]
	Layers, broilers, turkeys, ducks and guinea fowls		95 % [90–98]	
Recombinant vaccines (hatchery)	Layers, broilers and turkeys	100 %	98 % [95−99]	92 % [90–95]

(Peyre et al., 2016). As no AI vaccination is currently performed in France, data on vaccine efficacy were collected from the literature. The same vaccine efficacy was applied in the model for both vaccination types based on literature data (Peyre et al., 2016).

The vaccination coverage was considered sufficient above 80 % of the entire targeted population (Bouma et al., 2009). The immunity level was considered to be protective above 60 % based on the R0 estimations previously reported (Fine et al., 2011; Garske et al., 2007; Tiensin et al., 2007).

2.7. Step 4: spatial analysis section

The "spatial analysis" R script of the EVACs tool was used to map the distribution of the immunity levels according to the different vaccination strategies (Peyre et al., 2016). Poultry census data at the region level (Agreste, 2018) were used for the spatial analysis. Data were aggregated according to the production types (grandparents, breeders, indoor production, free-range production) and production sectors.

2.8. Step 5: Cost-benefit and break-even analysis

The "cost-benefit analysis" Excel spreadsheet of the EVACs tool was used to identify the most efficient vaccination strategy, i.e. which offers the highest benefit/cost ratio (BCR) (Peyre et al., 2016). The costs were defined as the vaccination costs (i.e. cost per vaccine dose and vaccination implementation costs) and the value of the losses in the non-vaccinated population As there is currently no vaccination against HPAI in France, the estimates of the vaccination costs for Newcastle disease vaccination in France were used. These costs include the cost of the vaccine but also the cost of its application for each type of vaccine (farm or hatchery application).

The benefits were limited to the value of the avoided production losses in the vaccinated population and calculated for a disease cumulated incidence of 2.5 % (level observed in France during the 2016–2017 H5N6 epizootics from surveillance data) (Bronner et al., 2017). This incidence level was considered to be fixed and equal for all poultry production types and sectors. The production losses due to AI infection were estimated as a function of the risk of infection at a certain point of time (disease cumulated incidence level) and the vaccine efficacy in terms of immunity rate and duration of protection. The parameters used in the cost-benefit analysis (CBA) are presented in Supplementary file 2.

A break-even analysis was conducted on the most efficient vaccination protocol for each sector (i.e. which provided an immunity level above 60 % for the total population) to estimate the level of disease cumulated incidence where vaccination would no longer be efficient (BCR < 1). A sensitivity analysis was also performed on the parameters used for the CBA: cost of vaccination, value of birds, cumulated incidence and level of immunity.

2.9. Stakeholder validation workshop

A participatory stakeholder workshop including poultry producers, vaccine producers and distributors, veterinary services and laboratory experts (both from public and private sectors) was conducted to validate the poultry production network models and the parameters used in the immunity simulation model, to present the results of the evaluation and to discuss on the recommendations.

3. Results

3.1. Network analysis of the French poultry production network

In 2018, almost 810 million commercial broilers (680 million indoor and 130 million free-range), 47 million layers, 42 million turkeys, 40 million meat ducks, 35 million fattening ducks (for "foie gras" production) and 30 million guinea fowl were produced in France. In France, most farms are integrated in a farmer association, which often includes a feed manufacturer as a horizontal integration system. Some farmers associations have one or several breeder hatcheries in a vertical integration system. In the layer, turkey, duck and guinea fowl production sectors, some breeder hatcheries are integrated with selection, i.e. grandparent hatchery (vertical integration with selection), but some hatcheries are independent. In France, no sector is fully vertically integrated i.e. all type of farms from grandparent farms to breeder farms and to production farms are integrated within the same company. Moreover, a few production farms do not belong to a farmer association and are considered as independent. These farms are mostly small farms with on-farm sales of their products (on-farm slaughter or with an individual contract with a slaughterhouse). Based on these observations, the level of integration makes it possible to divide production farms into three groups: farms integrated in a farmers' association with a hatchery, farms integrated in a farmers' association with no hatchery, and independent farms. The level of integration concerns all production sectors except layers (no hatcheries are integrated with production). No distinction was made between farms integrated in a farmer association with a hatchery and farms integrated in a farmer association with no hatchery because of the limited number of hatcheries and producers in these sectors compared to the broiler sector. This structure was validated by representatives of the turkey, meat duck and guinea fowl sectors. The network analysis conducted in broiler production sector is presented in Fig. 2. The network analysis conducted in the other French poultry production sectors are presented in Supplementary file 3. The spatial distribution of poultry density for each production sector is also provided in Supplementary file 4.

3.2. Evaluation of vaccination protocols for each sector

3.2.1. Immunity distribution profile

For all sectors, the model predicted that targeted integrated production farms (indoor and free-range) with vaccination protocols using inactivated farm and/or recombinant hatchery vaccines were enough to provide a protective vaccination coverage and immunity level for the entire poultry population (more than 80 % and 60 % respectively). The vaccination of higher risk population only (free-range) is not enough to reach a protective immunity level (< 60 %). For broiler, layer and turkey sectors, hatchery vaccination seems to lead to a higher number of vaccinated farms (independent farms included).

3.2.2. Spatial distribution of the immunity level

For broiler, turkey, duck and guinea fowl sectors, vaccination protocols including at least integrated production farms (indoor and free-range) allowed to provide a geographically homogeneous immunity level above 60 % of the total sector population. For layer, only vaccination protocols including all farms allowed to reach this geographically homogeneous level.

3.2.3. Cost-benefit analysis

For all sectors, except the broiler sector, all vaccination protocols tested (immunity level > 60 %) were efficient (BCR > 1) (Table 4). For layer and turkey sector, vaccination protocol including hatchery vaccination of all day old birds (P 7) was the most efficient. For duck and guinea fowl sector, all protocols tested were equivalent in terms of cost-benefit. For broiler sector, none of the tested vaccination protocols was efficient (BCR < 1) but the protocol including hatchery vaccination of all day-old birds was the one with the highest ratio (Table 4). The break-even analysis showed that vaccination is efficient for short lifespan birds (i.e. broilers) when the cumulated incidence is high, while vaccination can be efficient even when the cumulated incidence is low for long lifespan birds (i.e. layer, turkey and duck). Hatchery vaccination ensure a positive BCR at a lower cumulated incidence than farm vaccination. The results of the sensitivity analysis are presented in Supplementary file 5.

3.2.4. Conclusion on the most efficient vaccination protocol for each sector

The vaccination protocol including hatchery vaccination for all day-old birds was considered as the most efficient protocol for broiler, layer and turkey sectors (Table 5). Both vaccination protocols including farm vaccination in all integrated farms (P5) and all farms (P6) were efficient protocols for duck and guinea fowl sectors.

3.3. Evaluation of vaccination strategies at the national level

Vaccination strategies tested at the national poultry production level combined the most efficient vaccination protocols identified for each individual sector with the risk level of each production type (free-range and/or long production life) (Tables 2 and 5). For broiler, layer and turkey sectors, the selected vaccination protocol was hatchery vaccination applied in all hatcheries. For duck and guinea fowl sectors, the most realistic protocol (farm vaccination in all integrated farms, P5) was used in the vaccination strategies 5 and 6 while the most idealistic protocol (farm vaccination in all farms, including independent ones, P6) was used in the vaccination strategy 7.

3.3.1. Immunity distribution profile

The vaccination of layer and free-range production (S 1) did not allow to reach a protective vaccination coverage and immunity level for the entire poultry population (more than 80 % and 60 % respectively) (Fig. 3, S 1). While the vaccination of all sectors except indoor broilers was not enough to reach an immunity level above 60 % (Fig. 3, S 2), the vaccination of indoor broiler production only was enough to reach this level (Fig. 3, S 3). The vaccination including at least all farms in layer, broiler and turkey sectors, without duck and guinea fowl sectors, was sufficient to reach a national vaccination coverage and an immunity level above 80 % of the entire poultry population (Figs. 3, S 4, 5, 6 and 7).

3.3.2. Spatial distribution of the immunity level

A protective immunity level (> 60 %) was reached in the area at

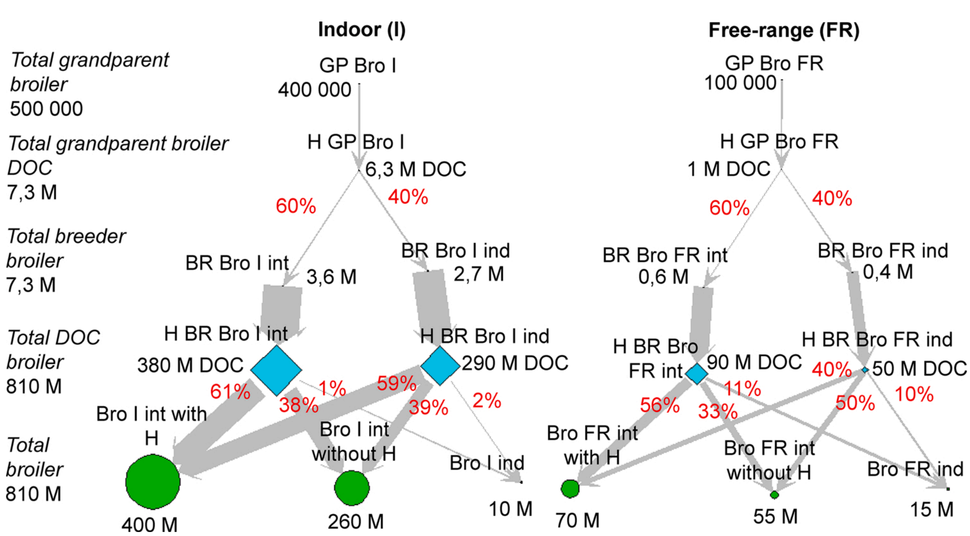

Fig. 2. French broiler production network. The type of nodes represents the different types of production (indoor (I) or free-range (FR); integrated (int) or independent (ind)): grandparents (GP) and breeders (BR) (point), hatcheries (H) (diamond), commercial broilers (Bro) (circle). (DOC: day-old chicks, M: million).

Table 4
Cost-benefit analysis of the different vaccination protocols.

Sector	Vaccination protocols [a]	Immunity level (%)	Cost		Benefit (million euro)	Benefit/cost ratio
			Vaccination cost (million euro)	Losses cost (million euro)		
Layer	P 4	80	8.5	3.1	14.5	1.2
	P 5	76	9.2	3.8	13.8	1.1
	P 6	88	10.7	2.1	15.5	1.2
	P 7	**90**	**2.5**	**1.8**	**15.8**	**3.7**
Turkey	P 4	88	4	1.8	14.9	2.6
	P 5	86	4	2	14.7	2.5
	P 6	88	4	1.9	14.8	2.5
	P 7	**90**	**2.4**	**1.7**	**15**	**3.7**
Duck	**P 5**	**82**	**6.7**	**4**	**22.2**	**2.1**
	P 6	**88**	**7.2**	**3**	**23.2**	**2.3**
Guinea fowl	**P 5**	**77**	**2.5**	**0.6**	**3.3**	**1.1**
	P 6	**88**	**2.8**	**0.4**	**3.5**	**1.1**
Broiler	P 4	87	68.2	5	38	0.5
	P 5	85	72.4	6.3	36.9	0.5
	P 6	88	74.7	5	38.2	0.5
	P 7	**90**	**42.3**	**4.3**	**38.8**	**0.8**

P 4 (broiler, layer and turkey): farm vaccination of breeders and grandparents and integrated indoor farms and hatchery vaccination of all day-old-birds for free-range production.
P 5 (all): farm vaccination in grandparent and breeder farms and in all integrated farms (indoor and free-range).
P 6 (all): farm vaccination in all farms (breeders and indoor and free-range).
P 7 (broiler, layer and turkey): farm vaccination in grandparent and breeder farms and hatchery vaccination of all day-old-birds (indoor and free-range).
[a] P: Protocol.

Table 5
List of the selected protocol per sector.

Sector	Selected protocol [a]	Justification
Broiler	P 7	Highest BCR [b]
Layer	P 7	Highest BCR
Turkey	P 7	Highest BCR
Duck	P 5 and P 6	Equivalent BCR
Guinea fowl	P 5 and P 6	Equivalent BCR

[a] P: Protocol.
[b] BCR: Benefit-cost ratio.

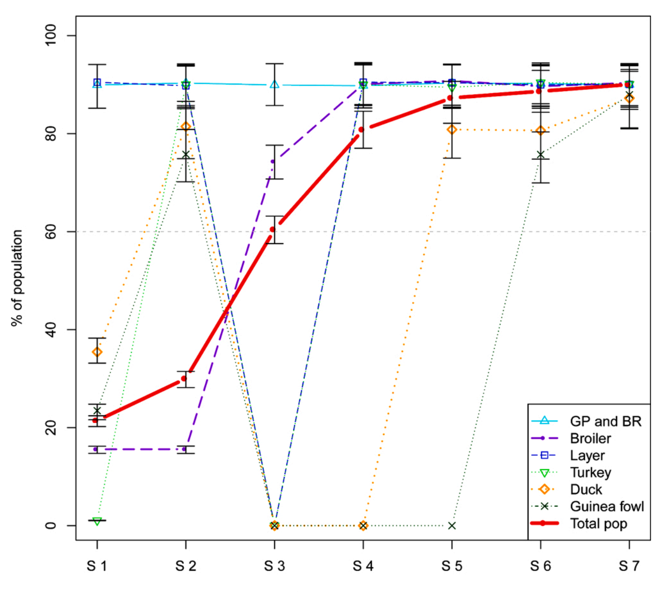

Fig. 3. Overall immunity level per production type (total population (total pop), grand-parent (GP) and breeder (BR) of all sectors, broiler, layer, turkey, duck and guinea fowl) according to the different vaccination strategies at national level (S1 to S7).

higher risk (linked to the highest population density (Shapiro and Stewart-Brown, 2009), located in West of France) when vaccination strategies included at least layers, broilers and turkeys sectors (indoor and free-range productions included) (Figs. 4, S4–S7). Vaccination strategies also including at least integrated duck farms led to a very good immunity level (> 80 %) that was spatially uniform at the national level (Figs. 4, S5, 6 and 7). Indeed, indoor meat poultry productions (broiler, turkey, meat duck) are localised in West of France and fattening duck production is mainly localised in South West of France while free-range productions are mainly localised in South of France. A vaccination strategy focused on high risk populations (layer production and free-range broiler, turkey, duck and guinea fowl productions) and breeders did not provide a protective immunity level (> 60 %) (Figs. 4, S 1).

3.3.3. *Cost-benefit analysis*

All tested vaccination strategies had good BCR (BCR > 1) at the disease cumulated incidence level of the previous epizootic event (2.5 %) except the strategy including only indoor broiler (Tables 6, S 3). Vaccination strategies including at least integrated duck farms (Tables 6, S 5, 6 and 7) offered the highest BCR.

4. Discussion

This study demonstrated the added value of the EVACS evaluation tool for comparing potential vaccination strategies for avian influenza (AI) in French poultry production networks. The best efficiency was obtained with vaccination strategies deploying hatchery vaccination with a recombinant vector vaccine in all species for which such vaccine is commercially available (i.e. broilers, layers and turkeys) and for the other species (i.e. ducks and guinea fowls) on-farm vaccination with a inactivated vaccine on all integrated farms. This work is the first to provide the evidence decision makers need to design a vaccination strategy against AI customized to the capacity and needs of French poultry production networks.

A vaccination strategy limited to the high-risk population (i.e. layers and free-range production in all sectors) and to breeders did not ensure protective immunity level at the sector level, except in fattening ducks, or at the whole poultry population level. Free-range production is often considered more at risk of AI than indoor production mainly because of

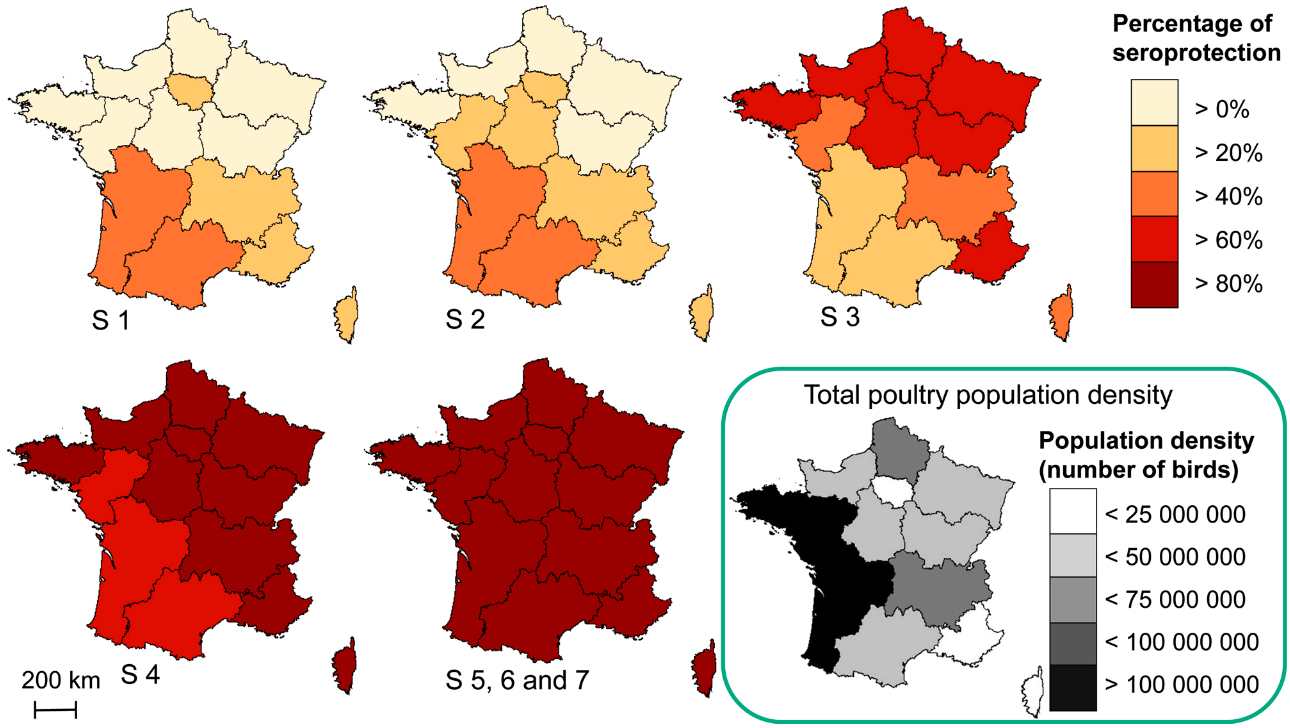

Fig. 4. Spatial distribution of the poultry population immunity against AI according to the different vaccination strategies (S) tested in the model.

Table 6
Cost-benefit analysis of the different vaccination strategies.

Vaccination strategy	Immunity level (%)	Cost		Benefit (million euro)	Benefit/cost ratio
		Vaccination cost (million euro)	Losses cost (million euro)		
S 3	60	36	53	54	0.6
S 4	81	48	23	84	1.2
S 5	86	54	14	94	1.4
S 6	89	56	12	95	1.4
S 7	90	57	11	96	1.4

S: Strategy.
For all strategies: farm vaccination of all breeder and grandparent farms.
S 3: hatchery vaccination of all indoor broiler day old chicks.
S 4: hatchery vaccination of all day old bird broilers, layers and turkeys.
S 5: S4 + farm vaccination of integrated duck farms.
S 6: S 5 + farm vaccination of integrated guinea fowl farms.
S 7: S6 + farm vaccination of independent duck and guinea fowl farms.

the higher risk of contact with infected wild birds (Elbers and Gonzales, 2019; Singh et al., 2018). Free-range production represents only 20 % of French poultry production. The fattening duck sector is the exception as the whole production is free-range at least during the grow-out stage (Delpont et al., 2018). Moreover, the risk of mutation of low-pathogenic avian influenza virus into an HPAI virus increases with the duration of the productive life of the birds. As the productive life of layers is longer than in other poultry sectors, layers are considered more at risk of inducing this mutation than other types of poultry production (Barnes et al., 2019; Singh et al., 2018). A vaccination strategy focusing on duck production sector, like the one conducted in 2006 (Capua et al., 2009), would not be sufficient to provide a protective immunity level for the whole French poultry production. If a similar choice were made in the future, vaccination of all the animals in the duck production sector would offer the highest level of immunity possible in the sector. But a vaccination protocol focusing only on integrated duck farms would be equally efficient (i.e. BCR). Previous studies recommended focusing vaccination strategies on the most at-risk population (Spackman and Pantin-Jackwood, 2014; Swayne et al., 2014). This option was implemented in some countries to prevent the introduction of the disease or to protect specific bird populations such as zoo birds (Peyre et al., 2009; Swayne et al., 2011). Nonetheless, the risk of large outbreaks is high as this strategy does not provide protective immunity level for the whole poultry population (Bouma et al., 2009; Iwami et al., 2009). Should the choice be made to target only the most at-risk population (e.g. free-range) for vaccination, strict biosecurity measures and a high level of surveillance in the other populations would be required (Peyre et al., 2009; Swayne et al., 2014).

The absence of vaccination of indoor broilers has led to a low immunity level nation-wide (<60 % of the whole poultry population), as broilers represent the largest part of birds produced in France yearly. Vaccination of short lifespan birds like broilers is rarely recommended mostly due the low price of broilers compared to the cost of vaccination (Spackman and Pantin-Jackwood, 2014). Indeed, in our study, even if the vaccination strategy including only broilers raised indoor offered a good level of immunity, this strategy was not efficient (BCR < 1). In this study, only the avoided production losses were included in the CBA. The real cost of HPAI outbreaks is often higher due to the broader impact of the disease on the poultry industry as a whole and a drop in poultry consumption, with a resulting demand shock on the price of poultry (McLeod, 2009). Moreover, trade bans would increase the impact of the disease on costs (live birds but also meat and egg products), especially when the country is a large exporting country (Wieck et al., 2012). The objective of the CBA in the EVACS tool is to compare the efficiency of different vaccination strategies to provide information on the best one to implement but not to provide an exhaustive economic analysis of the impact of the disease. As the wider impacts would be the same for any vaccination strategy, they were not included in this study. This implies that the benefit of vaccination would have been under-estimated. Anyhow, the sensitivity analysis showed that vaccination would still be efficient even if there was a drop in the price of meat or egg (up to a 70 % drop in prices for the layer and turkey sectors for a protocol using hatchery vaccination).

A vaccination protocol based on hatchery vaccination systematically provided the highest BCR compared to the same protocol based on farm vaccination in the sectors in which hatchery vaccination is available (i.e. broilers, layers and turkeys). However, the exact price of an AI vaccine to be applied in France is currently not known. Under the hypothesis used in this study, the vaccination strategies which provided the highest immunity level (S5, S6 and S7) would be efficient if the vaccination costs (including vaccine application and the number of application) were less than 2% of the value of birds. As fewer applications is are needed for recombinant hatchery vaccines than for inactivated farm vaccines (1 versus 2–5), inactivated farm vaccines would need to be cheaper than recombinant hatchery vaccines to reach an equivalent BCR. Furthermore, implementation of the vaccination is often considered as the critical aspect in reaching protective immunity level (Swayne et al., 2011). Hatchery vaccination makes it possible to reduce the number of applications thereby limiting vaccination implementation constraints and hence the impact on vaccination coverage compared to vaccination at farm level.

As AI vaccination is currently not authorised in France, no data are available on AI vaccine application in the French context. To get round the lack of information, two hypotheses were used in a context of a mandatory vaccination: 1) the vaccination coverage to be reached would be optimal and 2) the applied vaccines would be effective. Inactivated farm vaccines and recombinant hatchery vaccines were considered to have a good and comparable level of efficacy based on the literature (Table 3). As a result, the immunity level and the BCR simulated in this work were mostly differentiated by the vaccine protocol (on-farm, at the hatchery, application frequency) rather than by the type of vaccine. But, the limits of the vaccination strategy used in France in 2006 were not vaccine application but poor response in duck to the vaccine, especially when vaccinated at an early age (Capua et al., 2009). The effectiveness of current AI vaccines in duck is thus questionable (Cha et al., 2013; Pantin-Jackwood et al., 2015; Pfeiffer et al., 2010). Limited studies have been conducted in guinea fowl (Bertelsen et al., 2007). Our study shows that the vaccination strategy targeting other poultry production sectors than duck and guinea fowl (i.e. the broiler, layer and turkey sectors) was sufficient to induce protective immunity level in the whole poultry production. As the previous AI epizootic waves mainly concerned ducks farms in France, an effective vaccine is needed to protect these important production sectors in France. Promising vaccine solutions exist for ducks (Niqueux et al., 2018; Tatár-Kis et al., 2019) but the absence of a secure vaccine market does not encourage vaccine manufacturing companies to invest in vaccine registration costs. Break-even analysis showed that for long lifespan birds (i.e. layer, turkey and duck sectors), vaccination protocols were efficient (BCR > 1) even at low cumulated incidence level (up to 2% for farm vaccination protocol (P6) and to 0.5 % for hatchery vaccination protocol (P7) in the layer sector). These cumulated incidence levels are below the cumulated incidence rate observed during the 2016–2017 epizootic. For the broiler sector, the break-even analysis showed that a vaccination protocol with hatchery vaccination (P 7) or farm vaccination (P 6) would be efficient if the cumulated incidence level was above 3% or 5.5 % respectively. This was under the cumulated incidence level actually observed in the most affected area in 2016–2017 epizootic which was 15 % in the Landes administrative department (Bronner et al., 2017). The difference in cumulated incidence rates at local scale underlines the importance of regionalised vaccination, a choice made by some countries (Swayne et al., 2011).

The impact of AI vaccination on international trade, particularly on exports, would be high due to export ban. The OIE code states that if a country can prove that the exported birds are free of the disease using an effective surveillance system, the epidemiological status of the country should not be linked to a ban on exports (OIE, 2018). As exports account for a large proportion of the French poultry production revenues, this decision would be taken only in the case of extensive uncontrolled spread and with an effective vaccine. During the stakeholders' workshop implemented as part of this study, participants considered that if a vaccination policy were applied in France, it would only be deployed in the case of an emergency, with only the geographical area where the outbreaks occurred being targeted. The EVACS tool has initially been developed to compare preventive vaccination strategies and not emergency vaccination strategies. This is more relevant in countries where the disease is endemic (Peyre et al., 2016). The application of the tool in France allowed to identify some critical aspect that should be considered when defining vaccination strategies even in an emergency context. The results of our study could also be applied in the case of an emergency vaccination strategy. We have shown that vaccination of free-range production would not provide a protective level of immunity for the whole production. In the case of an HPAI outbreak in a geographically limited production sector such as the fattening duck sector, the use of vaccination in this specific sector as a complementary tool to culling and increased biosecurity is an efficient option to protect the specific production network while limiting the economic and psychological impact of culling for the farmers. If an emergency vaccination strategy was to be applied, the questions relating to management of vaccinated birds (culling or slaughter for consumption) should be clearly defined.

The vaccination of grandparents and breeders included in all strategies tested was also discussed during the stakeholders' workshop. The participants considered that these productions represent a low risk of HPAI introduction due to the high level of biosecurity on these farms. Moreover, as selection companies export the majority of their production, vaccinating their flocks would actually prevent them from exporting. Compartmentalisation is one possible option to focus vaccination policies on production stages while allowing breeding companies to continue business-as-usual (Hagenaars et al., 2018). Compartmentalisation is also recommended by the OIE for an infected country to continue exports of live birds (OIE, 2018).The development of an epidemiological model linked to the EVACS tool will make it possible to include these levels of biosecurity in the evaluation of vaccination strategies.

The effectiveness of the vaccination applied in 2006 in the duck sector could not been assessed due to the absence of outbreaks in the area where vaccination took place (Capua et al., 2009). Nonetheless, if no vaccination had been applied, the situation in France could have evolved like in Hungary, where there were 29 outbreaks of HPAI H5N1 in the duck and geese production sector (Capua et al., 2009). Interestingly, during the H5N8 epizootic wave in 2016–2017, France and Hungary were the two countries with the highest number of reported HPAI outbreaks, mainly in the duck production sector (Napp et al., 2018). Vaccination was not implemented in either country. Even if the poultry production system has increased in both countries since the 2006 H5N1 wave (FAO, 2016) and the virus strains implicated in the epizootic waves were not the same, this observation should encourage reconsidering vaccination as a valuable option combined with surveillance and other control strategies such as culling and biosecurity, to control a future epizootic. As previously highlighted by Swayne et al. "there is no one AI control solution for all countries; each AI strategy must be specific to the country and production sectors concerned" (Swayne et al., 2011). The EVACS tool is able to support decision makers in defining a vaccination strategy specific to their country and their production sectors.

5. Conclusion

In our study, we have used the EVACS tool to compare multiple national strategies based on the use of two main types of vaccination (farm versus hatchery) and targeting different production sectors. Our study has shown that vaccination of only high-risk poultry productions (free-range, layer) did not produce protective immunity level and that the vaccination strategies including the highest number of birds were the most efficient. Moreover, vaccination protocol based on hatchery vaccination with a recombinant vaccine were most efficient than the same protocol based on farm vaccination with an inactivated vaccine, for the sectors in which hatchery vaccination is available (i.e. broilers, layers and turkeys). Such approach can support decision makers to compare the expected efficiency of these strategies. At this stage, the tool provides evidence in terms of vaccination coverage, immunity level, spatial distribution of this immunity level and benefit cost ratio. Combining EVACS with an epidemiological model will add information on the expected effectiveness of the strategies tested to control HPAI. This work is the first one to provide the evidence decision makers need to design the most efficient AI vaccination strategy in France.

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Appendix A. Supplementary data

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