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Towards a better understanding of transmission determinants of avian influenza in southwest France

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"The function of education is to teach one to think intensively and critically. Intelligence plus character - that is the goal of true education."

Martin Luther King, Jr.

"I have no special talent. I am only passionately curiou.s"

Albert Einstein

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"Let us be grateful to the people who make us happy; they are the charming gardeners who make our souls blossom."

Marcel Proust

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SUMMARY

Managing sanitary crises linked to avian influenza viruses has become a crucial challenge for the long-term sustainability of the European poultry sector. In the last decade, Europe has experienced four major epizootics of the highly pathogenic avian influenza (HPAI), resulting in severe socioeconomic consequences in the poultry sector. France was one of the most impacted countries in Europe, with around 500 poultry outbreaks reported in 2016-2017. These outbreaks were primarily clustered in southwest France, a region with the country's highest concentration of duck farms. Furthermore, more than 80% of detected outbreaks were in duck farms, and they were shown to play a vital role in HPAI epidemiology.

This Ph.D. thesis aimed to provide insights on transmission determinants of highly pathogenic avian influenza in France. Using various quantitative epidemiological tools, including network analyses and mechanistic modeling, we described direct and indirect contact patterns of duck farms resulting from the exchange of live-duck, untangled the role of live-bird movements in the spread of HPAI, and finally evaluated how duck farm density contributed the dissemination of HPAI viruses in southwest France.

Using network analysis of live duck movement data (2016-2018), we first described the contact patterns between farms, including direct contacts through the exchange of live ducks and indirect contacts through transit of transport vehicles used to exchange these live ducks. We estimated that a farm epidemiologically linked with outbreak farms through these networks had a 33% probability of becoming infected. This indicates that networks resulting from these movements were efficient transmission routes for HPAI. However, their contribution to the epidemic has been limited, as highlighted by the very few transmission events that were likely due to these transmission routes, likely due to the stringent movement bans implemented to stop the epizootic. Then, we took

advantage of an individual-based model developed to evaluate the epizootic crisis in the southwest region and implemented different scenarios related to the reduction in duck farm density to help guide decision-making in the event of a new epizootic. We assessed whether a reduction in the density of duck farms in the densest communes would have improved the sector's resilience to the spread of the HPAI H5N8 subtype virus during the 2016 – 2017 epizootic. We found that the basic reproduction number would remain higher than one in large parts of the southwest region, even with a strong reduction of duck farm density. Based on these results, strategies focused only on reducing the commune density of duck farms would be insufficient to eliminate the risk of avian influenza propagation. However, the combination of the reduction in duck farm density and the implementation of the control measures that were in place during the 2016 – 2017 epizootic would have halved the final size of the epizootic.

Despite the potential biases discussed, this Ph.D. presents some insights on transmission routes and how that understanding is vital in developing mechanistic models. Considering these results, we encourage 1) the further investigation of farm contact patterns to decipher their impact in avian influenza transmission, 2) the exploration of alternative structural changes of the poultry production system to improve its resilience to HPAI threats, and 3) the development of analytical pipelines to provide real-time support to policy-makers.

Keywords: epidemiology, infectious diseases, avian influenza, modeling, network analysis, transmission route, management

RÉSUMÉ

La gestion des crises sanitaires liées aux virus de l'influenza aviaire est devenue un défi crucial pour la viabilité à long terme du secteur avicole européen. Au cours de la dernière décennie, l'Europe a connu quatre épizooties majeures d'influenza aviaire hautement pathogène (IAHP), entraînant de graves conséquences socio-économiques dans le secteur de la volaille. La France a été l'un des pays les plus impactés en Europe, avec environ 500 foyers aviaires déclarés en 2016 – 2017 et en 2020-2021. Ces foyers étaient principalement regroupés dans le sud-ouest de la France, une région où se trouve la plus forte concentration d'élevages de canards du pays. En outre, plus de 80 % des foyers détectés concernaient des élevages de canards, et il a été démontré qu'ils jouaient un rôle essentiel dans l'épidémiologie de l'IAHP.

Cette thèse de doctorat visait à fournir des indices sur les déterminants de la transmission de l'influenza aviaire hautement pathogène en France. En utilisant divers outils épidémiologiques quantitatifs, y compris des analyses de réseau et des modèles mécanistes, nous avons décrit les schémas de contact direct et indirect des élevages de canards résultant de l'échange de canards vivants, déchiffré le rôle des mouvements d'oiseaux vivants dans la propagation de l'IAHP, et enfin évalué comment la densité des élevages de canards a contribué à la dissémination des virus de l'IAHP dans le sud-ouest de la France.

En utilisant une analyse de réseau des données sur les mouvements de canards vivants (2016 – 2018), nous avons d'abord décrit les patrons de contact entre les fermes, prenant en compte les contacts directs par l'échange de canards vivants et les contacts indirects par le transit des véhicules de transport utilisés pour échanger ces canards vivants. Nous avons estimé qu'une ferme liée épidémiologiquement à un foyer épidémique à travers ces réseaux avait une probabilité de 33 % d'être infectée. Cela indique que les réseaux résultant de ces mouvements étaient des voies de

transmission efficaces de l'IAHP. Cependant, leur contribution à l'épizootie a été limitée, comme le soulignent les très rares événements de transmission dus à ces voies de transmission, vraisemblablement en raison des interdictions strictes de mouvements mises en place pour stopper l'épizootie. Ensuite, nous avons exploité un modèle mécaniste individu-centré développé pour évaluer la crise épizootique dans la région du sud-ouest et avons mis en œuvre différents scénarios liés à la réduction de la densité des élevages de canards pour aider à guider la prise de décision en cas de nouvelle épizootie. Nous avons évalué si une réduction de la densité des élevages de canards dans les communes les plus denses aurait amélioré la résilience du secteur face à la propagation du virus IAHP de sous-type H5N8 pendant l'épizootie de 2016 – 2017. Nous avons constaté que l'indice de reproduction de base resterait supérieur à un dans de grandes parties de la région sud-ouest, même avec une forte réduction de la densité des élevages de canards. Sur la base de ces résultats, les stratégies axées uniquement sur la réduction de la densité communale des élevages de canards seraient insuffisantes pour éliminer le risque de propagation de la grippe aviaire. Cependant, la combinaison de la réduction de la densité des élevages de canards et de la mise en œuvre des mesures de contrôle qui étaient en place pendant l'épizootie de 2016 – 2017 aurait permis de réduire de moitié la taille finale de l'épizootie.

En dépit des biais potentiels qu'on a discutés, cette thèse de doctorat améliore notre compréhension des voies de transmission. Au vu de ces résultats, nous encourageons 1) la poursuite de l'étude des schémas de contact dans les élevages afin de déchiffrer leur impact sur la transmission de la grippe aviaire, 2) l'exploration de changements structurels alternatifs du système de production avicole afin d'améliorer sa résilience aux menaces de l'IAHP, et 3) le développement de pipelines analytiques afin de fournir un soutien en temps réel aux décideurs politiques.

Mots clés : épidémiologie, maladies infectieuses, grippe aviaire, modélisation, analyse de réseau, voie de transmission, gestion.

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LIST OF ABBREVIATIONS

AI: Avian Influenza

AIN: Animal Introduction Network

CIFOG: Comité Interprofessionel des professionels à Foie Gras

DGAl: Direction Générale de l'Alimentation

EFSA: European Food Safety Agency

ESA: Epidemiosurveillance en Santé Animale platforme

EU: European Union

FAO: Food and Agricultural Organization

HPAI: Highly Pathogenic Avian Influenza

IBM: Individual-Based Model

LPAI: Low Pathogenic Avian Influenza

MBM: Metapopulation-Based Model

OIE: World Organization for Animal Health

STN: specific transit network

TN: Transit network

US FAS: United States Foreign Agricultural Services

PREAMBLE

Avian influenza is a viral infectious disease that causes economic and public health issues worldwide. Since 2015, Europe has experienced four major epizootics of highly pathogenic avian influenza (HPAI) caused by the H5N8 subtype. France was one of the most impacted countries in Europe, with around 500 poultry outbreaks reported in 2016-2017 and 2020-2021. These outbreaks were mostly clustered in southwest France, a region that is the world's leading producer of fattening ducks. With the increased occurrence of HPAI epizootics, managing sanitary crises has become a major challenge for the French poultry sector's long-term security. To design prevention and control measures that limit the impact of HPAI epizootics, it is vital that our understanding of transmission determinants be improved.

Most studies of HPAI epizootics have focused on Asian countries, which have been mainly affected by a zoonotic subtype of avian influenza (H5N1). Several of these studies, conducted to gain a better understanding of the risk factors and determinants of avian influenza, have shown that poultry systems and farming activities (wetlands used for double-crop rice production, free-grazing ducks fed year-round in rice paddies, live bird markets, etc.) present major risk factors for HPAI introduction and spread. However, poultry systems in Europe differ from their Asian counterparts in significant ways (e.g., specialized farms, no access to rice paddies, nor the use of live bird markets). In France, duck farms and associated activities are known to play a key role in the epidemiology of HPAI. Although much progress has been made, a comprehensive understanding of transmission routes remains elusive, hindering the implementation of effective mitigation measures that would limit the impact of HPAI epizootics.

To help fill the gap, this Ph.D. thesis aimed to understand better HPAI determinants related to duck production and provide evidence-based recommendations to improve mitigation strategies and

increase the resilience of the poultry sector against avian influenza epizootics. In the first part, we review the state of the art of HPAI research, present the main epidemiological characteristics of avian influenza, describe the most notable mitigation strategies currently enforced, provide a brief overview of the economic impacts of avian influenza epizootics, summarize the contribution of modeling to understanding avian influenza epizootics, evaluate mitigation strategies, identify remaining knowledge gaps, and describe the epidemiological context of HPAI in France. In the second part, considering the epidemiological context of HPAI spread in France, we analyze data on live duck movements and the transport vehicles involved. We build two networks to untangle the roles that direct (live duck movements) and indirect (mainly the transit of vehicles used to move live ducks between-farm the different stages of production) contacts may have played in the spread of the HPAI virus during the 2016 – 2017 H5N8 epizootic. In the third part, we study the resilience of the poultry system to HPAI virus introduction by assessing how the commune-level density of duck farms could impact HPAI transmission in the southwest region. Finally, in the overall discussion, we focus on the insights gained on transmission routes and how this understanding is vital for developing mechanistic models. We also discuss the remaining challenges that impede the construction of real-time modeling of HPAI epizootics and propose some perspectives for future research and policy recommendations to complement existing mitigation strategies.

CHAPTER 1: GENERAL INTRODUCTION ON AVIAN INFLUENZA

This chapter reviews avian influenza research's state of the art and presents the scope and scientific approaches used during this Ph.D. thesis. In the first part, we present general epidemiological considerations concerning avian influenza, describe its vast host range, present a brief global history of major avian influenza epizootics, and identify the most notable transmission routes. We also briefly describe the mitigation strategies used and the economic impacts of an epizootic. We then review the literature on mechanistic approaches used to study avian influenza epizootics and summarize the contributions of these mechanistic models to the field of epidemiology. In the second part, we provide a brief description of the epidemiological context of avian influenza epizootics in France, focusing in particular on the 2016-2017 epizootic caused by the highly pathogenic avian influenza subtype H5N8, summarize the mitigation strategies that were implemented to contain the epizootic, and briefly describe the economic impact in France.

I.1. General epidemiological considerations

Avian influenza, or *Influenzavirus A* (AI), is a highly contagious viral disease caused by RNA viruses of the family *Orthomyxoviridae*. This family comprises seven different genera: *Influenzavirus A, Influenzavirus B, Influenzavirus C, Influenzavirus D, Thogotovirus*, *Quaranjavirus* (tick-borne viruses that occasionally infect mammals), and *Isavirus,* the virus responsible for infectious salmon anemia (International Committee on Taxonomy of Viruses, 2010). Unlike the other genera of the *Orthomyxoviridae* family, which have more restricted host ranges, the AI genus affects many avian and mammal species (Fig. I.1 (OIE, 2018)). AI viruses are further divided into subtypes based on the antigenic relationships of two surface proteins: hemagglutinin (16 subtypes numbered from H1 to H16) and neuraminidase (9 subtypes numbered from N1 to N9) (Swayne, 2009; Wahlgren, 2011; Long et al., 2019). The combination of the two surface proteins constitutes the name of the subtype. The majority of the subtypes have been isolated in avian species. The recent discovery of two subtypes (H17N10 and H18N11) in multiple bat species suggests that there may be more subtypes that have not yet been isolated (Tong et al., 2013; Rejmanek et al., 2015; CDC, 2019).

I.1.1. Host range, subtypes, and clinical signs

Waterfowl (including ducks, geese, swans, gulls, waders) are known to be the natural host of AI viruses (Alexander, 2007; Krammer et al., 2018), which also can circulate in other birds and many animals, including humans (Fig. I.1). This characteristic is due to the ability of AI virus surface proteins to undergo genetic changes through two phenomena, antigenic drift, and shift. While antigenic drift in AI viruses arises from mutations (deletion, insertion, or substitution of nucleotides) in the surface proteins, antigenic shift arises from the reassortment of genes coding for the surface proteins when two AI viruses infect the same cell (Alexander, 2007; Wahlgren, 2011; Swayne,

2020). In some cases, the newly acquired genetic information, the novel AI virus can then infect and replicate in new hosts that were previously immunologically naive. It is worth noting that isolating AI viruses from a species does not imply that the particular species is a natural host. As pointed out by Long et al. (2019), newly acquired viruses only become endemic in a different species after genetic changes that allow the adaptation of the virus to its new host and support efficient replication and transmission.

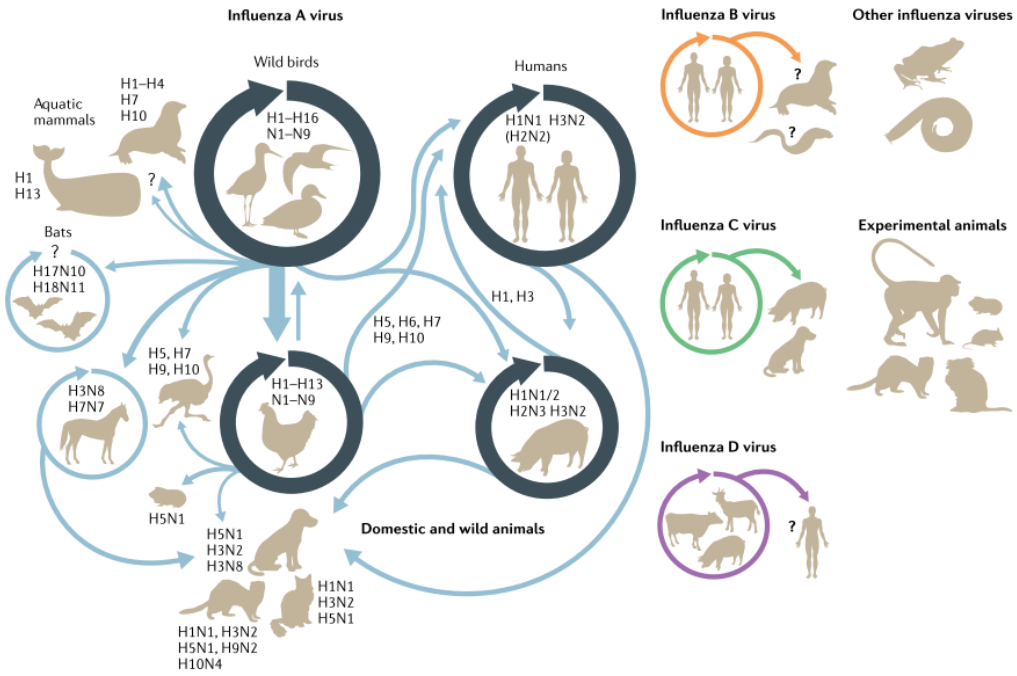

Fig. I.1. Host range of influenza viruses (Long et al., (2019)).

Host specificity has been observed in some AI subtypes. One example is gull H13 influenza viruses' inability to efficiently replicate in ducks (Munster and Fouchier, 2009). Adaptation to transmission in new hosts is usually multifactorial and could involve molecular modifications (amino acid substitution), environmental factors (temperature, pH), and overcoming species restriction (Long et al., 2019). Furthermore, H16 subtypes were recently described in Black-headed Gulls in Sweden and were related to the H13 subtype. The genotyping of these two subtypes has shown that they are genetically distinct from AI viruses found in other hosts, suggesting that they

have been genetically isolated for enough time to allow genetic differentiation (Olsen et al., 2006). However, it remains unclear whether some of these mutations could be acquired first by the host or if all are selected in the new host after infection.

Avian influenza viruses have been reported on every continent where competent hosts are present. To date, most AI viruses were isolated in Europe, North America, and Asia (Munster and Fouchier, 2009; Rejmanek et al., 2015; CDC, 2019). The AI viruses isolated in these regions show more diversity in terms of subtypes than elsewhere (Suarez, 2000; Rejmanek et al., 2015). However, this diversity may be due to the level of surveillance in these regions rather than real differences in prevalence. Using publicly available AI virus subtype data from 2000 to 2011, Rejmanek et al. (2015) showed a trend in the global distribution of the number of subtypes (Fig. I.2A), hosts (Fig. I.2B), and subtype diversity when bias in reporting was controlled (Fig. I.2C). They were able to show that subtype diversity was, except for Guatemala and Zambia, highest in northern countries, particularly Russia, Sweden, Norway, Ireland, Hungary, Canada, Netherlands, Switzerland, Czech Republic, Mongolia, Kazakhstan, and two southern countries, Australia and South Africa.

Avian influenza viruses can be categorized into two forms based on their pathogenicity: highly pathogenic avian influenza (HPAI) and low pathogenic avian influenza (LPAI). According to OIE, an AI virus is considered to be a HPAI virus if it kills at least 75% of susceptible 4 to 6-week-old chickens within ten days post-inoculation by intravenous route. All other viruses are considered to be LPAI. Several molecular mechanisms have been proposed to explain this difference in pathogenicity. The best documented is the insertion of basic amino acid in the cleavage site of the hemagglutinin (HA) protein, which facilitates systemic virus replication, causing an acute generalized disease in poultry (Munster and Fouchier, 2009). This explains why virus transition from low to high pathogenicity is associated with the accumulation of multiple basic amino acids at the HA cleavage site (Horimoto and Kawaoka, 1994; Alexander, 2007). To date, only H5 and H7

subtypes have been shown to cause HPAI in susceptible species. However, not all H5 and H7 subtypes are considered to be HPAI (Alexander, 2007; Peiris et al., 2007). That is why the OIE recommends that all H5 and H7 viruses of low pathogenicity in chickens must be sequenced to determine if the cleavage site sequence is similar to that observed for HPAI isolates.

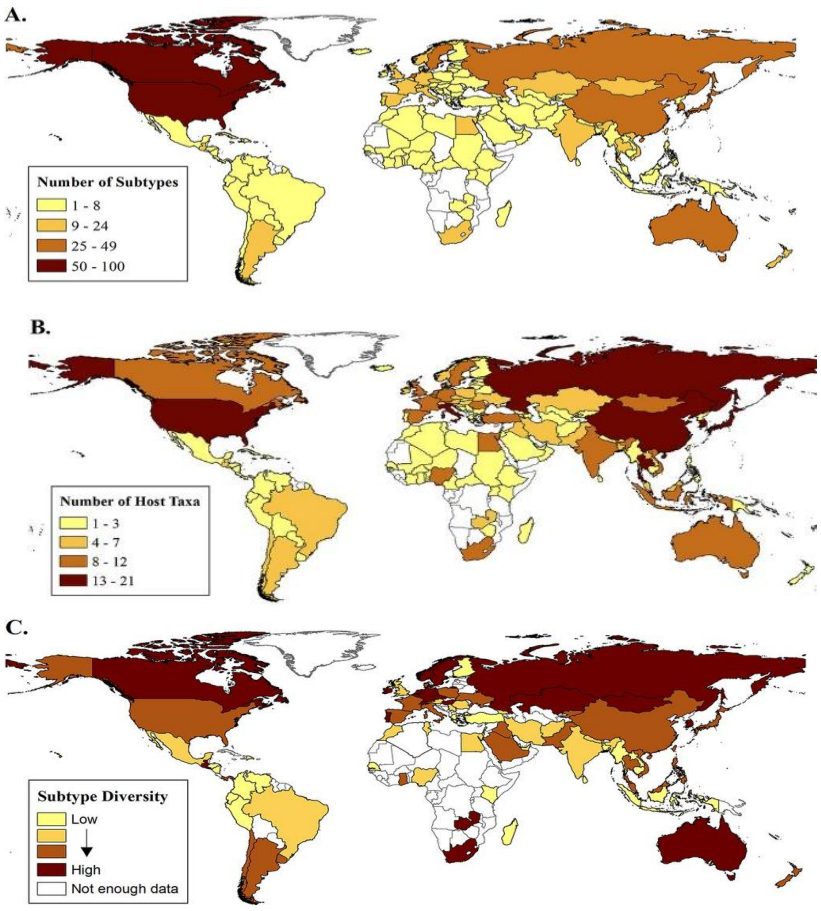

Fig. I.2. Global distribution of influenza A virus subtypes. (A) The number of unique avian influenza virus subtypes (subtype diversity) per country. (B) The number of unique avian influenza virus animal host groups with reported AI virus sequences per country. (C) Avian influenza virus subtype diversity, controlling for reporting effort. Data are presented as the log-normalized proportion of subtype diversity over the number of reported AIV strains per country. Data are based on GenBank and Influenza Resource Database (IRD) submissions as of April 2013 (Rejmanek et al. (2015)).

The clinical signs of AI infection vary widely among bird species. In wetland and aquatic birds, infection of AI (LPAI and HPAI) is generally associated with no clinical signs detected by visual inspection (Wahlgren, 2011). However, in Anseriformes (waterfowl, such as ducks, geese and

swans) and two families within the order *Charadriiformes*, the *Laridae* (gulls and terns) and *Scolopacidae* (shorebirds), AI clinical signs are common (Spickler, 2011). Experimental studies on wild birds suggest that some species can be severely affected by Asian lineage H5N1 HPAI viruses, while others may have much milder signs or shed viruses asymptomatically. For instance, the HPAI H5N1 subtype is estimated to have caused a 10% decrease in the global population of Bar-headed Geese (*Anser indicus*) during the 2005 epizootic (Olsen et al., 2006). In some other species, birds show very low susceptibility to the HPAI disease. Indeed, it has been shown on several occasions, using experimental infections, that many wild synanthropic birds (pigeons, sparrows, crows) could be readily infected with low viral doses, without exhibiting any clinical signs (Panigrahy, 1996; Yamamoto et al., 2012; Shriner et al., 2016), and required a high concentration of virus to show signs of infection and ultimately die from it (Hiono et al., 2016; Shriner et al., 2016).

In domesticated poultry, many factors influence the severity of clinical signs, including age, concurrent infections, and subtypes (LPAI or HPAI). Poultry infected with LPAI viruses generally show decreased egg production, ruffled feathers, and mild effects on the respiratory system, but do not present substantial mortality in the infected flocks. For example, while the subtype LPAI H9N2 appears to be relatively virulent and may cause significant respiratory signs in chickens and a decrease in egg production (Iqbal et al., 2013), the zoonotic subtype LPAI H7N9 subtype shows no apparent signs in affected birds (detection of the virus in poultry required testing) (Kang et al., 2015a), but could cause severe respiratory disease and fatalities in humans (Gao et al., 2013). The clinical signs of HPAI include those found with the LPAI subtype, with an increased mortality rate, apathy, reduced vocalization, marked reduction in feed and water intake, nervous signs, and diarrhea (FAO, 2009; OIE, 2018a). In acute cases, mortality can occur as early as 24 hours after the first signs of the disease, and frequently within 48 hours. In some circumstances, there are more obvious clinical signs, and deaths may be delayed for up to a week (FAO, 2009). Clinical signs are intensified

by various factors including the species, the host's immune status, the presence of any concurrent infection such as those from fowl cholera (*Pasteurella multocida*), turkey coryza (*Haemophilus gallinarum*), and colibacillosis (*Escherichia coli*), and environmental conditions. In certain host species such as Pekin ducks, some HPAI viruses do not necessarily provoke significant clinical disease (Spickler, 2011; Wahlgren, 2011; OIE, 2018a).

I.1.2. Global history of avian influenza disease

Avian influenza viruses are found throughout the world, and the highly pathogenic forms have regularly caused devastating epizootics in poultry (Webster et al., 1992; Lupiani and Reddy, 2009; Wahlgren, 2011). The earliest recorded cases of probable HPAI viruses in poultry were reported in Italy in the late 1870s, with the reports describing a contagious disease of poultry associated with high mortality[1] (Alexander, 2007; Lupiani and Reddy, 2009). By the mid-1900s, HPAI had been reported in most of Europe, Russia, North America, South America, the Middle East, Africa, and Asia (Lupiani and Reddy, 2009). Since then, AI viruses have caused several notable epizootics throughout the world. From 1955 to now, 12 epizootics have each resulted in the culling of over one million birds. Perhaps the more alarming is the increasing frequencies of these epizootics (three of the 12 epizootics occurred in the last six years) and the number of affected countries. In Table I-1, we synthesize the most notable epizootics that have been reported in poultry since 1983 (Alexander, 2007; Lupiani and Reddy, 2009; Swayne, 2020), causing important public health and economic consequences.

[1]At the time, no clear etiological distinction was made between chicken cholera and fowl plague (as it was called at the time). It was not until 1878 that the disease caused by AI was demonstrated to be different in pathological and clinical properties from fowl cholera (Wilkinson and Waterson, 1975).

Table I-1. Epizootics of highly pathogenic avian influenza documented since 1983. The table lists HPAI outbreaks with significant spread to numerous farms, resulting in great economic losses (Alexander, 2007; Lupiani and Reddy, 2009; Swayne, 2020).

Location of epizootic	**Epizootic year**	**Subtype**	**Species affected**	**Approximate number of birds affected**
United States(Pennsylvania)	1983 – 1984	H5N2	Chicken, turkey	17 million
Ireland (Monaghan)	1983	H5N8	Turkey, chicken and ducks	307,000
Australia (Victoria)	1985	H7N7	Chicken	240,000
Mexico (Mexico, Puebla, and Queretaro)	1994 – 1995	H5N2	Chicken	Millions?
Pakistan (Karachi)	1994 – 1995 and 2004	H7N3	Chicken	Over 5 million
Australia (New South Wales)	1997	H7N4	Chicken	160,000
Asia, Europe, Africa and North America	1996 – Present	H5N1	Chicken, duck	Over 400 million
Italy (Veneto and Lombardia)	1999 – 2000	H7N1	Turkey, chickens, guinea-fowl, quail, ducks, pheasants, and ostriches	Over 12 million
Chile (Valparaiso)	2002	H7N3	Chicken, turkeys	Over 700,000
Hong Kong	2002	H5N1	Wild birds and domestic poultry	Over 3 million
Netherlands (Gelderse vallei and Limburg)	2003	H7N7	Chicken	Over 34 million
Asia, Europe, and Africa	2003 - 2007	H5N1	Chicken, duck	100s of million
Canada (Columbia)	2004	H7N3	Chicken	16s of million
North Korea	2005	H7N7	Chicken	219,000
Spain (Guadalajra)	2009	H7N7	Chicken	Over 278,640
Taiwan (Taipei, Chang-Hua, PingTun, Yunlin, and Penghu)	2012 - 2013	H5N2	Chicken	Over 100,000
Mexico (Jalisco, Aguascalientes, Guanajuanto, Tlaxcala and Puebla)	2012 - Present	H7N3	Poultry	Over 19 million
Asia, Europe, Africa and the United States	2014 –Present	H5N8 H5N2	Duck, chicken, and wild birds	Over 75 million

Since the beginning of the 21st century, two panzootic periods have been identified involving multiple subtypes of HPAI and distributed over five continents (OIE, 2018b). The first started in 2004, peaked in 2006, then progressively decreased until 2012. The second period started in 2013 and is ongoing, with maximal activities detected in 2015 and 2017 (Fig. I.3). Table I-2 shows the subtypes and the region in which they were detected during the period 2013 to 2021. Although more outbreaks were reported in the first panzootic period, the number of subtypes reported in the current panzootic is three times higher, with all regions worldwide being affected (OIE, 2018b).

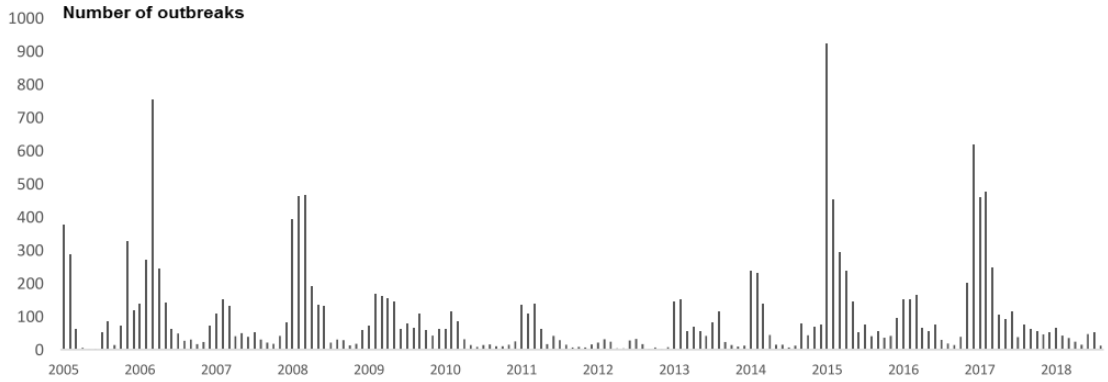

Fig. I.3. The number of outbreaks reported in domestic birds from January 1st 2005 to August 31st 2018. The number of outbreaks in domestic birds since 2005 are shown by month. Major peaks can be observed in 2006 (n=1,841), 2008 (n=1,954), 2015 (n=2,454) and 2017 (n=1,830) (OIE, (2018b)).

The presence of AI viruses in a broad host range (Fig. I.1) presents a high zoonotic risk (OIE, 2018b). The fear is that the co-circulation of AI viruses can foster opportunities for these viruses to reassort and acquire genetic materials that facilitate human-to-human transmission and cause major pandemics (Lai et al., 2016). Some of the HPAI (Table I-2) subtypes have caused sporadic infections where the AIV has spilled over from poultry to humans, resulting in numerous deaths (Table I-2) (Lai et al., 2016; Swayne, 2020; WHO, 2021). Fortunately, thus far, the risk of human-to-human transmission is considered to be low (WHO, 2021).

Table I-2. The different HPAI subtypes reported in domestic birds at the regional level from 2013 to 2021. The * indicates whether the subtype has caused zoonotic transmission in the particular region (OIE, 2018b; WHO, 2021)

Region	**Subtypes**	
	Non-zoonotic	**Zoonotic**
Africa	H5N2	H5N1*, H5N6, H5N8
Americas	H5N2, H7N8	H5N1, H5N8, H7N3, H7N9
Asia	H5N2, H5N3	H5N1*, H5N5, H5N6*, H5N8*, H7N4*, H7N9*, H9N2*, H10N3*
Europe	H5N2, H5N5, H5N9	H5N1, H5N6, H5N8*, H7N7
Oceania	H7N2	H7N7

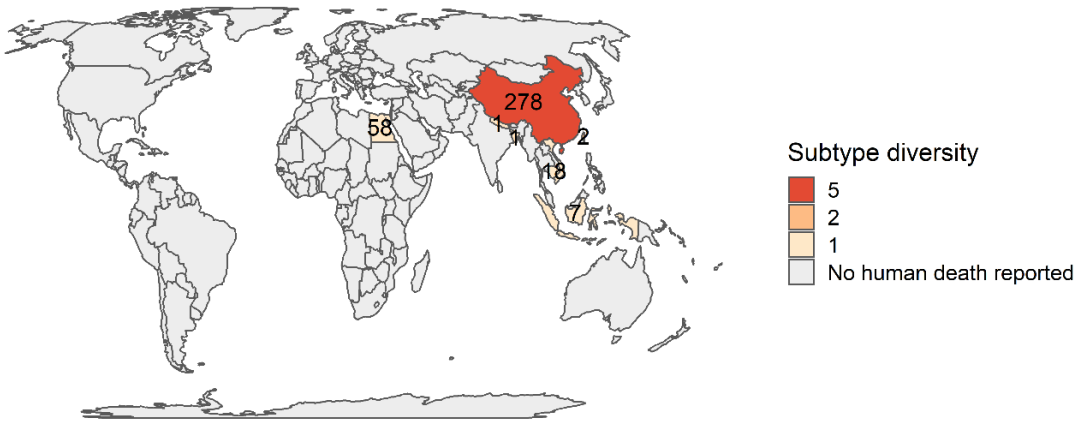

Fig. I.4. Spatial distribution of human deaths due to zoonotic transmission between 2013 to 2021. The number indicates the number of death reported, and the color indicates the number of different zoonotic subtypes reported in each region. Bangladesh (HPAI H5N1), Cambodia (HPAI H5N1), China (HPAI H5N1, HPAI H5N6, HPAI and LPAI of H7N9, and LPAI H10N8), Egypt (HPAI H5N1), Hong Kong (LPAI H7N9), Indonesia (HPAI H5N1), Nepal (HPAI H5N1), Taiwan (HPAI and LPAI H7N9), and Vietnam (HPAI H5N1). The map was created in R using data retrieved from FAO on September 14th, 2021.

The most common reported zoonotic subtype is H5N1, with the first zoonotic transmission reported in Hong Kong in 1997. During that episode, six of the 18 human cases were fatal (Shortridge, 1999). Then, between January 1st 2003 and August 2021, 127 human cases were reported in Vietnam, 56 in Cambodia, 53 in China, and three in Lao People's Democratic Republic. In total, 134 of 239 (56%) cases were fatal in the West Pacific Region (WHO, 2021). Outside this region, Egypt reported the highest number of cases (363) (Lai et al., 2016). Globally, of the 863

confirmed cases of HPAI H5N1, 456 (53%) were fatal. At present, H5N1 is endemic in Asia and in Egypt, causing periodic outbreaks in poultry (Peiris et al., 2007; Spickler, 2011; Tian et al., 2015; Lai et al., 2016).

H7N9 is the second most reported zoonotic subtype. The first human case caused by this LPAI subtype was reported in April 2013 in China (Yu et al., 2014; OIE, 2018b). The virus continues to circulate in several provinces in China. By February 2017, LPAI H7N9 had mutated into a HPAI subtype in poultry and spread to several provinces in China, where 616 of the 1,568 laboratory-confirmed human cases were fatal (WHO, 2021). After strong control measures, including vaccination programs implemented by the Chinese authorities, the number of outbreaks of H7N9 in poultry decreased and, consequently, fewer human cases were reported (OIE, 2018b).

All of the other zoonotic AI subtypes combined (H5N6, H7N4, H7N7, H9N2) accounted for approximately 189 documented human infections between 1959 and 2021, with 93 of these cases being attributed to the H7N7 Eurasian lineage reported in the Netherlands in 2003 (Fouchier et al., 2004; Alarcon et al., 2018; OIE, 2018b; Swayne, 2020; WHO, 2021).

Other subtypes of interest for animal health are H5N2, H7N3, and H5N8. They are associated with varying levels of pathogenicity in poultry and have caused significant losses in the poultry industry. HPAI H5N8 in particular has caused multiple epizootics on several continents over the past few decades. This subtype was the main causative agent of the last two major AI epizootics observed in Europe during the winters of 2016-2017 and 2020-2021 (EFSA et al., 2017, 2021). Furthermore, on 18 February 2021, WHO was notified of avian influenza A (H5N8) detected in seven asymptomatic poultry farmers from the Russian Federation. However, none of them showed signs of clinical illness during the rest of the monitored period (WHO, 2021).

Rejmanek et al. (2015) have suggested that if AI subtypes are detected in three or more animal host groups[2] within at least two different countries, these subtypes should be made a high priority for surveillance. The risk is with year-round incursion; the AI viruses might become endemic in local populations, increasing the risk of AI viruses to mutate and develop new characteristics that allow its reemergence to affect new hosts including humans.

I.1.3. Transmission routes

The transmission routes of AI depend on both the virus and the host (Spickler, 2011). This section illustrates the most notable transmission routes of AI at three scales: between birds, between farms, and between countries.

Avian influenza transmission between birds in the wild seems to be due to direct exposure to contaminated feces and respiratory secretions from infected waterfowl and shorebirds (Swayne, 2009; Spickler, 2011). Waterfowl excrete predominantly large amounts of viruses in their feces, and thus the fecal-oral route is thought to be the predominant route of transmission (Fouchier and Munster, 2009). In addition, once the virus is introduced in the environment, it can persist for several weeks or even months, particularly in water, if conditions are suitable (low temperature, low salinity, neutral pH) (Webster et al., 1992; Brown et al., 2007; Corrand et al., 2012). These environmental reservoirs may allow the local persistence of the virus from year to year, with migratory birds re-infecting on their return to their breeding grounds (Breban et al., 2009). In poultry farming systems, inter-individual AI transmission would most likely depend on the pathogenicity of the AI virus. For example, low pathogenic subtypes are usually excreted into the environment in high quantities via feces (Webster et al., 1992). This would suggest that inter-individual transmission is mainly fecal-

[2] Animal host groups used in Rejmanek et al. (2015) was defined according to taxonomical relatedness or similar ecological niches of individual species based on available taxon information associated with GenBank and IRD sequence submission data. It included human, swine domestic duck, farmed poultry see reference for the complete list Rejmanek et al. (2015).

oral via ingestion of contaminated water. The transmission of highly pathogenic viruses is different since they are mainly excreted by the respiratory route, although they can also be excreted by the fecal route (Spickler, 2011). Thus, transmission is mostly direct, from one individual to another. Moreover, the environment also constitutes a transmission route once it is contaminated via respiratory secretions or contaminated carcasses.

Between-farm transmission is believed to be human-mediated once the virus is introduced into the local environment. For HPAI viruses, most transmission events were shown to be short-ranged (less 70 km) in the Netherlands (H5N1 in 2003) and France (H5N8 in 2016-2017) (Boender et al., 2007; Guinat et al., 2020b). In France, proximity networks[3] were shown to be responsible for up to 66% of events of secondary transmission (Guinat et al., 2020b). These events were due to direct contact with infected birds, and indirect contact through contaminated materials[4] (fomites) (OIE et al., 2008; Guinat et al., 2020b; Verhagen et al., 2021). Indeed, transmission may arise from transporting contaminated materials and infected birds to and from farms. Other factors that increase transmission risk include the type of production system (with free-range practices significantly increasing the risk of coming in contact with wild birds), susceptible species on sites, and limited biosecurity measures (EFSA, 2006; Corrand et al., 2012). In countries where live-bird markets are present, they are considered to be an important element in maintaining and spreading the virus, and have been the source of infection in humans (OIE et al., 2008; Shi et al., 2020; Guinat et al., 2021b).

The global spread of avian influenza is mainly due to migratory birds, with evidence indicating that wild birds infected with HPAI viruses are responsible for long-distance transmission of HPAI outbreaks in geographically distant poultry populations (Kilpatrick et al., 2006; Olsen et al., 2006;

[3] Proximity network is based movement of ducks between farms that were infected close in time (differences in dates of suspicion were less than 14 days) and were close in space (both located within a radius of ten km of an infected farm (Guinat et al., 2020b).

[4] Several studies have shown transmission risk can arise via sharing of materials and staff or via contaminated vehicles (Soares Magalhães et al., 2010a; Gilbert and Pfeiffer, 2012; Fournie et al., 2013; Kurscheid et al., 2017; Guinat et al., 2020b; Shi et al., 2020)

Lycett et al., 2016; Russell, 2016; EFSA et al., 2017). The most probable mechanism is through the introduction of AI viruses in the Palearctic region (where migration flyways overlap) by wild birds migrating from Asia to Europe, North America, and Africa (Fig. I.5) (Olsen et al., 2006). This was observed with the global dissemination of H5N1 between 2005 and 2006: the AI viruses spread from Qinghai Lake, China, to Siberia, and then to various countries of Asia, Europe, and Africa (Olsen et al., 2006). Similarly, studies by the Global Consortium for H5N8 and Related Influenza Viruses suggest that wild birds play a major role in spreading HPAI H5N8 globally. During the migration season, migrating birds rarely fly the full distance in one flight. They make stopovers to rest along the way. Those stopover sites allow many different species to come in close contact, resulting in contamination of the local environment and infecting other local susceptible hosts (Olsen et al., 2006; Lee et al., 2015; Alarcon et al., 2018; Briand et al., 2021). This perhaps explain why in Europe outbreaks usually occur in domesticated poultry during the winter and spring season in countries with either a high density of susceptible birds or located along the pathway of migratory birds (Lycett et al., 2016, 2020).

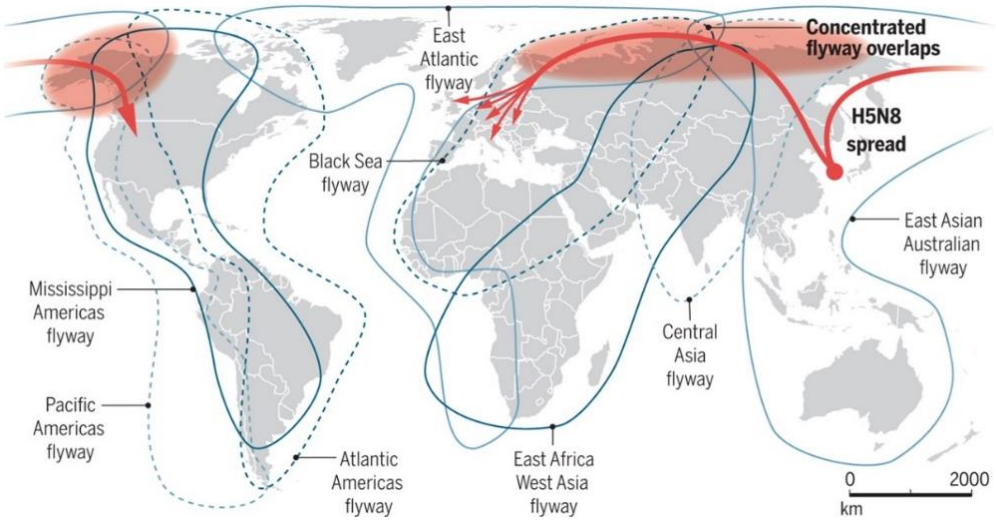

Fig. I.5. The complex overlap of flyways provides numerous opportunities for long-distance virus spread by migratory birds (Russell, 2016).

I.2. Management of avian influenza

The OIE, the Food and Agricultural Organization (FAO), and the European Commission (EU) recommend a set of minimum measures that member states can use to protect themselves from the introduction and spread of pathogens without setting up unjustified sanitary barriers (FAO, 1999; OIE, 2018c; The European Commission, 2018). They include preventive, surveillance, and intervention measures, and constitute what are hereafter referred to as mitigation strategies. These strategies are complementary and make it possible to quickly identify the risk of AI virus introduction, stop it from spreading, and establish a region's health status. Furthermore, they must be accompanied with the proper disposal of dead birds and effective cleaning and disinfection of affected areas (OIE, 2018a).

Until recently, the mandatory mitigation measures were only required for H5 and H7 subtypes, even though both are LPAI subtypes. This is due to their potential of becoming highly pathogenic (Alexander, 2007). In developed countries, the primary strategies consist of preventing the introduction of AI viruses into poultry farming systems. For example, LPAI management strategies that have been successful in the USA consist of a comprehensive plan that includes education, exposure prevention, monitoring, and reporting (Swayne, 2020). Once AI is detected in domestic and wild birds, the mitigation strategy enforced must consider the nature of the outbreak (wild birds, domestic/commercial birds and whether it can be transmitted to human), and the location (OIE, 2018c; Swayne, 2020).

I.2.1. Prevention of virus introduction: biosecurity measures

Biosecurity is defined as “the implementation of measures that reduce the risk of the introduction, persistence, and spread of disease agents through traffic control (barriers to limit the potential opportunities for infected animals and contaminated materials to enter an uninfected site)

and sanitation measures (such as downtime, cleaning, and disinfection) to and from an animal population" (OIE, 2018c). It entails adopting a set of attitudes and behaviors to reduce risks in all activities involving domestic, captive, exotic, wild birds and their products (OIE et al., 2008; Delpont et al., 2021b). Biosecurity measures can be subdivided into external biosecurity measures[5] and internal biosecurity measures[6]. Together, they prevent or limit the introduction, circulation to other disease-free zones, and persistence of AI viruses.

Biosecurity is crucial to prevent the introduction of AI viruses into poultry farms (EFSA et al., 2017; OIE, 2018a). In their assessment following the 2017 epizootic of HPAI H5N8 in Europe, the EFSA Panel on Animal Health and Welfare recommended improving external biosecurity measures, including the restriction at all times of interaction between wild bird and poultry holdings, limited access to poultry holdings by non-workers, biosecurity training for the professional staff of poultry holdings and holding-specific training for staff provided by a competent professional familiar with the particular holding (EFSA et al., 2017). Thus, efforts have been made to change the behavior of stakeholders (farmers, hunters, producers, suppliers, traders, etc.) in order to decrease the risk of disease transmission (OIE et al., 2008; Delpont, 2021). However, farmers' profiles are not homogeneous. Their attitude and knowledge of the risk affect their compliance, as has been shown in southwest France (Delpont, 2021). The poultry production sector also is not homogeneous; it is made of different species types (*e.g.* palmipeds, galliformes), farms have different sizes, and different production systems (free-range vs. indoors) (OIE et al., 2008; Guinat et al., 2020a; Delpont, 2021). Moreover, when biosecurity measures are created, flaws in their application can increase the risk of AI virus introduction (EFSA, 2006; Corrand et al., 2012; Guinat et al., 2020a). This is why

[5] Internal biosecurity includes any measures (cleaning and disinfection, delimitation between clean and unclean area, proper sanitation practices, etc.) that help to reduce the spread of pathogens within a farm (Conan et al., 2012; Delpont, 2021).

[6] External biosecurity includes the design of farm entrance, the flow of vehicles, management of dead birds and manure disposal, protection from wild birds, that are applied to prevent pathogens from entering the farm or AI-free zone (Conan et al., 2012; Delpont, 2021).

biosecurity is such an important tool, and compliance with these measures is essential to prevent and control the spread of AI viruses (EFSA et al., 2017).

I.2.2. Surveillance strategies

Surveillance is defined as "a tool to monitor disease trends, to facilitate the control of infection or infestation, to provide data for use in risk analysis, for animal or public health purposes, to substantiate the rationale for sanitary measures and for providing assurances to trading partners" (OIE, 2018c). Traditionally, epidemiological surveillance is divided into passive surveillance and active surveillance.

Passive surveillance is defined as an "observer-initiated provision of animal health related data (e.g., voluntary notification of a suspect disease) or the use of existing data for surveillance. Decisions about whether information is provided, and what information is provided from which animals is made by the data provider" (Hoinville et al., 2013). By definition, passive surveillance is a continuous surveillance, implemented by field workers, those who are closest to the farmers and therefore best able to investigate and report any health event that may lead to a suspicion of the disease (Dufour et al., 2011). In poultry, this includes the spontaneous notification of clinical manifestations of the disease, such as a sudden drop in egg production, appearance of neurological signs, or rapid increase of the mortality rate. In wild birds, passive surveillance includes dead birds being reported to the veterinary authorities that are subsequently tested for HPAI virus (EFSA et al., 2017). Indeed, this type of surveillance and monitoring of wild birds at-risk of spreading AI viruses has been required within the EU block since 2005 (The European Commission, 2018).

Decision 2018/1136/EU[7] requires EU member states to submit the results of these surveillance programs to the competent authority. This directive also includes a list of wild bird target species which is under constant review as new evidence is generated when HPAI epizootics occur in Europe (EFSA et al., 2020). A study conducted by EFSA on the surveillance practices in the EU member states and Iceland, Norway, Switzerland and the United Kingdom in 2019 showed that more than 19,661 wild birds were surveyed, including 8,926 (45%) sampled by passive surveillance, and that this surveillance has helped determine the presence/absence of AI within the EU (EFSA et al., 2020). Despite the logistical challenges associated with maintaining effective surveillance in migratory wildlife, it is instrumental. It can provide an early warning of virus incursion, generate a better understanding of the ecology and epidemiology of AI viruses circulating and give a health status of the wildlife in the area.

Active surveillance is defined as an "investigator-initiated collection of animal health related data using a defined protocol to perform actions that are scheduled in advance. Decisions about whether information is collected, and what information should be collected from which animals is made by the investigator" (Dufour et al., 2011; Hoinville et al., 2013). Active surveillance usually consists of multiple components that are based on the objective of the surveillance. Hoinville et al. (2013) and Dufour et al. (2011) provide an overview of each component. According to EU legislation, member states are also required to have annual serological surveillance in their active surveillance programs of domesticated poultry (The European Commission, 2018). The programs are based on serosurveillance with virological analysis of seropositive results. Serosurveillance detects prior exposure to HPAI viruses and the presence of subtypes in circulation. Thus, active surveillance is particularly useful in determining the risk associated with susceptible hosts based on

[7] Guidelines for the implementation of the surveillance programs in wild birds https://eur-lex.europa.eu/legal-content/FR/ALL/?uri=CELEX%3A (accessed on 06/10/2021)

their location, proximity to waterbodies (EFSA et al., 2017), production type/biosecurity level (Kang et al., 2015b; Biswas et al., 2017; Mellor et al., 2018), trade, and the timing of sampling (Turner et al., 2017; Guinat et al., 2021b), and provides reassurance to trading partners that disease is no longer circulating in poultry populations.

The relevance of the two above surveillance approaches depends on the virulence of the subtype in circulation. In particular, passive surveillance is highly sensitive in detecting HPAI in poultry systems as domesticated species are particularly susceptible to HPAI and the disease can result in rapid high mortality within 36 – 48 hours post infection (Spackman, 2008; OIE, 2018a). In contrast, the detection of LPAI in Anseriformes populations is very difficult unless clinical signs are exacerbated by coexisting diseases on the farm (EFSA et al., 2017). Passive surveillance has been complemented with "testing to exclude[8]" notifiable avian diseases. Indeed, this would increase the surveillance and early detection of notifiable LPAI and allow the rapid implementation of other stringent measures (enhanced surveillance and/or intervention measures) following a confirmation test. However, testing to exclude is not covered by existing EU legislation (it is done on a voluntary basis), and the cost is usually left to the producers (EFSA et al., 2017).

I.2.3. Intervention strategies

Once an AI virus is detected on a farm, quick interventions are necessary to limit and control the virus' spread. These interventions include culling, zoning and vaccination programs. In addition to the previously stated measures, under EU legislation European countries are obliged to enhance biosecurity and implement surveillance measures, including contact tracing, whenever an outbreak of HPAI is detected (The European Commission, 2019).

[8] Testing to exclude is a surveillance component that supplements existing passive surveillance of notifiable monitoring. It enables a veterinary service to transmit samples to either private or public laboratories to rule out the presence of notifiable avian illness (without informing the appropriate authorities) although it considers the disease is very low on their differential diagnosis list (EFSA et al., 2017).

Culling can be used both as a reactive or preventive measure. As a reactive measure, culling is used to eradicate the outbreak by stamping out birds in farms where AI virus circulation has been confirmed (based on virological and/or clinical signs) (OIE, 2018c). As a preventive measure, culling is applied within a radius of an outbreak to decrease the number of susceptible hosts in an affected area and consequently decrease the risk of the spread of AI viruses from affected farms to susceptible farms as well as in farms where AI virus circulation is suspected, based on contact tracing information.

Culling remains the strategy of choice to eliminate the AI viruses in developed countries (see the subsection Contribution of mechanistic modeling in avian influenza epizootic). However, in developing countries such as Vietnam, Egypt, and Mexico, where some AI subtypes have become endemic, virus elimination through culling is not viable, in part due to the structure of the poultry industry. In Vietnam, for example, although over 45 million poultry were culled in 2004, the subtype causing the outbreak (H5N1) was not successfully eliminated. The massive culling of birds to eliminate the AI viruses H5N2 LPAI and H7N3 HPAI in Mexico, and H9N2 LPAI in many Asian, northern Africa and the Middle East countries, has likewise been unsuccessful (Swayne, 2020).

There is no doubt that culling has been useful in halting virus spread. However, due to the destruction of great numbers of non-infected birds to control epizootics, culling raises concerns about sustainability, social-ethical issues and animal welfare (Cohen et al., 2007). Indeed, the psychological and economic impacts of such measures are substantial (CIFOG, 2017). Consequently, there is increasing interest in finding alternative mitigation measures that would limit such losses and help halt the spread of the AI viruses.

Zoning is another intervention strategy that is usually used to combat the spread of AI viruses. It consists of dividing a country into geographical regions, enabling the drawing of infected and infection-free zones during crises in which the movement of susceptible host and repopulation of

farms are restricted (Hagenaars et al., 2018; The European Commission, 2019). This zoning includes protection and surveillance zones (Fig. I.6). A protection zone is set around an outbreak with a minimum radius of 3 km for a minimum duration of 21 days as a means to prevent the disease from spreading outside this zone. A surveillance or containment zone is set around the protection zone with a minimum radius of 10 km for a minimum duration of 30 days as a means to prevent the spread of the disease from the protection zone to the rest of the country (OIE, 2018c; The European Commission, 2019). In general, these zonings allow the enforcement of mitigation measures to quickly eradicate the AI virus.

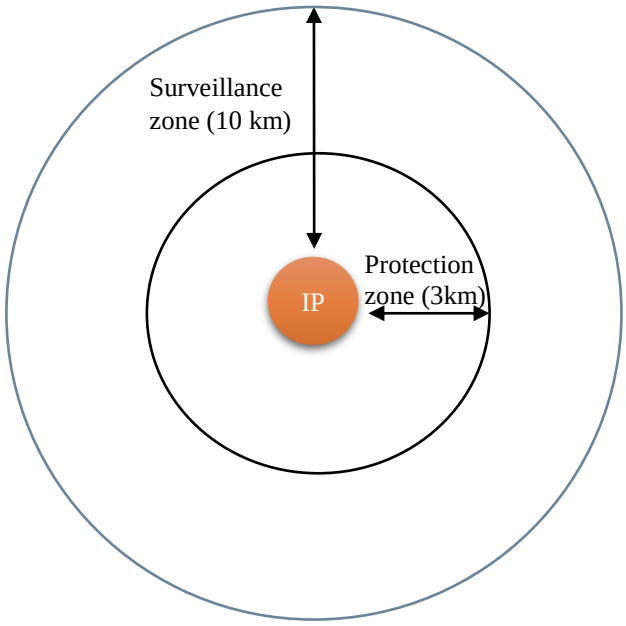

Fig. I.6. Graphical description of zoning measures. It shows the establishment of protective and surveillance zone around an outbreak.

The vaccination of susceptible birds within a short radius around infected farms is sometimes applied to decrease the number of susceptible hosts during an epizootic. The first use of vaccination in AI eradication programs was against LPAI H5/H7 in the 1970s in the USA (OIE, 2018a). In the 1990s, it was used with mixed success in Mexico and Pakistan against both LPAI and HPAI subtypes. In Mexico, the HPAI subtype was eradicated. However, the LPAI H5N2 subtype

continued to circulate. In contrast, in Pakistan, the HPAI H7N3 subtype continued to be detected as late as 2004 (OIE, 2018a), which raised concerns over silent transmission after vaccination and not differentiating between vaccinated and infected poultry (Van Der Goot et al., 2005). To overcome this problem, the DIVA[9] strategy has been proposed as a solution to eradicate HPAI and H5/H7 LPAI (OIE, 2018a). Several vaccines have been developed to combat H5 and H7 influenza viruses in poultry. The use of vaccination in combination with culling has helped to bring under control epizootics caused by AI viruses in Egypt (Kilany et al., 2015) and some Asian countries (Soares Magalhães et al., 2010b; Sun et al., 2017).

In Europe, H5 and H7 vaccines were practiced in parts of Italy to prevent LPAI H5/H7 in the early 2000s (Peyre et al., 2009) and in France in 2006 against H5N1 (Capua and Marangon, 2007). However, at the moment, vaccination campaigns are rarely used as part of the EU's mitigation strategies mainly due to the concern over silent transmission and the potential of masking disease outbreaks, thereby delaying detection and increasing the risk of virus spread.

Other intervention measures include movement bans and trade restrictions. They aim to limit AI virus introduction in disease-free farms and countries. According to the OIE, the importation of eggs must be made from AI-free zones (OIE, 2018c). In countries with live bird markets, closure, cleaning and disinfection have shown promise in decreasing the risk of transmission (Fournié et al., 2011; Yu et al., 2014; Teng et al., 2018; Chen et al., 2020). In EU member states, the implementation of movement restrictions of susceptible animals and the restriction of all non-essential movements from and to outbreak farms are required (The European Commission, 2019). The movement bans and restrictions are usually confined to a certain distance from affected farms (e.g., 10 km radius) to

[9] DIVA stands for differentiation of infected from vaccinated animals (DIVA). This strategy has the benefits of reducing the level of virus in the environment (reduce bird shedding), and also has the ability to identify infected flocks. In the event of detecting AI in vaccinated flock, it would still allow the implementation of additional control measures, including culling (OIE, 2018a)

limit unnecessary burden. In France, virological screening is required before birds are moved over long distances (more than 20 km) from breeding to fattening farms when the risk of HPAI is considered high due to the confirmed circulation of HPAI in wild birds or current or recent circulation of the virus on the farm (DGAL, 2017a).

I.3. Economic Impact of Avian Influenza

The growing number of AI epizootics observed in recent years has had public health and economic consequences. As demand for poultry products is growing in both developing and developed countries, these increasingly frequent AI outbreaks represent costly production losses and threaten the livelihoods of vulnerable people. That is why, in December 2005, to better prepare for the occurrence of AI, the EU Commission hosted an international conference on AI with the World Bank and the People's Republic of China. One of the outcomes of the conference was a pledge by the international community of €1.57 billion to fight AI viruses and prepare for a possible pandemic (The European Commission, 2021). In the Europe block, the European Commission anticipated an additional investment for the Community budget of approximately €3-8 million per year per member state for surveillance and culling measures (The European Commission, 2005).

The overall impact of an AI epizootic undeniably depends on the pathogenicity of the subtype circulating, the number of affected farms, and the duration of the epizootic. A diagram inspired by Knight-Jones et al. (2013) is presented below to illustrate the economic impact of AI epizootics (Fig. I.7). The items listed are not exhaustive as publicly updated information related to the cost of managing AI epizootics are scarce.

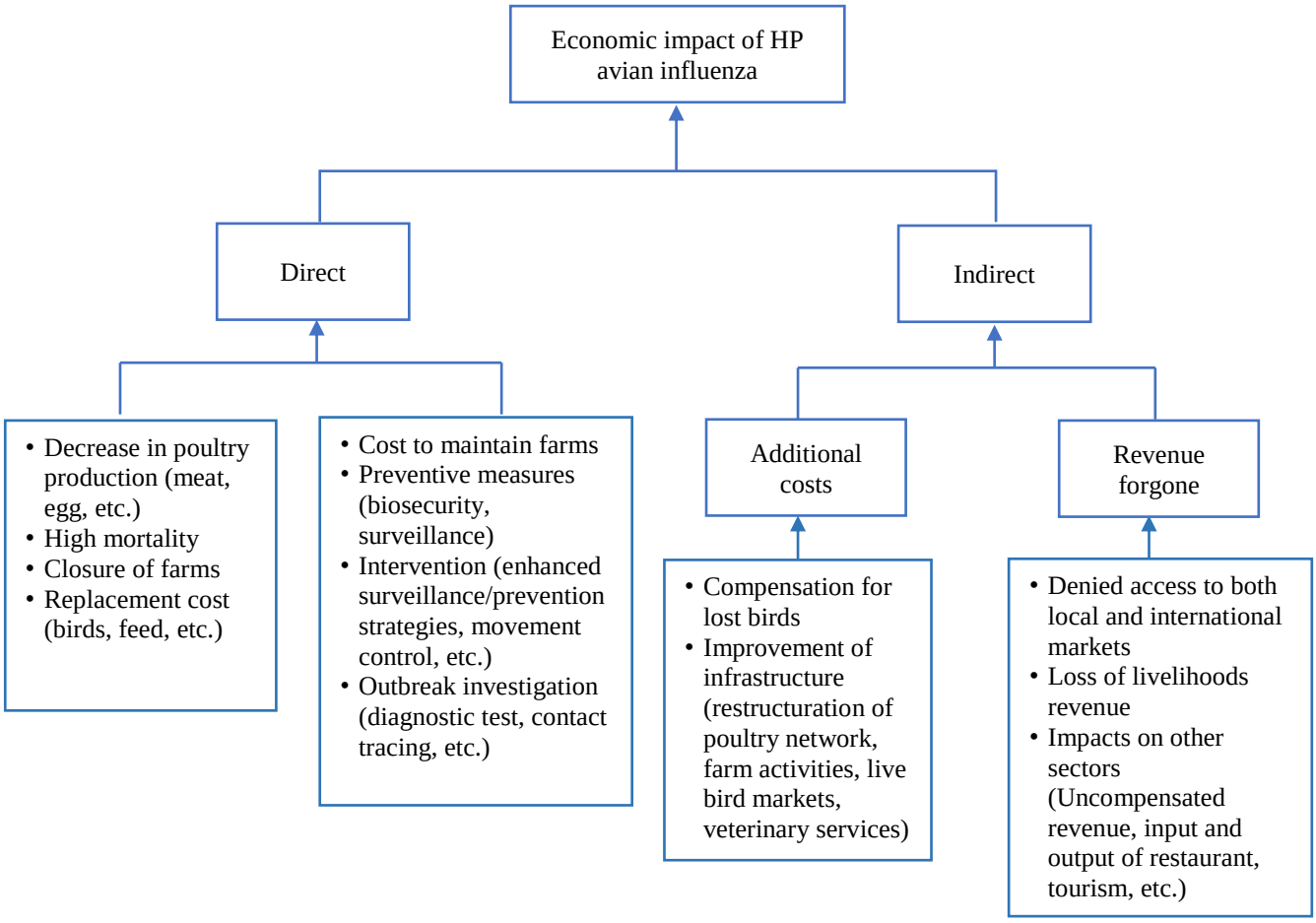

Fig. I.7. Economic impacts of avian influenza.

I.3.1. Direct impact

The direct impacts of AI outbreaks originate from losses resulting from the disease and mitigation measures implemented to end the epizootic. This includes (and is not limited to) the decrease in the production of poultry products due to dead birds, affecting all those relying on this industry (upstream and downstream sectors) and the losses from the culling of birds and disposal costs, high morbidity and mortality losses, cleaning and disinfection, surveillance costs, and indemnities paid to poultry farmers (Gashaw, 2020). OIE estimated that between 2013-2018, more than 122 million birds were culled around the world as a response to control AI epizootics (OIE, 2018b). This number was estimated to be eight to fifteen million in Europe alone, which might be an under-estimation (Alarcon et al., 2018). In Vietnam, for example, during the 2004-2005 epizootic,

44 million birds were culled, amounting to approximately 17.5% of the poultry population (Gashaw, 2020). In the United States, the direct cost of the 2015 HPAI H5N2 outbreak was estimated at USD 850 million and destroyed over 50 million poultry (Swayne et al., 2017). These losses undeniably impacted the livelihood of both upstream and downstream stakeholders.

The direct impact of LPAI (reduction in egg production, surveillance and prevention measures, etc.) can also be substantial. Furthermore, the cost is likely to skyrocket if the circulating AI subtype can affect humans. This was demonstrated by a case study conducted between February – May 2013 in China where the LPAI H7N9 subtype caused losses to the poultry industry estimated to be in the upper USD 1.5 billion, and close to USD 6 million in medical cost (Stamoulis, 2017), with a heavy impact on both the private and public sectors.

I.3.2. Indirect impact

The indirect impact of AI can be further divided into two groups, namely additional costs associated with structural or management changes following an epizootic, and revenue foregone linked to loss of revenue resulting from uncompensated losses and those associated with limited to no access to local and international markets.

Indirect impact due to revenue foregone can be considerable (escalating the impact of the AI losses by 5 to 10 fold) due to access to local and international markets being denied (Gashaw, 2020). Moreover, the lack of poultry products (due to dead birds) can result in loss of market share and higher prices for consumers. Developing countries that are highly dependent on the poultry industry are at a great disadvantage and often struggle to recover. In southeast Asia, model estimates suggest that a single large epizootic could result in a reduction of up to 1.5% of GDP growth. This is due to the impact of the epizootic that would likely spread from the poultry sector (as many stakeholders would be affected) to affect other industries such as tourism (Mcleod et al., 2005). In the US, a 26%

decrease in broiler exports was observed in 2015 (USD 1.1 billion lower than in 2014); other poultry products (eggs, turkey meat, etc.) showed a similar decline (Ramos et al., 2017) [10].

I.4. Modeling in highly pathogenic avian influenza studies

Following encounters with diseases such as the 2001 foot-and-mouth disease epizootic in the UK, the SARS outbreak in 2003, the HPAI H5N1 epizootic in 2005, the 2009 influenza pandemic, Ebola, and more recently the Covid-19 pandemic, research is needed to identify which optimized mitigation measures would reduce the impact of an epizootic and stop disease spread. Mathematical models have provided powerful insights into how we can track the evolution of outbreaks, predict the pathway of disease transmission, and anticipate and adjust relevant mitigation measures to better control and prevent infectious diseases (Kao, 2002; Mathews et al., 2007; Lanzas and Chen, 2015; Knock et al., 2021). Furthermore, modeling has become a sub-discipline within epidemiology. Its development has benefited from advances in computing power, availability of data, and methodological approaches. The mathematical model paradigms that have been used in animal health, and how these models have contributed to the understanding of AI, are described below.

I.4.1. Definition and type

Mathematical models are defined as refined and precise descriptions of a system using algebraic formulae. Logical analyses are usually taken to ensure that the systems' most important features are taken into account. These logical steps are crucial as they are key to determining whether the output of a model can provide a realistic representation of "the real world" (Box, 1976; Vynnycky and White, 2010). Two approaches can be used to develop such models, one statistical (including eco-epidemiology, regression), the other mechanistic. For instance, statistical approaches focus on

[10] The 2014-2015 outbreak of highly pathogenic avian influenza (HPAI) was the largest poultry health disaster in U.S. history (USDA and Animal and plant health inpection Services, 2015; Ramos et al., 2017)

describing relationships in the data, disease exposures, risk maps (Boender et al., 2007; Shih et al., 2021), predicting the number of cases (Martinez et al., 2011; Alamil et al., 2019), or representing processes such as disease surveillance (Bourhis et al., 2019; Guinat et al., 2021b).

Mechanistic modeling explicitly provides mathematical expressions of the dynamics of transmission. These models can be summarized into three paradigms that include compartmental, metapopulation and individual-based models. Compartmental models are a type of model where the whole population is divided into broad subgroups ('compartments') according to the infection states of the epidemiological units, such as susceptible, infectious, or recovered (Vynnycky and White, 2010; Wiratsudakul et al., 2018). Metapopulation models are a type of model where the whole population can be divided into distinct spatial subgroups (or patches) based on shared characteristics. The concept is that each subgroup has its own dynamics and there is limited interaction between the subpopulations (Keeling and Rohani, 2011; Wiratsudakul et al., 2018). Individual-based models are a type of model that monitors the state of each host distributed on spatial landscape. They can include a wide variety of complex (more biologically realistic) behavior that often features a spatial component (Vynnycky and White, 2010; Keeling and Rohani, 2011; Wiratsudakul et al., 2018). The choice of which model paradigm should be used clearly depends on the questions of interest, the particular host-pathogen system under consideration, and the data available (Thompson and Brooks-Pollock, 2019).

I.4.2. Contribution of mechanistic modeling in avian influenza epizootics

In AI research, numerous mechanistic models have been used to gain insights on the spread of AI viruses and evaluate enforced or alternative mitigation strategies. By studying various AI epizootic data, multiple authors have inferred transmission parameters (Bos et al., 2007; Bavinck et al., 2009; Marquetoux et al., 2012; Tuncer and Martcheva, 2013; Smirnova and Tuncer, 2014;

Ssematimba et al., 2018; Vergne et al., 2021) and evalutated mitigation strategies (Smith and Dunipace, 2011; Walker et al., 2012; Pandit et al., 2013; Xiao et al., 2014; Lee et al., 2017; Li et al., 2017; Hagenaars et al., 2018; Lee and Lao, 2018; Andronico et al., 2019; Chen and Wen, 2019) at varying geographical scales (within-flock, flocks, farms, administrative units, subnational and global). In doing so, they characterized the intensity of transmission and contributed to the general understanding of AI epizootics. Although not discussed here, the parameters estimated, the assumptions, and the model paradigm in which parameters were estimated warrant further consideration.

When mitigation strategies were studied in mechanistic models, culling was the most studied implemented strategy, either in the form of reactive culling or preventive culling. In addition to the evaluation of the implementation of reactive culling (Martcheva, 2014; Retkute et al., 2018), some articles estimated the effect of the delay between detection and reactive culling (Le Menach et al., 2006; Elbakidze, 2008; Andronico et al., 2019). The culling of infected flocks was consistently shown to decrease the epidemiological impact of the disease. When preventive culling was evaluated as a mitigation measure, the results, however, were mixed. For example, Andronico et al. (2019) showed for the 2016 – 2017 HPAI H5N8 epidemic that a quicker culling (from 5 to 2 days) of infected farms would have impacted the total number of infections more effectively than strengthening preventive culling measures. Other authors argue that preventive culling may reduce the final size of an epizootic, but increase the epizootic's impact (Pelletier et al., 2012).

Mechanistic models also have helped to assess the impact of implementing vaccination during an epizootic in poultry populations (Walker et al., 2012; Backer et al., 2015; Hill et al., 2018), and have been used in attempts to determine the necessary vaccination coverage to bring an epidemic to a halt (Lee and Lao, 2018; Retkute et al., 2018). At a national level, Walker et al. (2012) showed a reduction of 11% in the number of communes infected after the implementation of vaccination

campaigns in Vietnam. The implementation of such a campaign is costly and the benefit from such a feat may not offset this cost (Pelletier et al., 2012; Backer et al., 2015), especially when a high level of vaccine efficacy or a high proportion of the population must be vaccinated to have a significant impact on the course of the epizootic (Tiensin et al., 2007; Hill et al., 2018).

The efficacy of surveillance also has been studied over the years through mechanistic models. Andronico et al. (2019) studied the effect of implementing surveillance zones, as well as the size of these zones. The results showed that the creation of zones around infected farms, in which reinforced active surveillance is applied, reduced the final size of the epizootic. By doing so, the authors were able to show that the transmission rate was reduced approximately by half in these zones when compared to non-surveillance zones. This indicates that mitigation measures around infected farms (such as preventive culling, active surveillance, and movement restrictions) are vital to contain the disease in France. Others have observed similar results and reemphasized the importance of decreasing the delay of detection (Kim et al., 2010; Brown et al., 2015; Ssematimba et al., 2018) in South Korea, Nigeria, and Bangladesh.

Mechanistic models also have been useful in the absence of epizootic data. They have been crucial in helping countries anticipate the introduction of AI viruses through the study of worst-case scenarios. In the UK, for example, mechanistic models have helped gain an understanding of the risk that AI viruses present to the UK poultry systems and evaluate the efficacy of current mitigation strategies (Truscott et al., 2007; Sharkey et al., 2008; C. P. Jewell et al., 2009; Chris P. Jewell et al., 2009; Dent et al., 2011).

Certain aspects remained unexplored. For instance, while H5N1 continues to be the most explored subtype due to its zoonotic capability, the susceptibility and infectivity of the different hosts affected are rarely studied. When affected hosts are mentioned, they are usually considered in models as a single population. Moreover, parameters needed to understand epizootic transmission

dynamics are usually obtained from literature or assumed to be constant. Another limitation of current modeling practices regards the contact structure of hosts, which is assumed to be fixed over the course of the epizootic.

The field of infectious disease modeling is evolving quickly, and the accumulation of various data sources would certainly help gain further understanding of AI epizootic dynamics. Integrating these into models would undeniably improve the quality of model predictions, enabling us to better anticipate population-level epizootic dynamics based on individual-level knowledge of epidemiological determinants, long-term behavior based on early invasion dynamics, and the impact of mitigation strategies based on infection transmission (Grassly and Fraser, 2008; Herzog et al., 2017).

I.5. The epidemiological context of avian influenza in France

France is the leading producer of foie gras, accounting for 14,300 tons of the 23,700 tons produced globally (ITAVI, 2020), and the third-largest poultry meat producer in Europe, with a production of over 1.7 million tons a year, behind Poland (2.6 million tons) and Spain (1.71 million tons) (Eurostat, 2018). France also produces broiler chickens (1.19 million tons), turkeys (0.23 million tons), and guinea fowl (33,200 tons) (FranceAgrimer, 2020).

These high production rates pose challenges. Poultry are distributed in three main production basins in the country (Fig. I.8). The northwest has a high concentration of poultry farms with overlapping production systems (breeding laying hens, broilers, roasting ducks, and to a lesser extent, ducks for foie gras). The center (Rhône and Saône valley) has smaller poultry populations than the rest of the country, and is distinguished by a significant amount of egg production for consumption (Delpont, 2021). Lastly, the southwest has a high density of duck farms destined for foie gras (FranceAgrimer, 2020; Delpont, 2021).

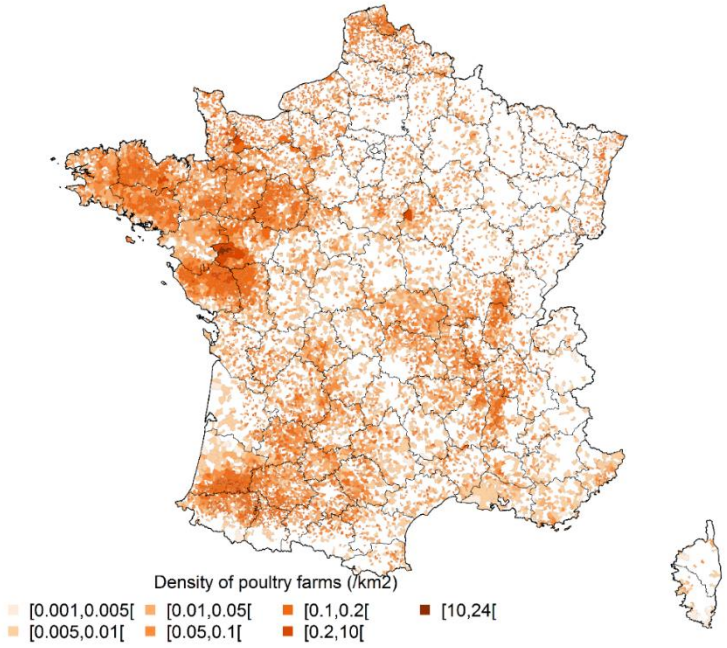

Fig. I.8. Spatial density of poultry production in mainland France (per km^2) (Delpont et al. 2021).

The foie gras production system is organized in a pyramidal structure with three stages that are often handled on different sites: rearing (1-day old ducklings reared indoors for three weeks with an average size of 5,000 birds), breeding (ducks reared outdoor with access to shelter for nine weeks with an average size of 10,000 birds) and fattening (ducks force-fed indoor for up to 12 days with an average size of 1,000 birds) (Guinat et al., 2019). In some cases, one farm manages more than one stage (e.g., breeding and fattening), although birds in each stage are housed in separate buildings. Due to their different sizes, flocks are usually divided into smaller flocks to be moved to different fattening holdings, resulting in large numbers of movements to fattening holdings.

I.5.1. Avian influenza epizootics in France

During the first panzootic period (2004-2013), very few outbreaks were detected in France. During the winter of 2005 – 2006, several countries in Europe in farms where HPAI virus circulation has been confirmed (based on virological and/or clinical signs reported their first cases of H5N1

infection (primarily in mute swans *Cygnus olor*). By 13 February 2006, the first cases of H5N1 were detected in eastern France in dead wild ducks (La Dombes area). By mid-April, 42 cases involving more than 60 wild birds (mostly mute swans) had been reported, and only one commercial turkey farm had been found with the HPAI H5N1 subtype. This commercial farm was located 1 km away from the index case (Gall-Reculé et al., 2008). Sanitary measures implemented at the time, including culling and emergency vaccination of free-range domestic waterfowl, made it possible to stop the spread to other farms (Capua et al., 2009). This resulted in the culling of more than 11,000 birds (Gall-Reculé et al., 2008; Alarcon et al., 2018). Between 2007-2010, no epizootics occurred in domestic poultry. Then in April 2010, an unregulated LPAI H6N1 was isolated in the northwest region on a commercial turkey farm where an abnormal drop in water and feed consumption was observed, followed by the death of 5% of affected birds (Corrand et al., 2012).

In the ongoing panzootic period (2013 – to present), the number of outbreaks and subtypes detected have climbed sharply. Between November 2015 and August 2016, France encountered its first epizootic of HPAI, during which three particular subtypes were detected, H5N1, H5N2, and H5N9 (Briand et al., 2017; Bronner et al., 2017). In total, 100 outbreaks were detected in the southwest region (Fig. I.9A), of which 19 were LPAI and 81 were HPAI subtypes (Huneau-Salaün et al., 2016). All LPAI outbreaks were detected in palmipeds farms during active surveillance campaigns. For the HPAI outbreaks, palmipeds farms were the most affected, with 81% of the outbreaks located in nine départements[11] in the southwest part of the country (Le-Bouquin et al., 2016). This episode was shown to be linked to mutations that turned an LPAI H5 virus circulating in palmipeds for several years into an HPAI H5 form at the beginning of 2014 (Briand et al., 2017; Bronner et al., 2017).

[11] Département: the second administrative division level in France.

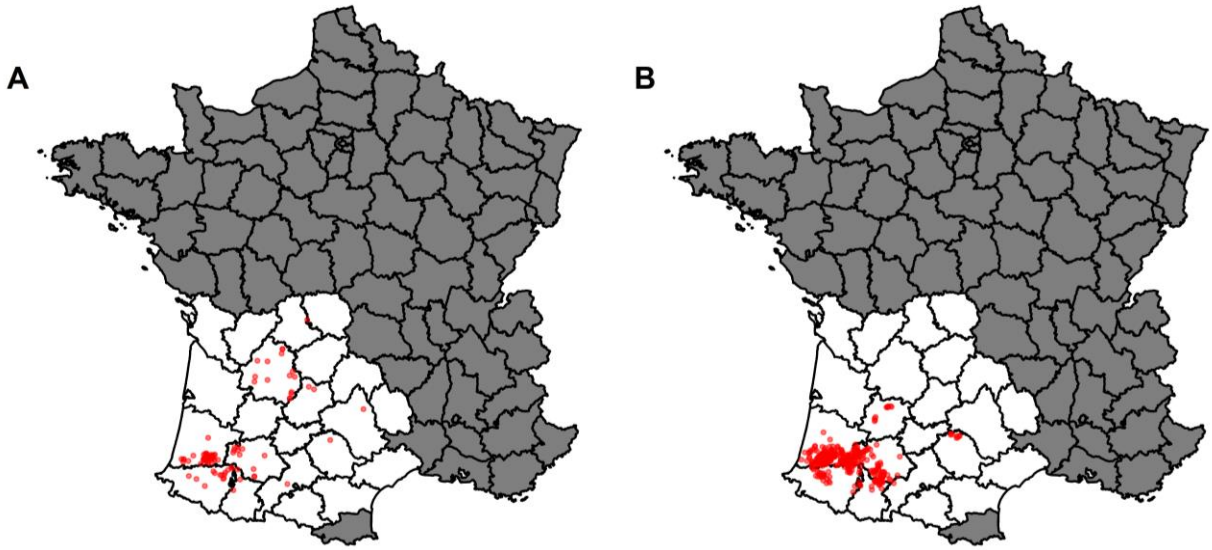

Fig. I.9. The epizootic of AI in southwest France (grey = outside epizootic area, white = southwest area in the context of the AI epizootic). A) shows the 2015-2016 HPAI epizootic with 81 cases reported in poultry. B) shows the 2016-2017 HPAI epizootic with 484 cases reported in poultry.

Toward the end of 2016, France was hit by a second epizootic, caused by the HPAI H5N8 subtype carried by migratory birds from Asia (Bronner et al., 2017). Again, palmipeds farms were the most affected, accounting for more than 81% of infected farms (Table I-3) (Guinat et al., 2018; Andronico et al., 2019). Furthermore, this epizootic was centered in the same region affected during the 2015 – 2016 epizootic; however, fewer départements were affected (Fig. I.9B). Nonetheless, an unprecedented number of cases (484) were detected and led to the culling of more than six million birds (Guinat et al., 2018). The first case of HPAI H5N8 was detected on 26 November 2016 in the northern part of France after neighboring countries (Germany, Netherlands) had declared cases in wild birds. Then, on 1 December 2016, the first case was detected in southwestern France in the département of Tarn, and within a few weeks, the virus was detected in five other départements (Gers, Lot-et-Garonne, Hautes-Pyrénées, Pyrénées-Atlantique, and Aveyron). These départements have a significant density of duck farms (Anses, 2017a; Guinat et al., 2018). The majority of the outbreaks were detected by passive surveillance (until mid-February 2017), then by active surveillance (3 February – 23 March 2017) (see subsection I.5.2 for details on surveillance

protocols), and the temporal distribution of cases showed two distinct epizootic waves (Fig. I.10). The first wave was characterized by short-range dissemination; the second was accelerated via long-distance spread (Guinat et al., 2018). Following strict control measures, the epizootic ended with the last detection on 23 March 2017.

Table I-3. shows the distribution of highly pathogenic avian influenza H5N8 outbreaks per type of poultry holding, species, and duck production in France, 2016–2017 epizootic (n = 484 outbreaks). * Multispecies refers to farms that raised chickens, ducks, and geese. ** Information on production stages was only available for 380 outbreaks (Guinat et al., 2018).

	Number of outbreaks	**Total**	**Percentage**
Type of poultry holdings in terms of commercial/backyard production			
Commercial poultry holding	464	484	95.9
Backyard poultry holding	20		4.1
Type of species			
Duck	395	484	81.6
Chicken	59		12.2
Multispecies*	28		5.8
Type of duck holding in terms of production stage**			
Breeding + Fattening	155	380	40.8
Breeding	131		34.5
Fattening	78		20.5
Other	16		4.2

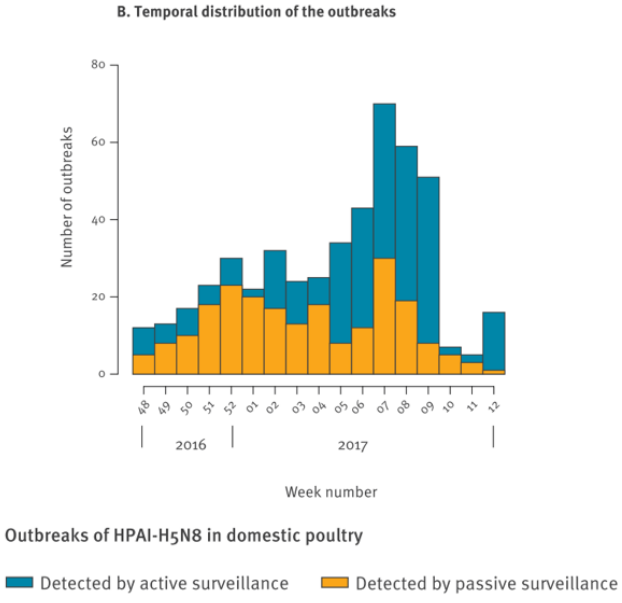

Fig. I.10. Temporal distribution of the outbreaks (Guinat et al., 2018).

As mentioned previously, wild birds can play different roles in the spread and epidemiology of AI around the globe via the Palearctic region. The 2016 – 2017 wave of the H5N8 virus affected mainly Barnacle Geese (*Branta leucopsis*) and other herbivorous anatidae such as Whistling Ducks (*Mareca penelope*) along the Baltic and North Sea, with only a few cases in France (Anses, 2017a; Guillemain et al., 2021). A study conducted on wildlife cases commensal to infected farms in southwestern France suggested that wild bird cases in the region were more of a reflection of the high viral pressure than an indicator that wild birds were playing a role of vector of HPAI H5N8. This means that wild birds play an epidemiological sentinel role, but are not a local reservoir of HPAI H5N8 infection. This has led to the hypothesis that the maintenance of the epizootic in southwest France is mostly linked to the spread of the virus by human activities associated with the palmipeds fattening industry (Anses, 2017a).

Following this epizootic, several hypotheses were proposed to understand the mechanism favoring this unprecedented spread. They included the movement of people, animals, or vehicles, an exceptional climatic event, avifauna, and airborne diffusion (Bronner et al., 2017; Guinat et al., 2021a). First, a risk map was generated using a boosted regression tree model (BRT), including several factors such as the density of the human population, chicken and duck holdings, the density of in and out-going movements of fattening ducks, density of poultry slaughterhouses per commune[12], and several others (Guinat et al., 2019). They concluded that the models which best explained the distribution of HPAI H5N8 were the ones that contained the explanatory variable, "human population density", as well as variables related to poultry production, i.e., "density of chicken farms", "density of duck farms" and "density of duck batch movements" by commune (Fig. I.11A) (Guinat et al., 2019). Given that the affected area has a high density of duck farms, it is not

[12] Commune: the commune is the smallest French administrative subdivision (https://www.insee.fr/fr/metadonnees/definition/c1468 assessed 03/10/2021).

surprising that the density of duck movements to and from fattening farms was associated with the distribution of the outbreak. However, the density of chicken farms was negatively associated with the proportion of infected farms. This perhaps explains why galliformes farm were less impacted during the epizootic (Bertran et al., 2016; Andronico et al., 2019; Guinat et al., 2021a).

Beyond descriptive analyses, live bird movement was further explored through a network analysis (Guinat et al., 2020b). Indeed, birds may be moved from one farm to another during production. This is particularly the case for hens of laying age (or pullets) and ducks ready for fattening. The network analysis of duck movement showed that two large geographical clusters were observed, northwest and southwest, and limited movements were observed between them (Fig. I.11B) (Guinat et al., 2020b). The authors were able to show that less than 11% of movements through the network may have contributed to the spread of the virus in the early phase of the epizootic (at-risk movements made between two infected farms with the dates of movement occurring within two weeks before their date of suspicions). Moreover, analysis of a proximity network to approximate epidemiological factors (including shared equipment, rendering, feed deliveries, movement of catching teams, etc.), showed that more than 62% of farms became infected through that network (farm situated less than 10 km from an infected farm) (Guinat et al., 2020b), further reinforcing the hypothesis that between-farm transmission is short-ranged and is mediated by human activities.

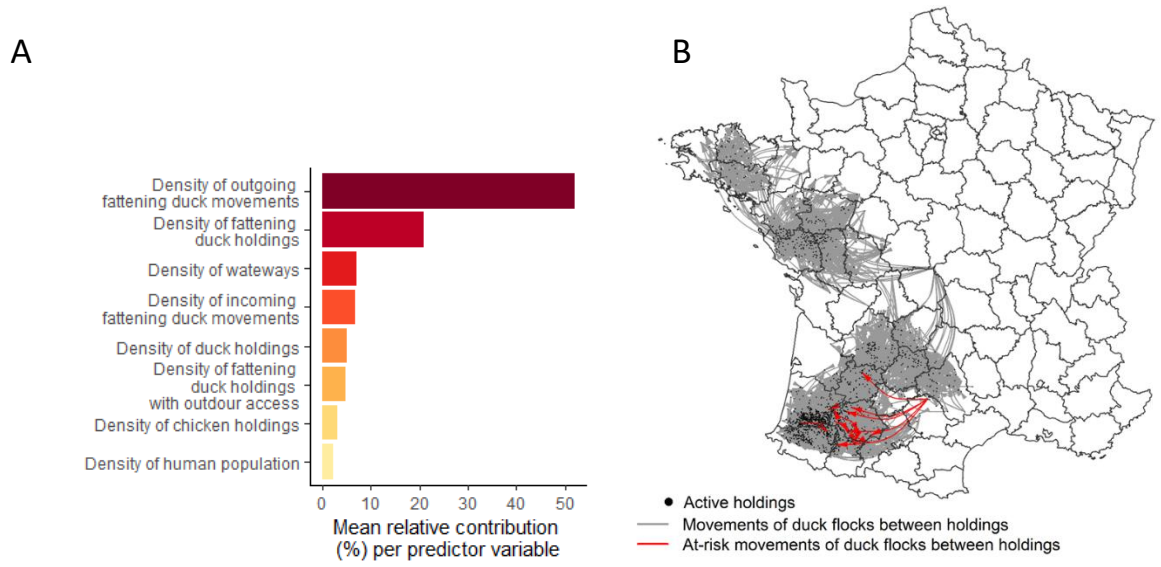

Fig. I.11. Risk factors associated with the distribution of HPAI H5N8 outbreak in France in 2016-2017. A) Ranking of risk factors associated with outbreaks resulted from boosted regression tree models. B) Spatial distribution of live-duck movements identified as contributing to the spread of the HPAI H5N8 through the movement network in France between 1 November and 2 February 2017. (Adapted from (Guinat et al., 2019, 2020b)).

Between 2018 – 2019, no epizootics occurred in poultry. Then during the winter of 2020-2021, another HPAI epizootic hit Europe, including France. This epizootic followed the same track as the previous 2016-2017 epizootic, resulting in nearly 500 outbreaks and the culling of more than three million ducks and other poultry between November 2020-May 2021 (Anses, 2021a). Contrary to the 2016-2017 epizootic, the first case in southwest France was detected in Landes, a département with one of the highest densities of palmipeds production, on 2 December 2020 on a mule duck farm (Vergne et al., 2021). The outbreak quickly spread to neighboring départements in the region (Gers, Lot-et-Garonne, Hautes-Pyrénées, Pyrénées-Atlantique). Of the 494 poultry outbreaks, 464 were detected in commercial poultry, 11 in backyard poultry located in the southwest region (> 96%), and 19 outbreaks were located in the rest of France. The last outbreak in poultry was detected on 4 April 2021 in the Ardennes. Once again, palmipeds farms were the most affected and were located in the Landes département (Fig. I.12).

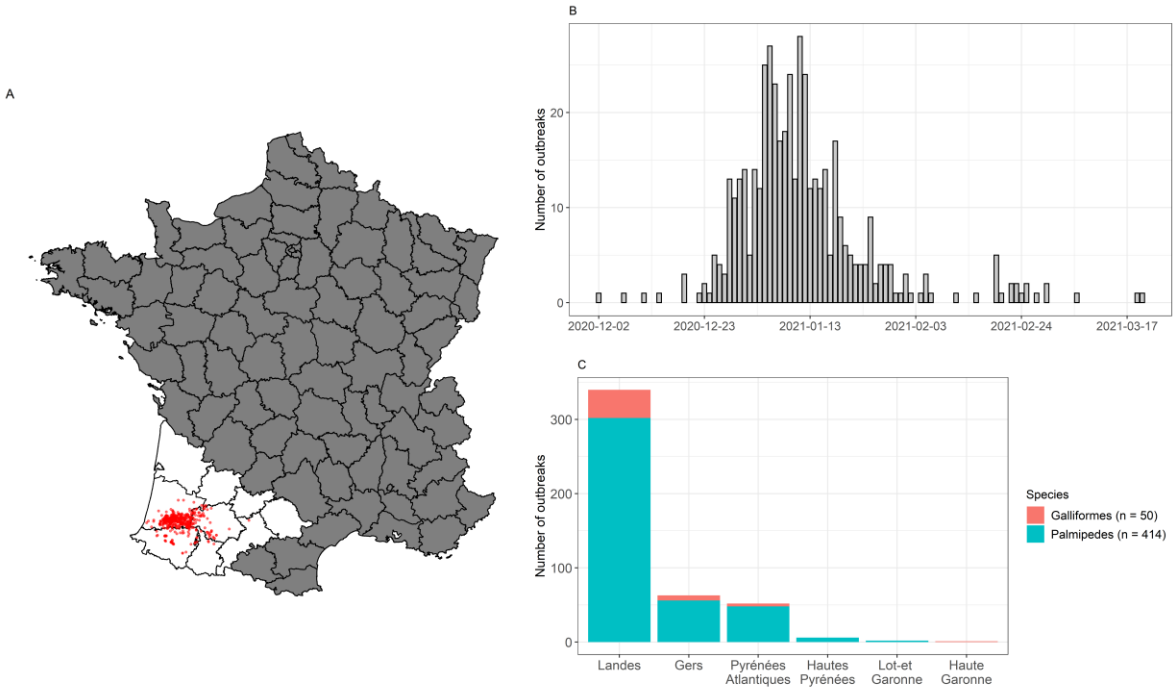

Fig. I.12. Distribution of highly pathogenic avian influenza in southwest France during the 2020-2021 epizootic. A: spatial locations of the 464 cases detected in domestic poultry in the southwest region (grey=outside of the southwest, white=southwest area in the context of the AI epizootic); B: temporal distribution of the cases detected during the epidemic; C: the number of outbreaks per department affected

Preliminary analysis seems to suggest that transmission of HPAI viruses to continental France is due to the migration of wild birds at the end of autumn. The presence of the HPAI virus was confirmed in twelve wild bird species, belonging to four families, between 1 August 2020 and 7 July 2021 (Anses, 2021b). Two distinct introductions of the virus were identified in poultry. One was in Landes, followed by a very wide local transmission (< 15 km) between farms via direct or indirect contacts (movement of animals, people, or equipment), and responsible for almost all of the outbreaks observed in this area. The second introduction was observed in backyard poultry in Hautes-Pyrénées, and the virus responsible for this incursion has not been found elsewhere (Anses, 2021c).

Due to time constraints, we were not able to analyse this epizootic any further. However, it offers potential to further advance our understanding of HPAI determinants as new data becomes available (as highlighted in the discussion section).

I.5.2. Control measures enforced during the 2016-2017 epizootic

As per the European Council Directive 2005/94/3C and OIE guidelines, the French government uses biosecurity, surveillance, zoning, and culling measures to limit and control the spread of AI within its borders. This section will concentrate on the 2016-2017 H5N8 epizootic, the focus of this Ph.D. thesis, because this epizootic set the precedent for how HPAI is handled in France.

Following the detection of AI viruses during the autumn of 2016 in other EU countries, measures to prevent contamination of farms were strengthened in France with regard to the risk linked to avifauna (DGAL, 2016). Bronner et al. (2017a) provide a timeline of these measures (Fig. I.13), which included increased vigilance after the detection of cases in wild and captive birds, passing from risk level "negligible" to "moderate" throughout France, except for high-risk areas where the risk level was rated "high" (Bronner et al., 2017). Consequently, duck farmers were ordered to keep their birds indoors to limit contact with wild birds during the high-risk period (DGAL, 2016).

Following the detection on 1 December 2016 of the first HPAI outbreak in poultry, the French Ministry of Agriculture and Food established protection zones (3 km radius), and surveillance zones (10 km radius) around outbreak farms. In these zones, affected farms were culled and cleaning and disinfecting measures were applied following European Union regulations (Bronner et al., 2017; Guinat et al., 2018; Andronico et al., 2019). Despite these measures, the number of cases continued to increase. By 5 January 2017, 89 outbreaks had been detected. The French authorities decided to reinforce the previously cited measures by implemented preventive culling of free-range palmipeds around affected farms located in four départements with a high density of palmipeds farms (Gers, Hautes-Pyrénées, Landes, and Pyrénees-Atlantiques) (DGAL, 2017b). Moreover, due to the high susceptibility of palmipeds to the HPAI H5N8 subtype, enhanced biosecurity and surveillance were applied, including pre-movement virological screening before any movement of palmipeds batches

(DGAL, 2016). Fast forward to 2 February 2017, these measures were applied systematically around all outbreaks. From then, the detection of an outbreak resulted in the culling of all poultry farms within a radius of 1 km, and breeding palmipeds farms were culled within a radius of 3 km (in case of a single outbreak) or 10 km (in case of several outbreaks) (DGAL, 2017c). The objective of these preventive cullings was to rapidly reduce the infection pressure and stop the spread of the virus. Even after the application of all of these measures, the number of outbreaks continued to rise. One hypothesis was that this continuing spread was due to the high density of farms in the affected regions, high shedding levels of palmipeds, and the difficulty of implementing effective preventive culling measures in the industry (Bronner et al., 2017).

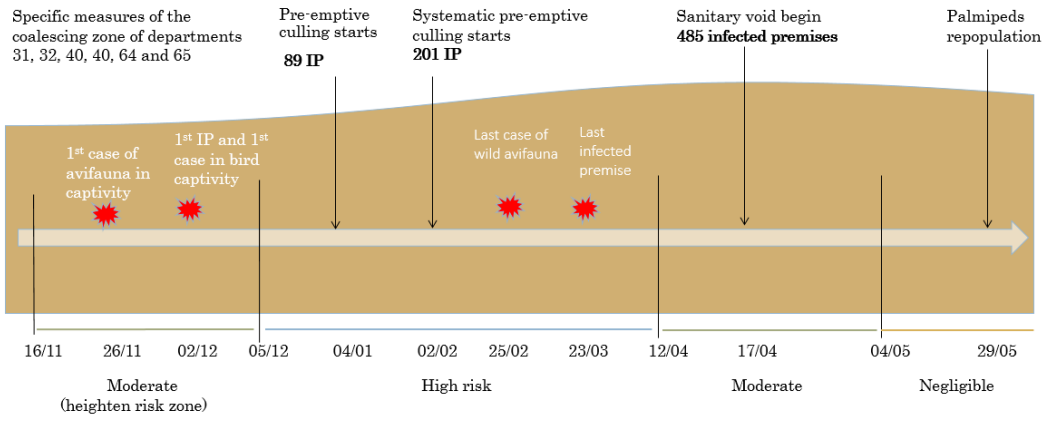

Fig. I.13. Chronology of the main measures implemented between 16 November 2016 and 29 May 2017. The numbers shown in bold are cumulative number of outbreaks. This graph was adapted from Bronner et al. (2017).

On 14 February, the number of communes under enhanced surveillance was doubled. By 21 February 2017, this included 500 communes in the southwest (DGAL, 2017d), in which the measures ordered on 2 February were applied. A 6-week sanitary void[13] was implemented in five départements (Landes, Gers, Pyrénées-Atlantiques, Hautes-Pyrénées Orientale, and Haute-Garonne) with the highest risk of infections from 17 April to 28 May 2017 (Anses, 2017b; DGAL, 2017e).

[13] The sanitary void includes the ban on duck repopulation and cleaning and disinfection of farms (DGAL, 2017c).

With recurrent epizootics and the increasing number of farms affected in France, managing AI epizootics has economic and public health impacts. Following the epizootic of 2015-2016, poultry production fell by 28% in 2016 and again by 16% in 2017 due to the culling of over 6 million birds. The indirect cost associated with the closure of export markets led to losses estimated for the French foie gras sector at €33.1 million during the 2015-2016 period and €31.1 million for 2016-2017. Consequently, France lost a portion of its international market share to Hungary and Bulgaria, which were less affected during the epizootics, notably involving exports to Japan (ITAVI et al., 2018).

Following the 2016 – 2017 HPAI epizootics, several structural changes were enforced through regulations and required investments from private and public sectors. These changes included improved biosecurity practices (the reinforcement of hygiene measures during transport), the prohibition of successive loadings of birds during a transport vehicle round, and the systematic virological screening before animals are moved over long distances from breeding to fattening farms (DGAL, 2016). These measures are extremely burdensome for all sector actors, both psychologically and financially. CIFOG estimated that without urgent financial support from the government, many famers and companies in the sector, already very weak, would not recover from this crisis and risked going out of business, leading to bankruptcies and layoffs. The companies are waiting in particular with impatience for the implementation of the refundable cash advances announced by the public authorities (CIFOG, 2017).

CHAPTER 2: UNRAVELLING DIRECT AND INDIRECT CONTACT PATTERNS BETWEEN DUCK FARMS IN FRANCE AND THEIR ASSOCIATION WITH THE 2016-2017 EPIZOOTIC OF HIGHLY PATHOGENIC AVIAN INFLUENZA (H5N8)

Bauzile B, Sicard G, Guinat C, Andraud M, Rose N, Hammami P, Durand B, Paul, M., Vergne, T. Preventive Veterinary Medicine. *https://doi.org/10.1016/j.prevetmed.2021.105548*

II.1. Foreword

During an outbreak of a contagious disease, a multitude of pathways of transmission could be responsible for the spread of the disease. While some are obvious, others remain difficult to quantify due to a lack of available data. Previous works have shown that the mean transmission distance is short-range (less than 10 km) (Guinat et al., 2018; Andronico et al., 2019) and airborne, and that wild birds have probably played a limited role in the spread of the virus in France (Andronico et al., 2019; Guillemain et al., 2021; Guinat et al., 2021a). As previously mentioned in chapter 1, the transport of fattening ducks has been shown to have contributed in the early phase of the HPAI H5N8 epizootic in 2016–2017 (Guinat et al., 2020b). We extended this analysis to account for indirect contacts between farms by the transit of transport vehicles during live-duck trade movements.

II.2. Abstract

Live animal movements generate direct contacts (via the exchange of live animals) and indirect contacts (via the transit of transport vehicles) between farms, which can contribute to the spread of pathogens. However, most analyses focus solely on direct contacts and can therefore underestimate the contribution of live animal movements in the spread of infectious diseases. Here, we used French live duck movement data (2016–2018) from one of the largest transport companies to compare direct and indirect contact patterns between duck farms and evaluate how these patterns were associated with the French 2016–2017 epizootic of highly pathogenic avian influenza H5N8. A total number of 614 farms were included in the study, and two directed networks were generated: the animal introduction network (exchange of live ducks) and the transit network (transit of transport vehicles). Following descriptive analyses, these two networks were scrutinized in relation to farm infection status during the epizootic. Results showed that farms were substantially more connected in the transit network than in the animal introduction network and that the transit of transport vehicles generated more opportunities for transmission than the exchange of live animals. We also showed that animal introduction and transit networks' statistics decreased substantially during the epizootic (January–March 2017) compared to non-epizootic periods (January–March 2016 and January–March 2018). We estimated a probability of 33.3 % that a farm exposed to the infection through either of the two live duck movement networks (*i.e.* that was in direct or indirect contact with a farm that was reported as infected in the following seven days) becomes infected within seven days after the contact. However, we also demonstrated that the level of exposure of farms by these two contact patterns was low, leading only to a handful of transmission events through these routes. As a consequence, we showed that live animal movement patterns are efficient transmission routes for HPAI but have been efficiently reduced to limit the spread during the French 2020–2021 epizootic. These results underpin the relevance of studying indirect contacts resulting from the movement of

animals to understand their transmission potential and the importance of accounting for both routes when designing disease control strategies.

II.3. Introduction

In 2016–2017, the emergence and spread of highly pathogenic avian influenza (HPAI) H5N8 in Europe resulted in 1,108 poultry outbreaks distributed in 21 countries (Alarcon et al., 2018). With more than 400 farms affected, France was the hardest-hit country in Europe, due to extensive farm-to-farm spread (Guinat et al., 2018). Control measures implemented during the epizootic included culling of infected flocks, movement bans from/to suspected farms and implementation of protection and surveillance zones (3 km and 10 km around infected farms, respectively) in accordance to French and EU regulations (DGAL, 2008; The European Commission, 2019). These measures were reinforced on three occasions with pre-emptive culling of all poultry flocks within 1 km from infected farms and of all duck flocks within 3 km of infected farms (Bronner et al., 2017; DGAL, 2017d, 2017f). This epizootic led to the culling of 6.8 million of birds and induced severe disruptions in the poultry industry, causing important economic losses for local producers and for the whole poultry sector (Guinat et al., 2018). In particular, 81.6 % of H5N8 outbreaks reported in 2016-2017 in France were in farms raising ducks to produce foie gras (hereafter referred to as fattening ducks), mostly located in the southwest region (Guinat et al., 2018). The foie gras sector involves distinct production stages, which may be handled by different farms: rearing (1-day-old ducklings are reared for around three weeks), breeding (1-day to 3-week-old ducks are bred for around 9–12 weeks), and fattening (12-week-old ducks are fattened for around 12 days) (Guinat et al., 2020b). Previous studies suggested that trade-related transport of fattening ducks have played a crucial role in the early stages of HPAI H5N8 epizootic(Guinat et al., 2019, 2020b).

Network analysis provides a useful analytical framework to study contact patterns between farms generated by animal movements. In addition to the risk posed by movements of potentially infected live animals, contaminated transport vehicles used for these movements can also play a significant role in the transmission process (Lockhart et al., 2010). These contacts are usually defined as indirect, as opposed to exchange of live animal movements which are defined as direct contacts. Investigating these different contacts is key to analyze their respective contribution to a potential spread of pathogens in the duck industry. In recent years, numerous studies have used network analysis to describe potential pathogen spread and inform disease control intervention in various livestock species, including cattle or small ruminants(Kao et al., 2006; Ortiz-Pelaez et al., 2006; Brennan et al., 2008; Dutta et al., 2014; Marquetoux et al., 2016; VanderWaal et al., 2016; Rossi et al., 2017; Bernini et al., 2019; Büttner and Krieter, 2020), pigs (Bigras-Poulin et al., 2007; Ribbens et al., 2009; Rautureau et al., 2011, 2012; Lentz et al., 2016; Thakur et al., 2016; Salines et al., 2017; Schulz et al., 2017; VanderWaal et al., 2018; Porphyre et al., 2020) and poultry (Soares Magalhães et al., 2010a; Kurscheid et al., 2017; Guinat et al., 2020b). Most of those studies focused solely on direct contact between farms, but some of them highlighted the potential indirect contact through the transit of contaminated transport vehicles used for the animal movements (Brennan et al., 2008; Ribbens et al., 2009; Thakur et al., 2016; Rossi et al., 2017; Salines et al., 2017; VanderWaal et al., 2018; Bernini et al., 2019; Büttner and Krieter, 2020; Porphyre et al., 2020). Findings suggested that transit of transport vehicles strongly increased the connectivity of farms, and emphasized that focusing only on live animal movements (direct contacts) would likely underestimate the risk of disease transmission.

The objectives of this study were three-fold: (i) to characterize the direct and indirect contact networks resulting from moving ducks between farms in France during a non-epizootic period, (ii) to analyze the impact of the 2016-2017 HPAI H5N8 epizootic on the topology of these two networks

and (iii) to analyze the respective contribution of direct and indirect contact networks in the distribution of HPAI H5N8 outbreaks.

II.4. Materials and methods

II.4.1. Data processing and network building

The recorded movements were collected from one of the most important French private transport companies. It conveys farm animals all over the country and accounted for around 70% of live-duck movements between farms in southwest France during the study period. The dataset contained records of fattening duck movements operated from January 2016 to December 2018. It included movement characteristics (number of ducks loaded and unloaded and the vehicle identification that performed the movement) and farm details (identification of the sending and receiving farms, geographical location of sending and receiving farms). Movement of ducks from fattening farms to slaughterhouses was not included in the dataset. A single transport vehicle usually loads ducks from one breeding site and unloads them at several different fattening locations visited successively during the same day (DGAL, 2018). Furthermore, French regulations stipulate that transport vehicles have to be cleaned and disinfected at the end of each round. To do so they have to go to specific cleaning and disinfection stations that are distributed all across the region (DGAL, 2018). Therefore, the dataset was reorganized into transport vehicle round records, defined as the loading of ducks on one farm followed by the unloading of ducks on successive farms by a given transport vehicle on a given day. Farm type was determined based on the type of movements they were involved in, *i.e.* breeding (for farms only sending ducks), fattening (for those only receiving ducks) or mixed (for farms sending and receiving ducks during the study period).

A network analysis approach inspired by Salines et al. (2017) was taken to describe these movements. One-mode directed networks were created: farms were considered as nodes, and

directional contacts between two nodes were considered as links. Two types of connections were considered, generating two different networks (Fig. II.1): (i) the animal introduction network (AIN) where links represented the movements of live animals being exchanged between breeding and fattening farms; (ii) the transit network (TN) where links represented the contacts between farms based on the successive visits of several farms by a transport vehicle during its round. Since the AIN is embedded in the TN, a subnetwork was created that contained only indirect contacts between farms that did not exchange live animals. Hereafter, this subset will be referred to as the "specific transit network" (sTN). Each network was simplified to remove loops and multiple links between farms for the study period.

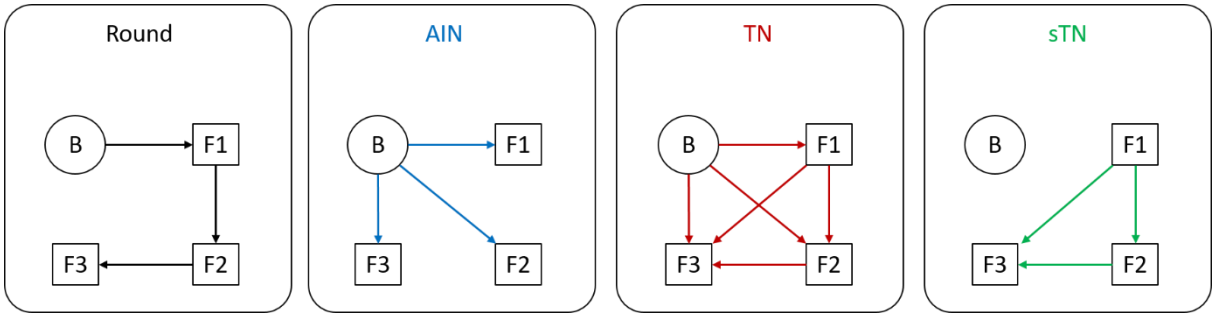

Fig. II.1. Illustration of the reconstruction of the different directed networks (AIN: animal introduction network; TN: transit network; sTN: specific transit network) based on a single round. B: breeding farm, FX: fattening farm, with "X" indicating the order in the round (e.g., F1 = first fattening farm visited during the round). The AIN links farms to all those to which it sent live animals; the TN links farms to every single farm located downstream in the round (irrespective of whether there was a live-animal exchange or not); the sTN links farms that did not exchange live-animal but were connected through the transit of transport vehicle.

II.4.2. Data analysis

II.4.2.1. Network description

Both networks were described using the farm-to-farm directed networks generated with the movement data for the period from January 2018 to December 2018. This period corresponded to an inter-epizootic period for which France did not experience any HPAI epizootic (therefore, the networks were not supposed to be altered by any HPAI-related interventions) and for which the data

was available. The movement data was aggregated on a yearly basis to compute both farm and network-level descriptive statistics for each network (Table II-1). We also investigated if there was an association between farm types, betweenness and in and out-degree for both networks using Kruskal-Wallis and Wilcoxon test. All networks were generated and analyzed using the igraph version 1.2.6 (Csardi and Nepusz, 2006) and tidyverse 1.3.0 (Wickham et al., 2019) packages in R version 4.0.2 (R Core Team, 2020).

Next, we assessed the node *in*-loyalty which measures the tendency of a farmer to purchase animals from the same sellers (for the AIN) and of a transport company to do the same rounds (for the TN) between two consecutive quarters in 2018. To do so, the data was aggregated on a quarterly basis to match the duration between the entry of two successive batches of ducks into a breeding farm. More specifically, the node *in*-loyalty index θ at time *t* measures the fraction of maintained contacts of a farm between periods $t-1$ and t. Therefore, the *in*-loyalty index varies between zero and one, with zero indicating that all connections were different between the periods, and one indicating that all links were maintained. The *in*-loyalty index for farm i at time t was calculated as follows:

$$\theta_i^{t-1,t} = \frac{\left| Y_i^{t-1} \cap Y_i^t \right|}{|Y_i^{t-1} \cup Y_i^t|} \quad (1)$$

with Y_i^t being the sets of in-going neighbours for farm *i* during the quarter *t* (Schulz et al., 2017).

II.4.2.2. Impact of the epizootics and related control measures on the topology of the network

We analyzed the impact of the H5N8 epizootic and related control measures on the topology of the two networks (AIN and TN) by comparing the network-level statistics defined in Table II-1 as well as the distribution of three farm-level statistics, in- and out-degree and betweenness, during the epizootic (January – March 2017) with those of before the epizootic (January – March 2016) and

after the epizootic (January – March 2018). To do so, movement data were aggregated for each these three study periods. Statistical comparisons between the periods and the networks were performed with Wilcoxon tests, using the Bonferroni correction to account for multiple comparisons.

II.4.2.3. Role of direct and indirect contacts in the spread of HPAI H5N8 in France during the 2016-2017 epizootic

We assessed the potential contribution of live-animal exchanges in the spread of HPAI H5N8 using a permutation-based approach, referred to as network k-test (VanderWaal et al., 2016; Guinat et al., 2020b), that was applied to the AIN. To assess the contribution of indirect contacts and because the AIN was embedded in the TN, we also applied the k-test to the sTN. The k-test was based upon the calculation of the k-statistic, in our case the number of "infectious" contacts that occurred in the networks. For the AIN, an infectious contact was defined as a live duck movement occurring between two outbreak farms (a breeding and a fattening farms) within *t* days before the date of suspicion of the most recent outbreak of the two. Similarly, for the sTN, an infectious contact was defined as a specific indirect contact (through the transit of transport vehicle but without live-animal exchange) occurring between two outbreak farms within *t* days before the date of suspicion of the most recent outbreak of the two. Because recent epidemiological findings suggest that duck mortality is likely to increase rapidly after HPAI (H5N8) virus introduction (Vergne et al., 2021) we considered a time-window of $t = 7$ days, but also tested longer periods of 14 and 21 days, similar to Guinat et al. (2020b). The rationale behind the k-test approach was that if the virus spread through the networks, the number of infectious contacts would be significantly greater than expected under the null hypothesis, *i.e.* if infected farms were randomly distributed in the network. The observed value of the k-statistic was then compared to the distribution of the same statistic obtained by randomly reallocating the date of farms' suspicion date, thus simulating a possible pattern of cases under the null hypothesis of an absence of association between HPAI H5N8 infection status and

contacts in the network. The empirical p-value of the k-test was calculated as the proportion of permutations for which the simulated k-statistic was greater than the observed one. We ran the permutation test with 10,000 trials to determine the p-value for the AIN and sTN. Finally, we calculated the risk of transmission by live-bird-movement-related direct (respectively indirect) contact, defined as the ratio of (i) the number of infectious direct (resp. indirect) contacts as defined above to (ii) the overall number of "at-risk" direct (resp. indirect) contacts originating from a farm that was reported in the following seven days and that did not necessarily generate a case in the receiving farm.

Table II-1. Network analysis terminology as used in animal movement networks (Lockhart et al., 2010; Büttner et al., 2013; Dutta et al., 2014; Thakur et al., 2016; Salines et al., 2017; Machado et al., 2021).

Term	Level	Definitions
Betweenness	Farm	The frequency at which a farm is located on the shortest path between any two pairs of farms in the network.
Degree	Farm	The number of unique contacts a farm has (sum of unique in- and out-degrees).
In-degree	Farm	The number of different farms from which a farm receives animals.
Link	Farm	The directed contact between two farms (in our case, the movement of live animals or transit of transport vehicles).
Node	Farm	The epidemiological unit of interest in the network. In our case, a farm that was active during the study period.
Out-degree	Farm	The number of different farms to which a farm sent animals.
Assortativity	Network	The Pearson correlation coefficient between the degrees of linked farms.
Average degree	Network	The mean number of unique contacts a farm has
Average path length	Network	The average number of links along the shortest paths between all possible pairs of farms.
Clustering coefficient	Network	The average proportion of neighbors of a farm that are linked to each other. As a global measure, clustering coefficient quantifies 'cliquishness' within the network.
Density	Network	The proportion of actual links present over all possible links in the network.
Diameter	Network	The number of links in the shortest path between the most distant farms of the network for which a path exists.
Strongly Connected Component (SCC)	Network	The subset of networks involving at least two farms in which every farm can be reached from every other farm via one or several directed paths.

II.5. Results

II.5.1. Data description

There were 614 farms identified in the dataset, with 7,447,838 ducks exchanged through 7,371 movements between January 2016 and December 2018. The year 2018 had the highest recorded number of ducks exchanged (3,451,662) and of movements (3,440). The most common farm production type represented in the data was breeding (278), followed by fattening (225), and then mixed (111). The majority of live animal movements occurred from breeding to fattening farms (59.2%), followed by mixed to fattening (17.2%), breeding to mixed (17.1%) and mixed to mixed farms (6.5%) (Table II-2). For that same period, 103 distinct transport vehicles were used to perform these live animal movements. The transport vehicles completed 7,359 rounds, with an average of 2.9 farms per round.

Table II-2. Number (and %) of live-duck movements operated between the different farm types in the southwest of France, January 2016 to December 2018.

	2016		*2017*		*2018*	
	To fattening	*To mixed*	*To fattening*	*To mixed*	*To fattening*	*To mixed*
From breeding	1,445 (60.3)	416 (17.4)	994 (64.8)	218 (14.2)	1,926 (56)	624 (18.1)
From mixed	395 (16.5)	141 (5.9)	225 (14.7)	97 (6.3)	649 (18.9)	241 (7)

II.5.2. Comparison of the animal introduction network (AIN) and the transit network (TN)

In 2018, the AIN and the TN contained 395 active farms (Table II-3). All statistics used to compare the two networks suggested that the TN was denser than the AIN, forming larger communities of farms with stronger connectivity. The overall number of links was around 1.4 times

higher in the TN than in the AIN (3,664 and 2,684 links, respectively). Over 2018, on average in the TN a farm was in contact with 19 other farms (average degree), while in the AIN, a farm was in contact with 14 other farms. One and four strongly connected component (SCC) were identified in the AIN and the TN, respectively. The largest SCC in the TN included 152 active farms (38 %) which is eight times larger than the size of the only SCC identified in the AIN (19 active farms (4.8 %)), suggesting that the TN was less fragmented than the AIN. Moreover, any two given farms located in the largest SCC were separated on average (average path length) by 3.1 links in the TN versus 2.6 links in the AIN. The TN was 45 % denser than the AIN, with density statistics of 0.03 and 0.02, respectively. Due to TN's components greater size, it also had a longer diameter (1.3 times longer) than the AIN (9 versus 7). The clustering coefficients of the network were two times higher in the TN than in the AIN, suggesting that nodes were more tightly connected in the TN than in the AIN. The assortativity was positive for both networks, indicating that farms were more often linked to farms with similar degrees.

Table II-3. Descriptive indicators of the animal introduction network (AIN) and transit network (TN) in the duck sector, southwest France, 2018.

Indicators	January – December 2018	
	AIN	TN
No. of active nodes	395	395
No. of active links	2,684	3,664
Average degree	13.6	18.6
Average betweenness	4.0e-4	1.9e-03
Average path length	2.6	3.1
Density	0.02	0.03
Diameter	7	9
Clustering coefficient	0.1	0.3
Assortativity	0.09	0.05
Number of strongly connected components (SCCs)	1	4
Size of the largest SCC (proportion of nodes included in the largest SCC)	19 (4.8 %)	152 (38.5 %)

The degree distribution in 2018 for both networks was right-skewed (figure not shown), indicating that the majority of the farms had a low degree. Statistically significant differences of centrality values (betweenness, in- and out-degree) were observed between AIN and TN for the different farm types (Fig. II.2) with higher values observed in the TN. There were also statistically significant differences of centrality values between farm types for each network (Fig. II.2). For in-degree, higher values were observed for fattening as compared to mixed farms in the AIN ($p < 0.0001$) while in the TN, mixed farms had higher values ($p < 0.0001$). Bear in mind that the networks were unidirectional, and as such, the in-degree of breeding farms were equal to zero (Fig. II.2) as they did not receive animals from mixed nor from fattening farms. For out-degree, breeding and mixed farms had higher values than fattening farms in the TN ($p < 0.0001$) while no significant difference was observed between mixed and fattening farms. For the TN, no significant difference in the betweenness distribution was observed between fattening and mixed farms (Kruskal-Wallis test: $p = 0.67$).

The distribution of loyalty values computed in both networks showed little variation between quarters (Fig. II.3). The average loyalty index was around 15% in AIN and 16% in the TN.

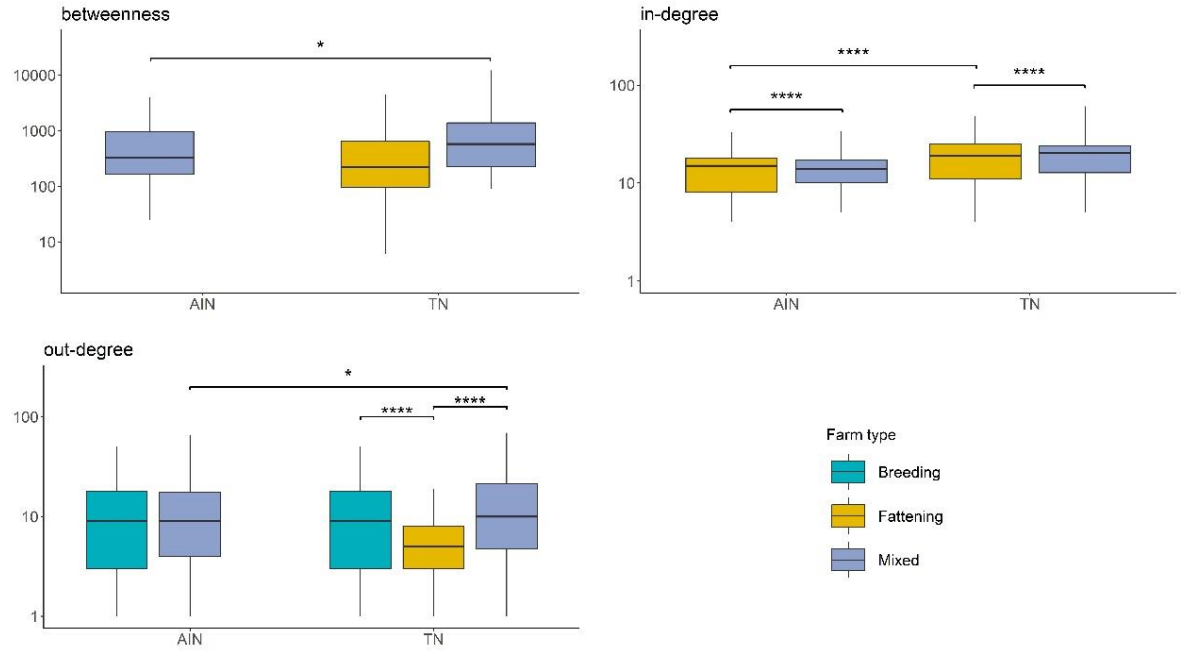

Fig. II.2. Distribution of betweenness, in-degree and out-degree centrality measures in southwest France, 2018, according to different duck farm types, for the Animal Introduction Network (AIN) and Transit Network (TN) using a logarithmic scale. For each comparison, the p-value of the Wilcoxon test is shown to indicate whether the difference observed is significant ($* : p \leq 0.05$, $** : p \leq 0.01$, $*** : p \leq 0.001$; $**** : p \leq 0.0001$). Note that breeding and fattening farms are not represented in the betweenness panel for the AIN since they either send or received animals during a round and thus, there is no transit through them; Breeding farms are not represented in the in-degree panel for the AIN and the TN since they do not receive ducks from other farms; similarly, fattening farms are not represented in the out-degree panel for the AIN since they do not send ducks to other farms.

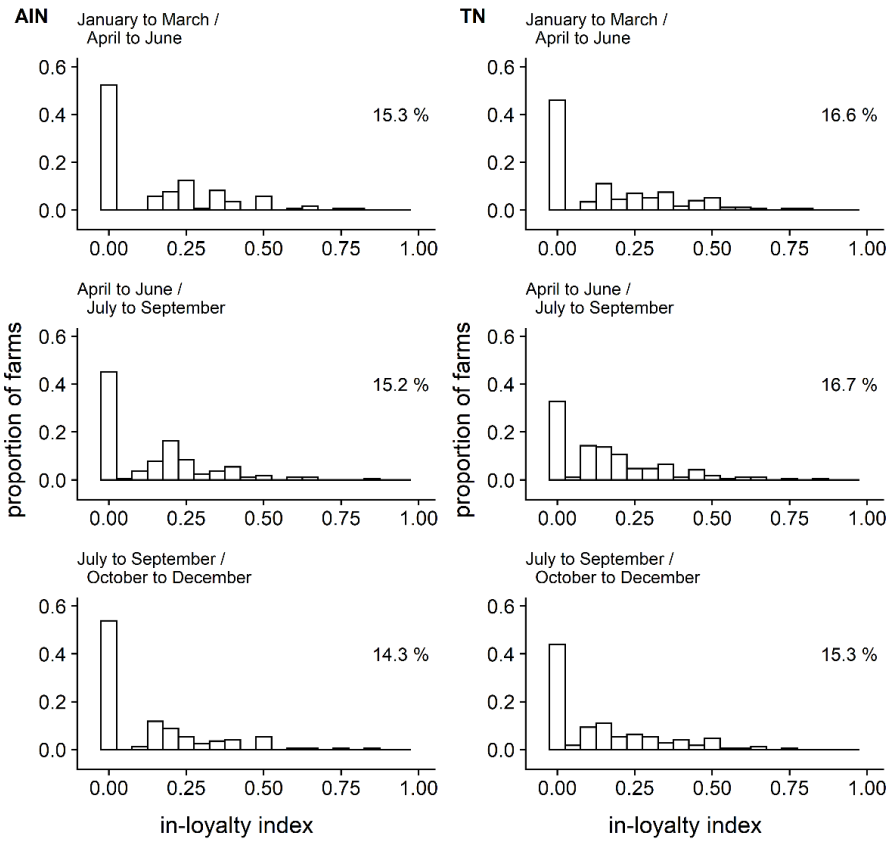

Fig. II.3. Node *in*-loyalty distributions in the animal introduction network (AIN) and transit network (TN) from the duck sector in southwest France in 2018. The average percentage of origins maintained from one period to another is shown in the upper right corner.

II.5.3. Impact of the epizootics and related control measures on the topology of the network

The AIN contained 2.45 times more active nodes (319) during the period before the epizootic (first quarter of 2016) than during the epizootic (130) (Table II-4). The number of links in the AIN before the epizootic (808) was 3.7 times higher than during the epizootic (218). On average, a farm exchanged animals with 5.1 different farms before the epizootic, while during the epizootic, this indicator decreased to 3.4 different farms (average degree distribution). The average path length dropped by 43 % during the epizootic from 2.3 to 1, due to a decrease of components size. Indeed, no SCC was detected in the AIN, as each component detected contained less than 1 % of active nodes for both periods. The assortativity remained constant (0.2) during both periods. In the AIN,

the clustering coefficient decreased from 0.03 to 0 between the period before the epizootic and epizootic period. In the TN, the clustering coefficient remained stable at around 0.16. The size of the largest SCC detected before the epizootic contained 71 active nodes as opposed to two active nodes during the epizootic. After the epizootic (January – March 2018), most network statistics returned to their values close to those before the epizootic. The number of active nodes and links were more than double that of the period during the epizootic. The number of different farms with which a given farm exchanged animals (average degree) was up by 23 % compared to during the epizootic, and the average path length was doubled. In the TN, the size of the largest SCC rose from two during the epizootic to 69 after the epizootic.

Table II-4. Descriptive indicators of the animal introduction network (AIN) and transit network (TN) of French duck movements for the first quarter (January-March) of 2016, 2017 and 2018 which correspond to the pre-epizootic, epizootic and post-epizootic periods, respectively.

Indicators	AIN			TN		
	2016	2017	2018	2016	2017	2018
No. of active nodes	319	130	310	319	130	310
No. of active links	808	218	676	1055	252	908
Average degree	5.1	3.4	4.4	6.6	3.9	5.9
Average betweenness	10.11	0.02	4.94	260.30	0.99	229.52
Average path length	2.3	1.0	2.0	5.1	1.4	5.0
Density	0.01	0.01	0.01	0.01	0.02	0.01
Diameter	6	2	6	15	4	18
Clustering coefficient	0.03	0	0.02	0.17	0.16	0.16
Assortativity	0.20	0.20	0.05	0.17	0.16	0.16
Number of strongly connected components (SCC)	0	0	1	3	5	3
Size of the largest SCC (proportion of nodes included in the largest SCC)	NA	NA	2 (0.7 %)	71 (22.1 %)	2 (1.5 %)	69 (22.3 %)

Similar to the network statistics, irrespective of the network and the farm type, all centrality measures dropped during the epizootic period and then increased again after, often statistically

significantly (Fig. II.4). However, in the AIN, the out-degree distributions for breeding and mixed farms did not statistically significantly change between the different periods (Fig. II.4).

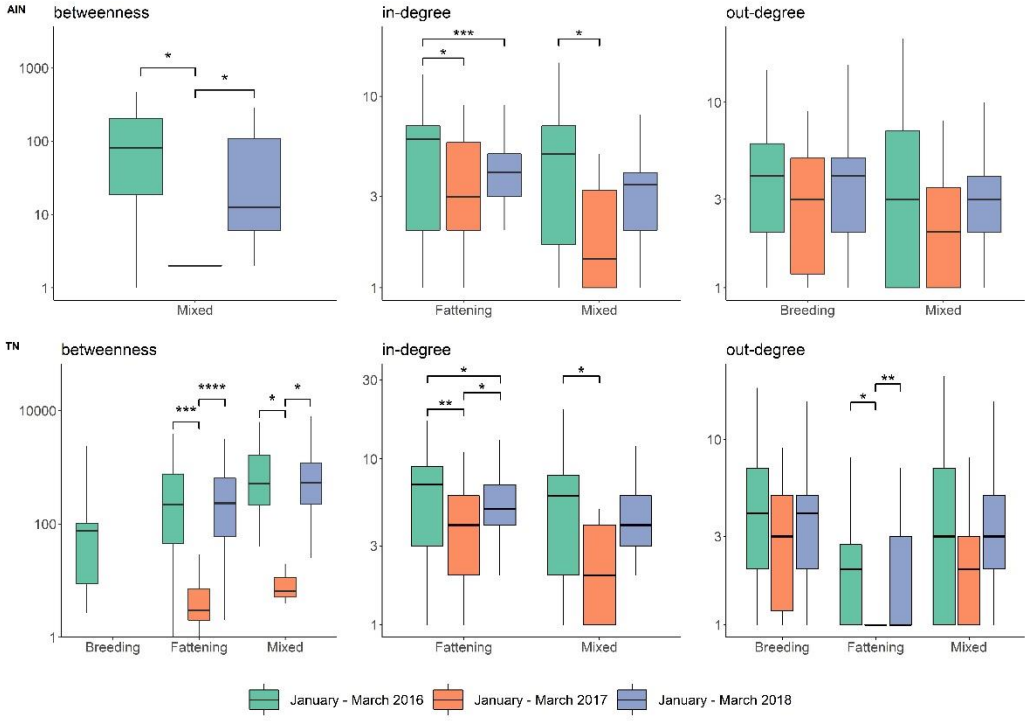

Fig. II.4. Centrality indicators for the animal introduction network (AIN) and transit network (TN) in different farm types in the southwest of France before (January – March 2016), during (January – March 2017) and after (January – March 2018) the HPAI H5N8 epizootic using a logarithmic scale for the y-axis. For each comparison, the p-value of the Wilcoxon test is shown to indicate whether the difference observed is significant. Note that breeding and fattening farms are not represented in the betweenness panel for the AIN since they either send or received animals during a round and thus, there is no transit through them; Breeding farms are not represented in the in-degree panel for the AIN and the TN since they do not receive ducks from other farms; similarly, fattening farms are not represented in the out-degree panel for the AIN since they do not send ducks to other farms.

Similarly, in the TN, the out-degree distribution did not drop statistically significantly, except for fattening farms. After the epizootic (January – March 2018), the distributions of the betweenness for all farm types and of the in-degree for mixed farms in the AIN and the TN were not statistically significantly different from the period before the epizootic. Nonetheless, the distributions of the in-degree for fattening farms in the AIN and the TN, despite increasing again after the epizootic, reached a level that was statistically significantly lower than before the epizootic (Fig. II.4).

II.5.4. Role of direct and indirect contacts in the spread of HPAI H5N8 in France during the 2016-2017 epizootic

Using a time-window of seven days, we identified two infectious contacts in the AIN out of 7,376 movements (0.03 %). It included two movements from one mixed farm to two distinct fattening farms in early December 2016. This number of infectious contacts was found to be statistically significantly higher than what would be expected under the null hypothesis ($p < 0.0001$). Similarly, using the same time-window, one out of 2,763 contacts was considered infectious in the sTN, which was also statistically significantly higher than what would be expected under the null hypothesis ($p < 0.01$). It corresponded to the transit of a transport vehicle between one fattening and a mixed farm at the end of November 2016. Using the time-window of 14 or 21 days, the number of infectious contacts in each network were still statistically significant greater that what would be observed under the null hypothesis. Finally, the risk of transmission given an at-risk contact was calculated at 33.3 % for both the AIN (2/6) and the sTN (1/3), assuming an at-risk period of seven days prior to the suspicion notification.

II.6. Discussion

Network analysis has been widely used to investigate the implication of network structure in disease spread for various production systems(Rautureau et al., 2011, 2012; Marquetoux et al., 2016; Porphyre et al., 2020). This study showed that duck farms in southwest France are highly connected through the exchange of live birds, which is consistent with a previous analysis (Guinat et al., 2020b). Most importantly, it demonstrated that the transport vehicles used to transport live birds were a significant source of inter-farm connectivity through the transit of the same transport vehicles to unload ducks in successive fattening farms. While only one transport company was studied here,

this trend is however expected to be the same for other transport companies since the successive unloading of loaded batches of ducks is not specific of a company but is a specificity of the foie gras duck production system. Results showed that the TN connected many more farms than the AIN, as its largest SCC was eight times bigger than the largest SCC in the AIN. These findings are consistent with similar studies focused on transport networks of pig production system (Bigras-Poulin et al., 2007; Thakur et al., 2016; Salines et al., 2017) which is vertically integrated, similar to the foie gras duck production system in France, although the duck production is associated with fewer stages. We need to keep in mind that introducing an infected animal into a farm is expected to be much more effective in spreading a virus than the transit of a contaminated transport vehicle. However, our work highlighted a general need for a deeper knowledge of transmission mediated by fomites, including better ways to properly capture the frequency and probability of contacts due to transport vehicle movements. Consequently, deciphering the contact pattern of these movements could prove essential in constructing fine-tuned epidemiological models, estimating the worst-case scenario in terms of the size of an epizootic (Kiss et al., 2006) and bring valuable information for disease management, including contact-tracing and surveillance.

For the French duck industry, our results suggested that mixed farms could be a key production type to consider in order to implement risk-based disease surveillance and to disrupt the contact network between duck farms in case of an epizootic. Indeed, despite their limited number in the dataset, mixed farms appeared more central (higher betweenness and degree values) than specialized breeding or fattening farms, irrespective of the network considered. As such, they present a higher risk to become infected through live-animal movements or the transit of transport vehicles and therefore could be relevant candidates for the implementation of risk-based surveillance approaches. They represent so-called bridges or hubs between different network components, what has been pin-pointed as a potential facilitator of disease spread in the French pig movement network (Rautureau

et al., 2011). Therefore, in case of an epizootic, removing these farms through the culling of their flock would decrease theoretically the connection between the network components and limit disease spread through both live-animal movements and the transit of transport vehicles. An alternative to this culling could be to decrease duck farm density by reducing the number of at-risk farms during the high-risk period by forbidding duck placement in these farms and compensating farmers for the production losses. These results also emphasize that strict cleaning and disinfection protocols applied to transport vehicles should be combined with good compliance to external biosecurity measures on farms to limit disease spread. These hypotheses should now be tested by using mechanistic models for simulating disease spread and evaluate targeted control strategies.

Our analysis showed that the live-animal movements and the transit of transport vehicles were associated with statistically significantly more infectious contacts than what would be expected if these networks did not contribute to the spread of the virus, suggesting that transmission events were likely to have occurred through these routes. In addition, it was shown that at-risk contacts (direct and indirect) through live-duck movements are relatively efficient at spreading the virus, since around 33 % of them led to an infection event. However, we only identified two and one infectious contacts in the AIN and the sTN, respectively, suggesting that the contribution of direct and indirect contacts to the overall number of transmission events was likely to be very small. The limited number of infectious contacts associated with the networks is likely to be the result of an effective implementation of movement control. These infectious contacts occurred at the very beginning of the epizootic (end of November 2016 and beginning of December 2016) so it is likely that their only contribution was to allow the epizootic to take-off. Then, following the rapid implementation of movement bans and regulations forbidding successive loadings of ducks during a round, the reinforcement of hygiene measures during transport and the systematic virological screening before animals are moved over long distances (more than 20 km) from breeding to fattening farms in early

December have likely contributed to curb successfully the importance of these transmission routes in the subsequent phases of the epizootic.

Our results also demonstrated that node loyalty in both networks was highly volatile. On average, node loyalty from one trimester to the next never exceeded 17 %, indicating future contacts might be almost impossible to predict. Even though the AIN and the TN were profoundly impacted by the epizootic (Fig. II.4), it is worth noting that most network characteristics after the epizootic returned to values similar to those from before the epizootic (Table II-4). The only exception we noted was for the in-degree of fattening farms which were statistically significantly lower than before the epizootic. These two concurring results suggest that the epizootic led fattening farms to reduce the amount of partnering breeding farms and to be more loyal to them. It must however be acknowledged that network topology in early 2016 may have been partially affected by the HPAI outbreaks which occurred during winter 2015.

A limitation to the results presented here is that the data used were collected from a single transport company. Bias in network-level measures (fragmentation and lack of exhaustivity) can thus exist, resulting in a potential underestimation of farms' true connectivity. However, as previously stated the trend observed with this company is not expected to vary by including the other companies, thus our conclusions regarding the respective contribution of direct and indirect contacts in the H5N8 spread should remain valid. The extension of the analytical framework presented here to a broader dataset consisting of all transport companies would be necessary to gain a comprehensive view of farms' connectivity. However, several challenges subsist to reach this goal, including incompleteness and heterogeneity in data recording for the period of interest. Also, our analyses focused on movements operated between farms and did not consider movements to slaughterhouses, since this data was not available. In addition, although movements from and to slaughterhouses could potentially increase farm connectivity and thus facilitate transmission through

indirect contact, this transmission route was deemed unlikely as strict cleaning and disinfection procedures were implemented for all transport vehicles leaving slaughterhouses (DGAL, 2017a).

Finally, it must be acknowledged that only a fraction of contacts which are established between farms were captured in the present study. Previous research (Lockhart et al., 2010) highlighted the variety of contact networks – including feed, live birds, poultry products, and manure and waste litter – co-existing in the poultry sector. While our results bring original insights on the respective contribution of direct and indirect contacts related to duck movements in the spread of H5N8 virus, further work is still needed to explore the role of other activities – including management of manure and waste litter, as well as rendering – in infectious contacts which may contribute to disease spread between farms.

CHAPTER 3: INTERPLAY BETWEEN DUCK FARM DENSITY AND THE RESILIENCE OF THE POULTRY SECTOR TO HIGHLY PATHOGENIC AVIAN INFLUENZA H5N8 IN FRANCE

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III.1. Foreword

Considering the risk associated with human-related farm activities, stringent measures were taken to secure the sector. Indeed, following the 2015- 2016 and the 2016-2017 epizootic, numerous efforts were put in place by the French government and CIFOG trade association, including enhanced biosecurity in farms, the collection of reliable movement data to facilitate contact tracing and several measures aiming at minimizing the risk for infectious contact related to transport of live ducks (forbidding successive loading during a round, using different sets of transport vehicles and cages to move flocks from breeding to fattening and from fattening to slaughterhouses) (DGAL and CIFOG, 2017; Guinat et al., 2020b). Yet again, during the winter of 2020-2021, the duck sector was affected by another H5N8 epizootic that followed the same track as the 2016 – 2017 epizootic. This second epizootic made a wide range of stakeholders of the poultry sector, as well as decision-makers, realize the vulnerability of the Southwest region of France with regards to the H5N8 subtype. In the absence of the updated data of the 2020 – 2021 epizootic and given the similarity of the two epizootics, we evaluate alternative strategies using the 2016 – 2017 data to help guide decision during the 2020-2021 epizootic. One of the questions we addressed was whether a reduction of commune-level density of duck farms would have improved the resilience of the sector to AI virus incursion.

III.2. Abstract

Here, we analyzed the interplay between duck farm density and the vulnerability of the production system to the HPAI H5N8 threat. To do so, we used a spatial mechanistic model that was calibrated to reproduce the observed spatio-temporal distribution of outbreaks in France during the 2016-2017 epizootic of HPAI to investigate five scenarios in which we decreased the density of duck farms in the communes with the highest duck farm density. Our results show that reducing duck farm density in the densest communes would have had a strong impact on the epizootic dynamics. However, it would not have been sufficient, even in combination with the intervention measures implemented during the 2016-2017 epizootic, to reduce the transmission rate to levels that were low enough to prevent the virus from spreading. This work will be extended to investigate the impact of alternative approaches, including reducing flock size and increasing biosecurity compliance.

III.3. Introduction

During the winter of 2016-2017, France was hit hard by a highly pathogenic avian influenza virus, subtype H5N8, causing almost 500 outbreaks in poultry farms. Outbreaks mostly clustered in the Southwest region of the country, where a substantial amount of ducks are raised to produce foie-gras (Guinat et al., 2018). In accordance with European regulations, the French government has implemented strict control measures to curb the epizootic, including the culling of infected flocks, preventive culling of at-risk flocks, movement restrictions in affected zones, and pre-movement testing of duck flocks. Retrospectively, epidemiological studies have highlighted the role of various transmission routes and the factors that influenced the transmission dynamics. Guinat et al. (2019) used a statistical approach to demonstrate that HPAI H5N8 outbreaks were much more likely to occur in zones with a high density of duck farms. This finding was subsequently confirmed by a

mechanistic modeling study that highlighted the importance of local transmission between poultry farms and the particular sensitivity and transmissibility of palmipeds farms as compared to galliformes farms (Andronico et al., 2019). Live-duck movements and the transit of trucks used for these movements seem to have generated only very few transmission events during the 2016-2017 epizootic (Guinat et al., 2020b; Bauzile et al., 2022), despite being an effective transmission route (Bauzile et al., 2022). Based on these results, important efforts have been devoted in the subsequent years to improve external and internal biosecurity practices in poultry farms to prevent the risk of HPAI occurrence and subsequent impacts (DGAL, 2016; Delpont et al., 2021a). Indeed, biosecurity is an important prevention tool for many important infectious diseases affecting poultry, such as HPAI (EFSA et al., 2017; Guinat et al., 2020a), infectious laryngotracheitis (Volkova et al., 2012), and Salmonellosis (Snow et al., 2010).

While no significant events were reported during the following winters, France experienced another devastating epizootic of HPAI, subtype H5N8, during the winter 2020-2021. The incriminated virus, which was shown to be extremely transmissible between birds (Vergne et al., 2021), led to more than 500 poultry outbreaks, in the same areas as 2016-2017. This second epizootic made a wide range of stakeholders of the poultry sector, as well as decision-makers, realize the vulnerability of the Southwest region of France with regards to the H5N8 subtype. Indeed, major improvements on biosecurity implemented all along the poultry chain (DGAL, 2016, 2018) have remained insufficient to control HPAI spread in case of virus incursion in areas with a high density of duck farms.

To investigate the effect of structural changes in the poultry sector on the transmission dynamics, this study aimed at evaluating how decreasing duck farm density in highly dense areas could improve the resilience of the poultry sector to highly pathogenic avian influenza viruses.

III.4. Material and methods

To address this question, we used a farm-based mechanistic spatial model that was calibrated to the observed spatio-temporal distribution of outbreaks in France during the 2016-2017 epizootic of HPAI H5N8 (Andronico et al., 2019). We further defined six scenarios of duck farm density. The baseline scenario considered all 8379 commercial farms (4238 and 4191 galliformes and palmipeds farms, respectively) as used by Andronico et al. (2019) to estimate transmission parameters. The five other scenarios simulated a decrease in duck farm density in the densest communes. To do so, we identified the 2, 5, 10, 15, and 20 % of the communes with the highest duck farm density (Fig. III.1) and removed randomly duck farms in these communes until the targeted density of the corresponding threshold was reached. These percentiles represented respectively a removal of 62, 188, 482, 658, and 8é(duck farms in 32, 80, 174, 256, and 341 communes (Table III-2).

For each of the six scenarios, we first calculated the basic reproduction number (R_0) for each farm, *i.e.* the expected number of farms a particular farm would be likely to infect, should all other farms be susceptible. For particular farm i, R_{0_i} was defined as

$$R_{0_i} = \sum_j \left(1 - exp\left(-\delta * \lambda_{i \to j}\right)\right)$$

with δ being the duration of the infectious period for a farm (in days) and $\lambda_{i \to j}$ being the daily force of infection exerted by an infectious farm i on a susceptible farm j as defined consistently with Andronico et al. (2019) by:

$$\lambda_{i \to j} = \psi_i * \phi_j * \left(\frac{\beta * I\left[d_{ij} \leq d_c\right]}{N_i(d_c)}\right)$$

with ψ_i being the relative infectivity of farm i ($\psi_i = 1$ for palmiped farms and $\psi_i = \psi$ for galliform farms), ϕ_j being the relative susceptibility of farm j ($\phi_j = 1$ for palmiped farms and $\phi_j = \phi$ for galliformes farms), β being the daily transmission rate, $I[d_{ij} \leq d_c]$ being an indicator function taking the value 1 if the Euclidean distance between farms i and j (d_{ij}) was smaller than a cut-off distance (d_c) and 0 otherwise and $N_i(d_c)$ being the number of farms located within a distance d_c from farm i. For each scenario, R_{0_i} was calculated by conducting 500 random samples of the parameter values in their corresponding posterior joint distributions as established in Andronico et

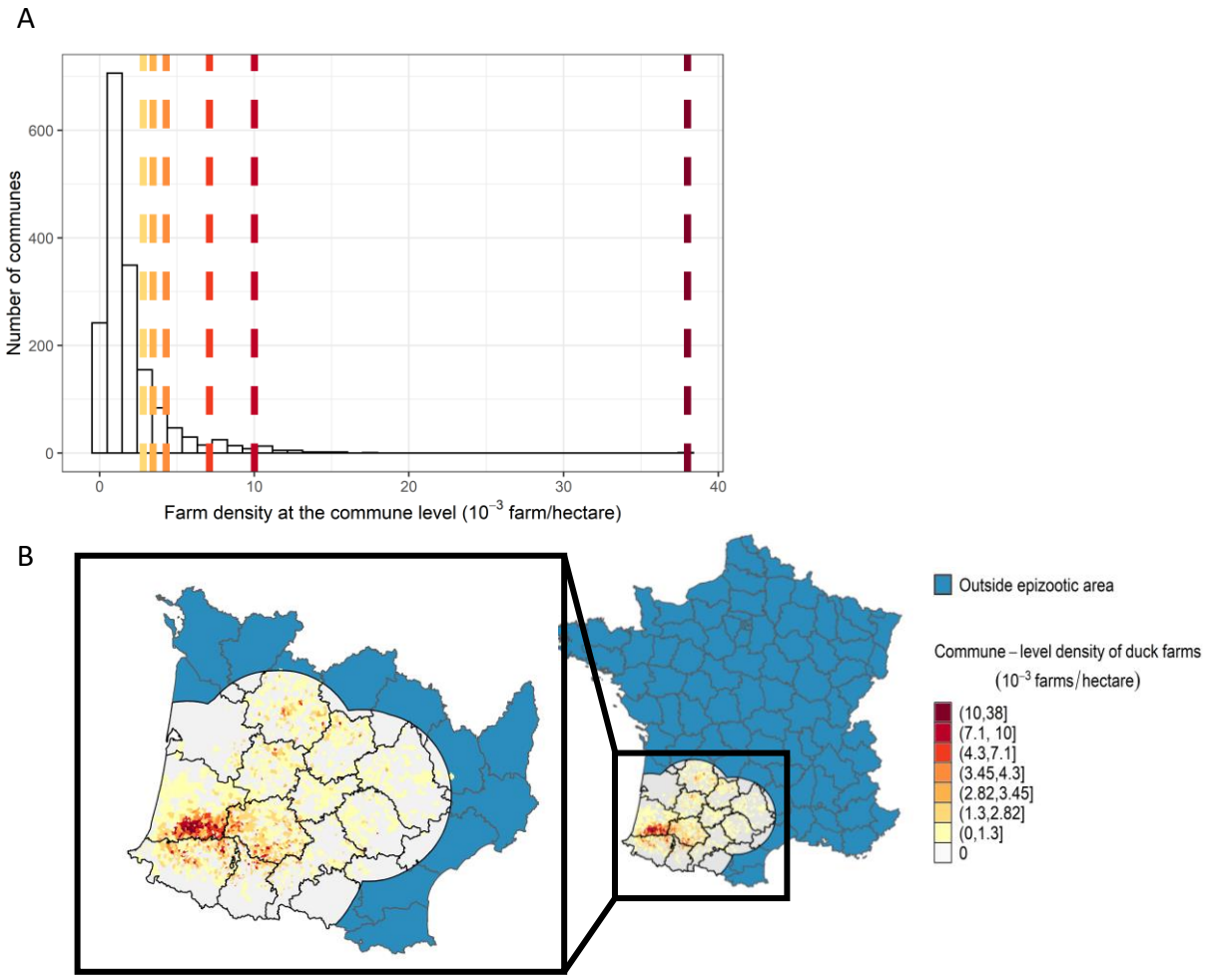

Fig. III.1. Distribution of duck farm density at commune level in the southwest region. A: Frequency distribution of the duck farm density; the vertical lines indicate the six thresholds that were used to define the five scenarios in which duck farm density was reduced in the 2 %, 5 %, 10 %, 15 %, and 20 % of the densest communes. B: Spatial distribution in the epizootic region; the map was created in R version 4.0.2. *(R Core Team, 2020).*

al. (2019) and summarized in Table III-1. The spatial distribution of R_0 was mapped using R software version 4.0.2 with packages "raster" (Hijmans, 2020), "rgdal" (Bivand et al., 2020), "maptools" (Bivand and Lewin-Koh, 2020), and "gstat" (Pebesma, 2004; Gräler et al., 2016), in the projection RGF93/Lambert-93 (EPSG: 2154).

Table III-1. Summary of the distributions or values of the parameters used to define the model.

Parameters	**Definition**	**Median (95% CI)**	**Reference**
ϕ	Relative susceptibility of galliformes	0.20 (0.15, 0.27)	Andronico et al. (2019)
ψ	Relative infectivity of galliformes	0.39 (0.09, 0.85)	Andronico et al. (2019)
β	Transmission rate	0.23 (0.16, 0.31)	Andronico et al. (2019)
d_c	Cut-off distance	15 km	Andronico et al. (2019)
δ	Duration of the infectious period of a farm (between the onset of infectiousness to the culling of the flock)	11 days	This paper

III.4.1. Infectious period

The infectious period (δ) was determined by using the latent period ($L = 1\ day$), the incubation period ($T = 7\ days$) estimated from Andronico et al. (2019). The schematic shown in Fig. III.2A depicts the time intervals needed to determine the infectious period. To determine δ, the distribution of culling delay observed during the epizootic was used (Fig. III.2B), with the mean culling delay $\gamma = 5\ days$, thus, $\delta = T - L + \gamma = 11\ days$.

We then investigated the impact the reduction in duck farm density would have had on the 2016-2017 epizootic. To do so, we ran 500 stochastic simulations of the model for each scenario with the same initial conditions than in the original model, with parameter values drawn from their posterior distributions and with the control strategies as implemented during the 2016-2017 epizootic, including culling of infected flocks, implementation of surveillance and protection zones

(SZ and PZ), enhancement of biosecurity measures in the SZ and preventive culling of duck flocks in the PZ and of all poultry flocks within 1km of infected premises starting in early January. For each scenario, these simulations allowed to reconstruct the average daily incidence as well as to compute the probability of each commune to have become infected.

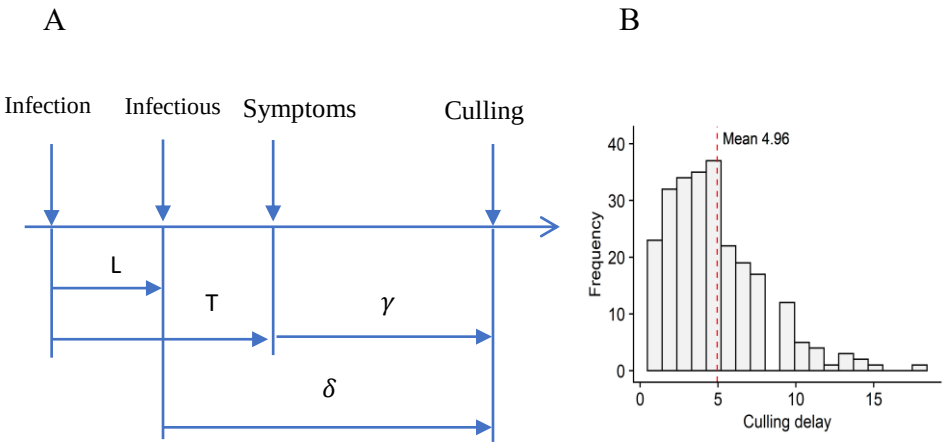

Fig. III.2 Time intervals needed to estimate the infectious period. L represents the latent period, T, the incubation period estimated in Andronico et al. (2019), γ the ,mean culling delay observed during the 2016-2017 HPAI epizootic in France and δ , the infectious period. This figure was adapted from Andronico et al. (2019).

Table III-2. The density of palmipeds farms per commune and the number of farms removed for each scenario tested. The baseline* scenario corresponds to the whole dataset. The other scenarios correspond to the reduction of duck farm density in the top 2, 5, 10, 15, and 20% communes with the highest duck farm density.

	Communes concerned (only those with duck farms)		Total no. of farms in the area (in the top percentile)		Farms removed in each scenario		Total no. of farms in the study area (whole dataset)
Scenario	Density threshold (no. of farm/ha)	No. of communes	All species	Duck farms	No. of farms	% farms removed	No. of remaining farms
Baseline*		1706	8379	4238	0	0	8379
Reduction to 98th percentile	10	32	(394)	(325)	62	19	8317
Reduction to 95th percentile	7.1	80	(820)	(670)	188	28	8191
Reduction to 90th percentile	4.3	171	(1481)	(1169)	482	41	7897
Reduction to 85th percentile	3.4	253	(1959)	(1522)	658	43	7721
Reduction to 80th percentile	2.82	340	(2367)	(1808)	825	46	7554

III.5. Results

The spatial distribution of R_0 in the Southwest region of France for the six different scenarios is represented in Fig. III.3. It suggests that reducing the density of duck farms in the densest communes has an impact on the distribution of R_0, mainly in Landes département, as for increasing efforts of density reduction, the zone associated with an R_0 >1 decreased in size (dark and light orange). However, even when the farm density was reduced in the 20 % most dense communes (scenario 6 in the bottom-right corner in Fig. III.3), *i.e.* when more than 47 % duck farms were removed in the top 20% dense communes, R_0 still remains higher than 1 in a wide region, suggesting that reducing duck farm density alone would not prevent viral spread without the implementation of surveillance and intervention strategies.

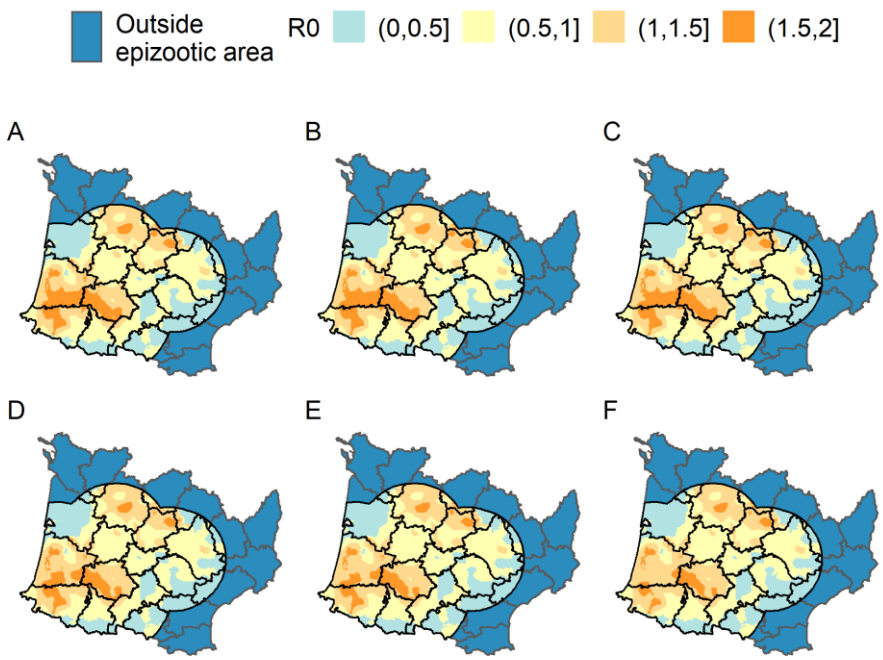

Fig. III.3. Smoothed spatial distribution of the basic reproduction number (R_0) greater than one for A. the baseline 0% reduction and each of the five scenarios simulating a reduction of duck farm density in B. 2%, C. 5%, D. 10%, E. 15% and D. 20% of the communes with the highest duck farm density.

However, when density reduction strategies are coupled with mitigations strategies implemented during the 2016-2017 epizootic (the commune-level probability of infections analysis),

a substantial impact on the distribution of outbreaks and on the epizootic size are observed (Fig. III.4). Indeed, decreasing duck farm density in the densest communes would have had a substantial impact on the 2016-2017 epizootic dynamics, especially during the second phase of the epizootic (February 2017) where the relative reduction of the mean daily incidence is the greatest (Fig. III.5). The duck farm density reduction would have had a much more limited impact on the first phase of the epizootic (December 2016 – February 2017).

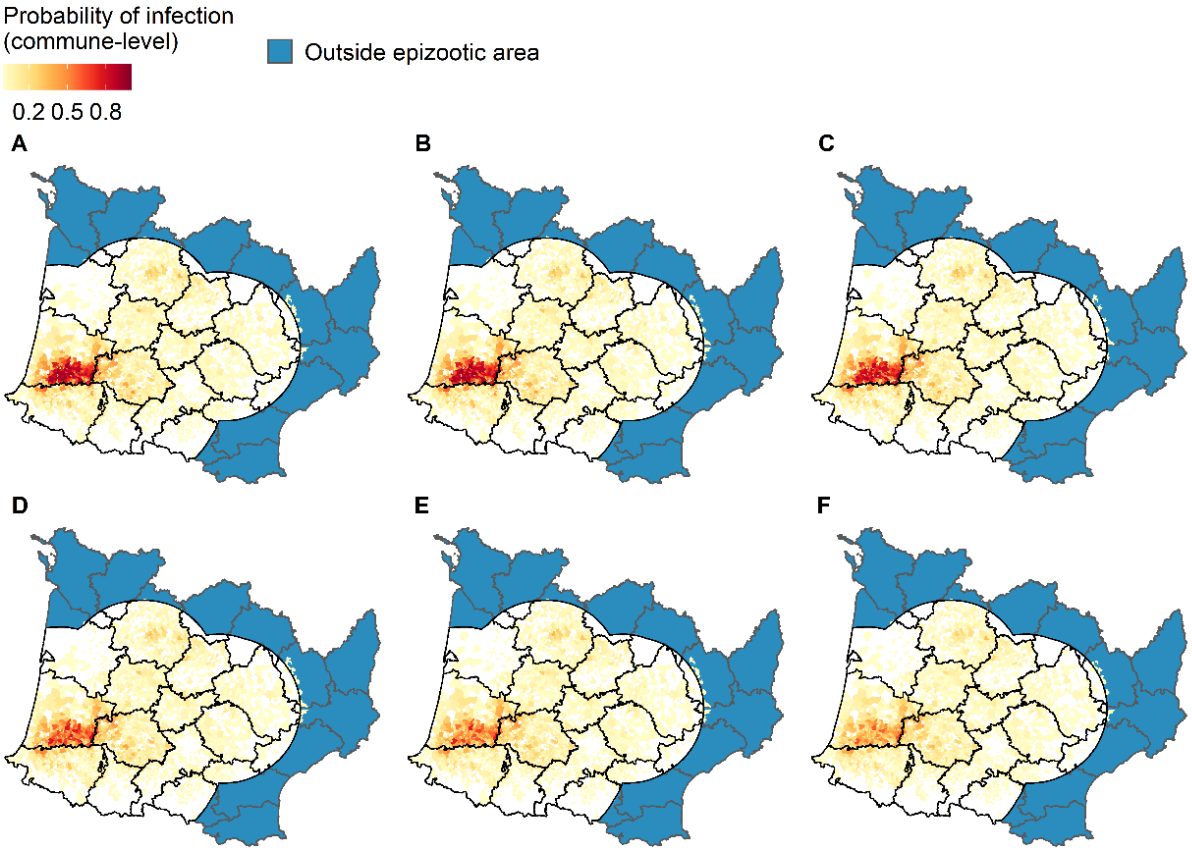

Fig. III.4. Commune-level probability of infection for each scenario simulating the proportion of simulations with at least one infected farm in the commune. A represents the scenario with the reduction of duck farm density in the 0% (baseline), B. 2%, C. 5%, D. 10%, E. 15%, and F. 20% of the communes with the highest duck farm density.

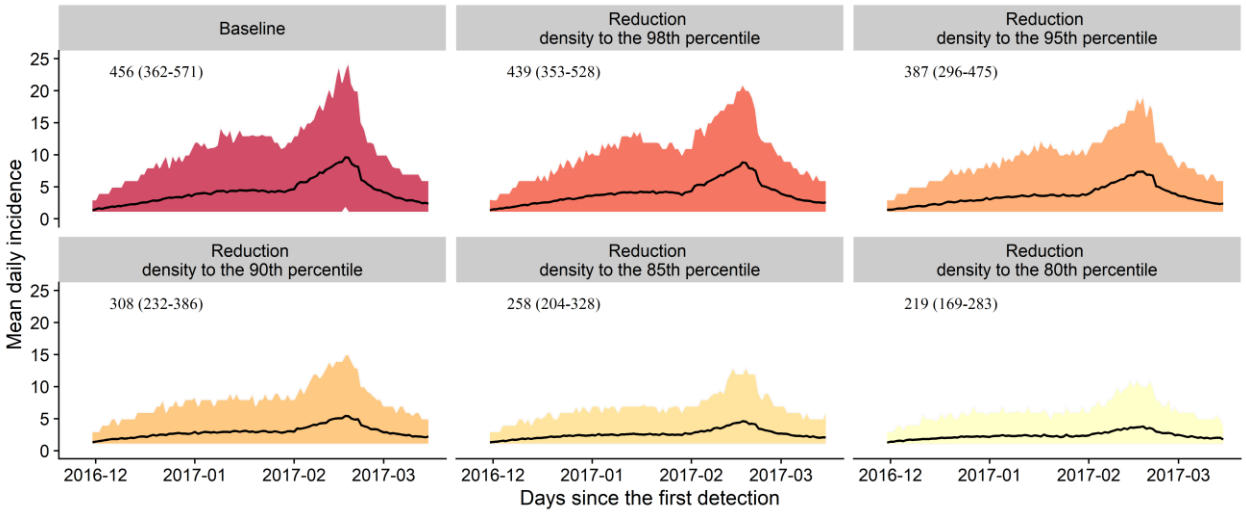

Fig. III.5. Expected epizootic dynamic of highly pathogenic avian influenza in France during the 2016-2017 epizootic for each of the six scenarios simulating a reduction of duck farm density in the 0% (baseline), 2%, 5%, 10%, 15% and 20% of the communes with the highest duck farm density. Solid lines represent the mean daily incidence while the colored areas represent their 95% prediction interval. The numbers inserted in the plot areas represent the expected epizootic size and its 50% prediction interval. This figure was based on 500 stochastic simulations of the model for each scenario with the same initial conditions, with parameter values drawn from their posterior distributions and with the control strategies as implemented during the 2016-2017 epizootic.

III.6. Discussion

This modeling study provides expected evidence that reducing duck farm density in the densest communes would reduce the vulnerability of the poultry sector to highly pathogenic avian influenza (H5N8). Indeed, it was previously shown that this HPAI H5N8 virus impacted more heavily the duck sector (Guinat et al., 2019) and was associated with farm susceptibility and infectivity that were respectively 2.6 times (95 % CI: 1.2-10) and 5.0 times (95 % CI: 3.7-6.7) greater in duck farms than in galliform farms (Andronico et al., 2019). As a consequence, it is logical that having fewer duck farms in the communes associated with the highest duck farm densities decreases the overall risk to the poultry sector, including the galliform farms.

Nonetheless, decreasing duck farm density, even in combination with the intervention strategies that were implemented in 2016-2017, was not sufficient to reduce the transmission rate to

levels that were sufficiently low to prevent the virus from spreading (Fig. III.3-4). As an illustration, even removing 843 duck farms in the densest communes only halved the total epizootic size. However, it is likely that our approach underestimated this effect as it was assumed that the effectiveness of the intervention strategies that were put in place in reaction to the detection of outbreaks (mostly the delay between the onset of infectiousness and the culling of the flock, and the reduction of farms' susceptibility if included in a surveillance zone) were constant across scenarios. One can argue that reducing the outbreak incidence would limit the risk that the veterinary services, which are in charge of implementing these measures, are overwhelmed what, in turn, could enhance the effectiveness of their intervention and their communication to farmers. To overcome this limitation and provide more realistic results, a perspective of this work would be to modulate the effectiveness of the interventions as a function of the number of reported outbreaks.

To further improve the resilience of the poultry sector to highly pathogenic avian influenza epizootics, it is now paramount to further investigate the effect complementary strategies could have on the virus dynamics. One important question that remains to be addressed is related to the impact of duck flock size on virus transmission risk, since an appealing alternative to asking some farmers in the densest communes not to produce at all during the high-risk period would be to ask farmers to produce less. Also, following the HPAI (H5N8) epizootic that occurred in France in 2020-2021, the Ministry of Agriculture has requested duck flocks to be confined during the high-risk periods to avoid contacts with wild birds, except for small flocks of less than 3,200 heads which could remain outside. Therefore, another important question would be to assess the impact of outdoor farming on virus transmission risk. The population data that were used to feed the model of the 2016-2017 epizootic were not sufficient to address these challenging questions. However, relevant data are now available and will be used to reconstruct the 2020-2021 epizootic and assess the impact of these two complementary strategies.

CHAPTER 4: GENERAL DISCUSSION

This Ph.D. thesis aimed to provide insights into determinants that favor the transmission of avian influenza. In this section, we first discuss the implications of our improved understanding of epidemiological drivers of HPAI and the impact that a reduced duck farm density could have on HPAI transmission dynamics. The perspective section highlights relevant future research directions concerning this work. We also list some of the remaining challenges which limit the implementation of a fully functional model that could be used to support decision-making in France.

IV.1. Improved understanding of epidemiological drivers

During an HPAI epizootic, several pathways can contribute to the spread of the virus. These contributions often are difficult to quantify due to incomplete knowledge of farm contact patterns and the limited availability of reliable data. Several hypotheses have been proposed in France regarding the mechanisms favoring the unprecedented spread of the disease in recent years. As summarized in chapter 1, they include the movement of people, animals, and vehicles, exceptional climatic events, infection through wildfowl, and airborne diffusion. The high density of poultry farms in southwest France, which accounted for 97% of the outbreaks detected during the 2016-2017 epizootic of HPAI H5N8, and the velocity of the spread of the virus (average 5.5 km/week), suggest that the disease spread was short-ranged (Guinat et al., 2018) and likely involved human activities associated with farming (Guinat et al., 2019). This observation is not specific to France, as the short-distance transmission of HPAI also has been observed in the Netherlands, where the movements of poultry and workers were identified as the likely main transmission routes (Le Menach et al., 2006; Boender et al., 2007). Furthermore, network analysis of live-duck movements in France showed that about 0.2% of transmission could have been caused by live-duck movement between farms early on in the epizootic (Guinat et al., 2020b)

We extended this previous analysis of the role of live-duck movements in transmitting HPAI in France. We analyzed both live-duck movement and the transit of transport vehicles using highly detailed data on transport truck rounds provided by private transport companies. While the introduction of live animals is a well-known risk factor for the spread of many zoonotic diseases, including avian influenza and foot and mouth disease (Ferguson et al., 2001; Fèvre et al., 2006; Natale et al., 2009; Bajardi et al., 2011), indirect contacts through the transit of transport vehicles are rarely scrutinized. We described networks generated from live duck exchanges to untangle the association of direct and indirect contact patterns between duck farms. Our results further confirmed that movement networks related to the exchange of live ducks are efficient transmission routes. We calculated that a farm has about a 33% probability of showing clinical within seven days after being exposed to infection via the movement of live ducks coming from a farm that itself became infected within seven days after the ducks were moved. We also showed that indirect contacts could transmit with the same probability. Due to the mitigation measures implemented around infected farms (such as preventive culling, active surveillance, and movement restrictions), few infectious contacts were identified in the networks (two in the AIN and one in the sTN). These movements may have contributed to a few long-range dispersals (Guinat et al., 2020b). An analysis undertaken by a veterinary student on the team as part of his veterinary thesis showed that the average distance of rounds was between 80 and 100 km throughout the study period in the southwest region (Sicard, 2021). Despite their limited contribution to transmission events, this further confirmed the potential risk associated with duck farms' direct and indirect contacts linked to live-duck movement.

Clearly, duck farming practices play an important role in spreading HPAI. Duck farms were shown to be both more susceptible and more infectious than galliform farms (Andronico et al., 2019), and infected communes were associated with a high density of duck farms (Guinat et al., 2018). However, our analysis shows that a limited number of transmission events occurred through the live-

bird exchange networks. This would suggest that other aspects of farming may be at play in spreading the virus. This includes rendering, feed, catching teams, veterinary services, and slaughtering services. Indeed, in the absence of good biosecurity practices, these elements can spread pathogens between farms (Dent et al., 2008). For instance, the presence of catching and slaughterhouse personnel have been thought to play a role as a risk factor for infection of remaining birds with bacterial diseases such Campylobacter (Hartnett et al., 2001) and Salmonella (Evers, 2004) through fomite transmission (Alexander, 2007). Detailed data on the different actors involved are required to evaluate the respective contribution of farming activities (live bird movements, rendering, feed, and catching teams).

The movement data used did not allow us to ascertain the level of biosecurity in the transport of ducks. However, once strict regulations and intervention measures were implemented early on the epizootic, the impact of the live-duck movement was drastically reduced. Most network characteristics have returned to their pre-epizootic levels despite the topology changes during the epizootic. This suggests that, if left unchecked, these networks could be an important transmission pathway in the future as we have shown that they spread the HPAI virus efficiently.

IV.2. Toward a restructuration of the production system

As per EU and French regulations, once a notifiable avian influenza virus is detected on the territory, mitigation strategies include at the minimum the culling of infected flocks, the designation of regulated zones in which the movement of birds is restricted, a ban on the repopulation of farms for at least 21 days, and the enforcement of enhanced biosecurity and surveillance measures. Preventive culling of flocks at a high risk of infection, either because they are close to or have had epidemiological links with infected farms, also was implemented during the 2016-2017 HPAI H5N8 epizootic in France. It has been shown that a more rapid detection of infection and culling of infected

farms has a more significant impact than reinforcing preventive culling at varying radii around infected farms (Le Menach et al., 2006; Andronico et al., 2019). Apart from these measures, a ban on repopulation has been shown to reduce the final size of the epizootic (Le Menach et al., 2006; Dorigatti et al., 2010), and the implementation of surveillance zones can slow the transmission process and allow the management team to deal with the situation and set up stringent measures to prevent further spread.

While these measures have proved helpful in containing epizootics, the total number of infected farms during the 2016-2017 epizootic and the reoccurrence of a large-scale epizootic in 2020-2021 indicate that complementary measures need to be investigated. For example, an investigation of an alternative culling radius has shown that even increasing the culling radius from 1 km to 5 km would not be sufficient to halt the epizootic, and would dramatically increase the number of birds to be culled when implemented in dense areas (Boender et al., 2007; Andronico et al., 2019). On the other hand, not implementing any culling measures would be associated with a considerably larger epizootic (Andronico et al., 2019). Both situations can result in saturating the management system by overwhelming the capacities of the veterinary services. The continuation of the spread observed during the 2016-2017 epizootic in the region was perhaps due to the difficulties in implementing such strategies in southwest France. The culling campaigns may have reached their limits due to the high density of farms in the area (Anses, 2021c). The worrisome implication of this observation is that the sheer number of the farms covered by the culling campaign may have delayed culling on infected farms. Consequently, infected farms continued to put infectious pressure on nearby farms. Therefore, there is an urgent need to investigate how structural changes of the production system (e.g., decreasing farm density in the densest regions, decreasing animal density in farms located in the densest regions, reducing the number of farms with outdoor grazing, etc.) may increase the resilience of the poultry sector to the threat of HPAI.

In chapter 3, we evaluated the impact of combining current mitigation measures with a reduction in the density of duck farms in the densest communes. While we showed some reduction in final epizootic size (i.e., an epizootic size up to 50% smaller than the size of the 2016-2017 epizootic in the scenario where duck farm density is reduced in the top 20% densest communes), it would not be sufficient to prevent an HPAI epizootic from taking off (as R0 remained higher than one in a large area of the region). This is consistent with an analysis done in the Netherlands, where the authors showed the impact of applying culling measures in two poultry-dense areas (Boender et al., 2007). Their approach did not investigate a reduction of density. However, the density of poultry areas evaluated was similar to some of the commune density we tested (baseline and the scenario where the duck farm density is reduced in the top 10% densest communes). The authors argued that once the HPAI virus is introduced in dense areas, the epizootic can only be brought to an end by the depletion of susceptible farms by massive culling. Our analysis showed that the spread would occur even in less dense areas (scenario with a reduction in the top 15 and 20% densest communes) once HPAI is introduced. Thus, targeted structural changes will be necessary to make the poultry sector resilient to the spread of the HPAI virus.

One important limitation is that we did not account for an improvement in the timeliness of the intervention in the scenarios tested. Indeed, with fewer outbreaks, the management team could have managed them more effectively (contact tracing, faster culling measures). Consequently, the effectiveness of the scenarios may have been underestimated. To overcome this limitation and evaluate more realistic measures (feasibility and acceptability), future analysis could modulate the timing of culling as a function of the number of farms to be depopulated. This also should make it possible to determine whether the capacity of the culling system is versatile enough to adapt during a crisis. Moreover, the feasibility and acceptability of decreasing duck farm density are challenging and should be considered in the long term. To achieve a 50% reduction in the epizootic size, new

farms should be prevented from opening in dense areas rather than temporarily closing 800 farms during the high-risk period. This long-term approach associated with the closure of farms due to the retirement of some farmers would eventually reduce the density of duck farms in highly dense communes.

One question that remains is whether there is an optimal density that would prevent the spread of the AI virus in the southwest region. Implementing a more stringent scenario that would reduce the value of R0 below one was deemed impractical. Indeed, the most stringent scenario, consisted of reducing the number of farms in the densest communes (>80th percentile or the top 20% densest commune) to match the 80th percentile value, already corresponds to removing 47% of the farms included in these communes.

Given that the duck farm density reduction in the densest communes was insufficient to prevent the epizootic from taking off, the impact of other structural characteristics (flock size, outdoors rearing practices, etc.) on epizootic dynamics requires further attention. In addition, deeper evaluation of the interplay between wildlife and commercial poultry is needed to assess whether avifauna (especially commensal birds, which may play the role of "bridge host" between wild waterfowl and poultry farms) play a role in HPAI maintenance and spread, and thus provide some clarification on missing transmission links that have been observed in the past two epizootics in the region.

The 2020-2021 HPAI epizootic raised new challenges for which the findings of this Ph.D. thesis could be useful. The newly collected dataset contains updated demographic data and new types of data that have become available, namely the number of animals present in farms and presence of outdoor grazing. These new data were unavailable for 2016-2017, so we could not investigate these questions. One piece of data that remains to be obtained is the list of farms (with flocks containing less than 3,200 birds) exempted from sheltering (or had not sheltered their poultry).

This dataset would be necessary to evaluate whether outdoors farming practices present an increased risk of HPAI infection, and hence play a role in the HPAI transmission process.

IV.3. Perspectives of this work

Much progress has been made in developing mathematical tools to study and prevent the spread of HPAI viruses. This includes the now accumulated knowledge on a variety of mechanistic tools (discussed in chapter 1- section contribution of mechanistic models to AI epizootic), the importance of contact patterns of hosts (Guinat et al., 2021a; Bauzile et al., 2022), the estimation of key AI transmission parameters (incubation and latent period, subtype, susceptibility) as shown in Andronico et al. (2019) and Vergne et al. (2021), to name a few. Epidemiological models can help identify key transmission drivers and simulate outbreaks to determine optimal mitigation measures. To do so, modelers and policymakers need to join forces in identifying pragmatic solutions to improve current tools and consider available data, information, and resources.

IV.3.1. Account for heterogeneity in farm connectivity.

IV.3.1.1. Improving our knowledge of farm contact structure

In chapter 2, both direct and indirect contact networks were described, but key characteristics linked to disease transmission (small world or scale-free) remained unresolved. These characteristics have been found in similar integrated farm system networks (Natale et al., 2009; Lockhart et al., 2010; Rautureau et al., 2011; Thakur et al., 2016). In scale-free networks, the in-degree and out-degree distributions can be fitted with a power-law distribution (Dubé et al., 2009). The characteristic of these distributions is the presence of long tails. In such networks, the majority of farms have very few contacts, and a few farms have many contacts creating hubs (Fig. IV.1). When viewed from an epidemiological and disease spread dynamic perspective, scale-free networks have

high numbers of hubs (compared to a random network of the same number of nodes and links), which can act as superspreaders. Theoretical analysis of these types of networks shows that targeting these superspreaders (by contact tracing, preventive culling, or through temporary closure during high-risk periods) can fragment the network sufficiently to break the chain of transmission. Ensuring that these hubs follow strict biosecurity measures could also decrease their importance in disease propagation. It is worth noting that flaws in the application of biosecurity measures can increase the risk of AI virus introduction and spread (Scolamacchia et al., 2019).

In small-world networks (Fig. IV.1), farms are highly clustered, and they can be reached through a small number of contacts (short path length) (Watts and Strogatz, 1998). This allows the disease to spread very quickly in a large section of the network and even to distant farms in the network by using very few contacts (compared to a random network of the same number of nodes and contacts) (Natale et al., 2009; Thakur et al., 2016), and has major implications for disease control as the efficacy of ring management (culling and zoning) may be limited. Targeted measures should focus on those connected to distant farms to fragment such a network.

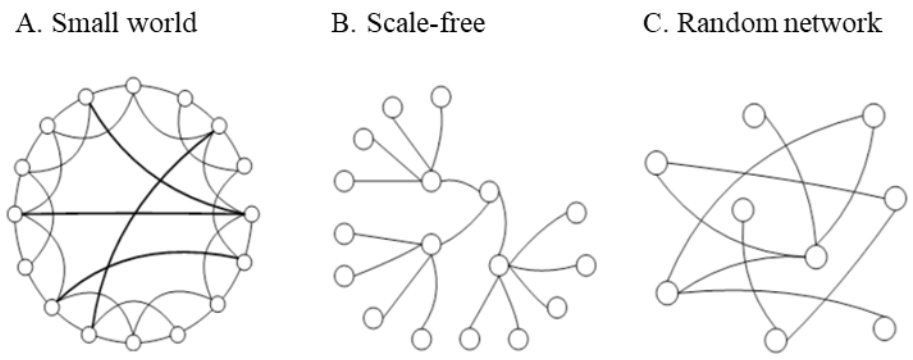

Fig. IV.1. Examples of different types of networks (Huang et al., 2005).

It is worth noting that scale-free and small-world properties are not mutually exclusive (Wang and Chen, 2003), especially in complex networks resulting from overall farm contacts. This complexity is the result of the various activities of farms. While contacts through live-bird movements or veterinary services may be scale-free, the transit of transport vehicles and catching

teams may be small-world. Therefore, categorizing the overall farm contacts rather than the individual networks is expected to generate precise insights into the contact structure of farms, insights that can guide mitigation strategies (e.g., contact tracing, targeting hubs in scale-free or culling connected farms in the small world or a combination of those two in the case of complex/multilayer network).

Newly collected and available data regarding rendering movement and the exchange of live birds can be combined and exploited to categorize farm contact patterns. This approach would benefit from data on other facets of farms that have yet to be collected (feed, catching companies, slaughterhouse services, veterinary services, etc.). This is an issue that the new national database (SINEMA) launched by the French government will rectify when it becomes operational. The protocol developed in chapter 2 can be applied to the combined datasets to identify their impact on disease spread as contact patterns resulting from such activities were associated with the risk of disease transmission (Gittins and Canning, 2006; Dent et al., 2008; Rossi et al., 2017; Yang and Wang, 2020).

IV.3.1.2. Moving toward transmission models with contact patterns

In the construction of models, uncertainties around transmission parameters are common. Particularly, accounting for heterogeneity (which can arise from differences in host susceptibility, infectivity, spatial location, contact structure) in transmission risk remains one of the major challenges in epidemiological modeling. One approach is to use a transmission kernel that determines the probability of disease transmission from an infected to susceptible farms based on the inter-farm distance (Keeling and Rohani, 2011). The rationale behind this kind of transmission model is that farms close in space would exert a higher infectious pressure on each other than on farms further away.

Transmission models of different forms have been used frequently to assess inter-farm transmission as described in Boender et al. (2007). Transmission models have provided invaluable insights about generating risk maps (Boender et al., 2007), evaluating the impact of mitigation measures (Dorigatti et al., 2010; Pelletier et al., 2012), and have enabled the acquisition of needed understanding into disease progression (Kao, 2002; Le Menach et al., 2006; Keeling and Rohani, 2011; Hagenaars et al., 2018). However, describing the tail of transmission kernels used in these models presents a challenge. The tail of the transmission kernel is of particular importance as it determines the speed of propagation of the virus (Keeling and Rohani, 2011). As highlighted in Boender et al. (2007), estimations of the parameters of transmission models with long-tails can result in identifiability issues, with different transmission models of varying complexity pointing to the same conclusion. This has worrying implications indicating that other transmission mechanisms may be at play. A possible alternative is to consider that transmission is only possible for distances below a cutoff distance, as was done in Andronico et al. (2019). But, determine such cutoff distance can only be done *a posteriori*.

Indeed, transmission depends on a combination of factors, including local conditions, contact patterns, and farm density, among others. An alternative to the current approach is to rebalance the transmission kernel with farm contact patterns (Rohani et al., 2010; Antonovics, 2017). Lanzas and Chen (2015) pointed out that transmission parameters are sensitive to the host population's contact structure, especially for diseases that spread rapidly. Network analyses have provided some clues on the predictability of future contacts through movements (loyalty analysis). To determine patterns in contact structure, multiple data sources need to be combined. For instance, knowing whether farms always trade within their professional organization rather than with farms in their proximity may help explain the low loyalty level observed and, in turn, guide targeted surveillance within professional organizations rather than within a large spatial delimitation.

In the past, attempts to account for contact structure in animal disease usually encountered difficulties due to a lack of detailed and complete data describing farm connectivity (direct and indirect contacts). However, the recent effort to collect data on farm contact patterns and the need to find optimal strategies to limit the impact of recurrent waves of epizootics offer the opportunity to fine-tune the transmission model and gain a clearer understanding of epizootic dynamics. Thanks to this accumulation of data, we are starting to scratch the surface of the potential role farm contact patterns may play during an epizootic. Future investigations on contact structure integrated into the transmission kernel would allow us to evaluate their respective contribution to HPAI propagation and determine which mitigation measures may limit their impact.

Implementing several transmission pathways to quantify their role in spreading the HPAI virus and evaluating relevant mitigation strategies to curb their influence would require the building of complex models. Precautions must be taken to limit unnecessarily complex models. The choice of complexity is usually based on the objective of the model, which helps to identify the components of the system to consider. In different studies, model complexity did not correlate with prediction accuracy when the objective was to determine the development of an epizootic (Viboud et al., 2018b). As a case in point, during the analysis of a series of models in forecasting human cases of Ebola, semi-mechanistic models with only two parameters performed better than more sophisticated models. Conversely, when the objective is to provide more spatial details, determine the role of transmission routes, and evaluate the effectiveness of mitigation measures (preventive culling, surveillance/protective zones), a more complex model would be required to make predictions at a finer resolution (Viboud et al., 2018b). While a simple model may predict a set of metrics, it may fail to capture key components of the system, and the interventions implemented may consequently fail to deliver on their promise. A complex model may require too much computing power due to data needed to parameterize the model and model tractability (Lanzas and Chen, 2015). Furthermore,

the complexity of the model should be based on the underlying assumption of the model, the available data, input from policymakers on key prediction targets that are relevant, and the ability of the model to represent the most important drivers of the system and their interactions, while ignoring the less important ones (Basu and Andrews, 2013; Lanzas and Chen, 2015). A balance thus must be found. As mentioned by Probert et al. (2016), discussions between policymakers and modelers may help identify the relevant metrics for their management objectives and focus resources on developing models with a set of metrics that would provide needed insights during an epizootic.

IV.3.2. Optimization of mitigation strategies

As previously mentioned, epidemiological models have been particularly beneficial in describing past epizootics, providing worst-case projections as well as evaluating current and alternative mitigation strategies (Boender et al., 2007; Dent et al., 2011; Nickbakhsh et al., 2013; Probert et al., 2018; Andronico et al., 2019). Contrary to classical approaches that analyze and compare a finite set of mitigation strategies (1, 2, 3, or 5 km radius), future research might obtain better insights by moving toward designing optimized mitigation measures. This involves determining which combinations of strategies would minimize the number of birds culled or shorten the epizootic's length to regain disease-free status. This could be investigated through optimization algorithms that incorporate the parameters defining the mitigation strategies as input to determine the set of strategies to attain the desired outcomes (e.g., minimize the overall epizootic impact) (Moore et al., 2010). For instance, such approaches were taken to determine the cost-effective surveillance strategies for invasive species management in Australia (Hauser and McCarthy, 2009) and to determine the optimal allocation of biosecurity resources between quarantine and surveillance for protecting islands from pest invasion (Moore et al., 2010).

IV.3.3. Towards real-time modeling for decision making

Given the dramatic impact emerging diseases have on society, having a mechanistic model that can guide decision-making in real-time would be invaluable in anticipating the impact of epizootics and acting quickly to curb their impacts. By real-time, we mean mechanistic tools that can be plugged into data (epizootic[14], demographic[15], contact patterns[16], policies applied[17]) during the early phase of an epizootic to provide insights into where the epizootic is likely to go next (predict the transmission pathway; which departments, communes, or farms), predict the peak of the epizootic (when and how many infected farms can be expected), and determine the optimal mitigation strategies that would minimize the epizootic burden (e.g., lower number of culled animals, shorter length of the epizootic, or smaller final epizootic size) on a weekly, bi-weekly or monthly basis (Probert et al., 2018).

To construct a fully functional real-time model, modelers would need to capture the underlying transmission mechanism and within-farm dynamics, and have prompt access to reliable data. Beyond gaining access to resources (analysts and hardware), they also would need to identify a set of metrics with stakeholders (policymakers and decision-makers of the sectors), and improve already developed modeling tools that can be implemented with the necessary dataset to determine the key drivers of the epizootics

[14] Epizootic data: infected farm ID, detection, confirmation and culling date (necessary to determine detection type: passive, active or preventive culling),
[15] Demographic data: farm ID, farm type (breeding, fattening, etc.), species on site (galliformes or palmipeds), capacity, spatial location, date of entry and leaving of flocks, professional organization membership
[16] Contact pattern: movement
[17] Policy applied: measures enforced during the epizootic (farm ID culled, date of enforcement, surveillance zone, protection zone, infection-free zone, culling radius, etc.)

IV.3.3.1. Access to data

One of the major challenges to modeling in real-time the propagation of avian influenza in France is related to access to relevant data. During the early phase of the 2020 – 2021 epizootic, efforts were made to adapt the model presented in Andronico et al. (2019) to the epizootic data to help guide decision-making. Despite our best effort to collect demographic and epizootic data, it was impossible to study this epizootic within a reasonable time frame. This hurdle is one of the consequences of the challenges associated with the centralization and standardization of heterogeneous data. For instance, following the 2016 – 2017 HPAI epizootic, one of the objectives of BD Avicole (*base de donnée avicole:* poultry database) was to consolidate data of the French production system at the national level to meet regulatory obligations. It was initially created in 2012 by the national organizations representing poultry farmers (CFA: *Confédération Française de l'Aviculture* and *Coop de France Aviculture).* By 2015, it also included CIFOG and the National Egg Promotion Committee (CNPO: "*Comité National de promotion de l'Œuf*"). It contained farm information (i.e., farm identification, location, etc.) and animal movements (sender and receiver farm information, number of animals exchanged, etc.). Its goals are to facilitate administrative procedures, including animal health surveillance, improve responsiveness, and foster better knowledge of the French production sector (BDAvicole, 2021). However, as observed during the 2020 – 2021 epizootic, BD Avicole records only part of poultry production (farms and movements of foie gras palmipeds, laying hens, and partially broiler poultry), the other farms and poultry movements are recorded in another database which mainly contains information on broiler poultry farms. Moreover, BD Avicole requires different identifications to access the data of each poultry sector available on its database. This meant that each sector (foie gras sector, broiler, laying hens, etc.) had to be contacted individually to obtain their data. Multiple parties hence had to be contacted, and the creation of various data-sharing agreements required numerous exchanges and legal opinions

(Anses, 2021d). Consequently, it was impossible to model the 2020 – 2021 epizootic even six months after the epizootic's end.

IV.3.3.2. Modeling tools

To cope with the emergence of infectious, we need models that can be readily applied during a crisis. One way to move forward is to create a close working environment between modelers and policymakers. Indeed, policymakers are increasingly interested in having decision tools to improve their understanding and explore the impact of different strategies. Such tools have been developed for many diseases, including Influenza, Ebola, Middle-East Respiratory Syndrome, and more recently COVID-19, enabling their use by non-specialists (Thompson et al., 2019; MRC Centre for Global Infectious Disease Analysis and Imperial College London, 2020). For example, the tool provided by the MRC Centre for Global Infectious Disease Analysis and Imperial College London supported the decision-making of health authorities on the importance of non-pharmaceutical intervention in the early phase of the COVID-19 pandemic. In Thompson et al. (2019), the authors present a modeling tool that can be used to infer disease transmissibility, informing mitigation strategies during future outbreaks of a wide range of invading pathogens. The web application allows users to use their incidence data or one of the pre-loaded datasets of past human incidence cases to explore the model presented and gain insights into the impact of the mitigation strategies implemented.

Another way forward would be to bring the modeling community together with experts to organize infectious disease modeling challenges. Infectious disease modeling challenges (also known as 'hackathons') allow a porous environment between modelers and stakeholders (policymakers, public health officials, etc.) who can make decisions based on the output of the models (Ramatowski et al., 2017). This event is very common in the meteorological field, as illustrated by the intergovernmental panel on climate change predictions (IPCC) (Viboud et al.,

2018a). In the field of human diseases, such events are a decade ahead of the veterinary field, as illustrated by numerous epizootic forecasting challenges already taken with the Ebola challenge in 2015 – 2016 led by the US National Institute of Health (Viboud et al., 2018b), and the dengue challenge by the National Oceanic and Atmospheric Administration (NOAA, 2015), to name a few. In animal health, it was not until 2020 that the first one was organized around African swine fever (Picault et al., 2021). Following in the footsteps of previous epizootic modeling challenges, HPAI modeling can benefit from such exercises. Such challenges could foster the construction of forecasting models by improving coordination, inspiring collaborations between modelers and stakeholders, and constructing useful models. As was observed in previous forecasting challenges, such initiatives make it possible to gain needed insights on which types of models can be helpful, especially during the early phase of an epizootic when few outbreaks are detected, and transmission pathways and other key features are unknown (Viboud et al., 2018b). Moreover, such challenges can help develop tools that are readily available to be deployed during an unfolding epizootic and determine between multiple interventions the one(s) that could halt the spread of a virus before it becomes a fully-fledged epizootic.

CONCLUSION

Between 2015 and today, four separate epizootic waves hit the same area in southwest France. The latest epizootic (which began in November 2021 and is ongoing) emphasizes the need to better anticipate the spread of diseases and work towards increasing the resilience of the poultry sector to limit, or at the very least reduce, the impact of HPAI incursion.

The work carried out in this Ph.D. thesis has enabled us to gain some insights into HPAI determinants related to duck production. We have used statistical and mechanistic modeling methods to describe live-duck movements, unravel their role in the spread of HPAI, and highlight the need for structural changes in the sector to prevent the spread of HPAI. These insights allow us to provide evidence-based recommendations to improve mitigation strategies and increase the resilience of the poultry sector against HPAI epizootics.

This Ph.D. thesis offers new perspectives in the face of current challenges. The tools presented in this Ph.D., along with newly available epizootic data, could help categorize the other important transmission routes of HPAI, notably the impact of duck flock size and outdoor grazing on virus transmission risk. We hope that the resulting practical implications of this Ph.D. will be considered.

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VALORIZATION OF THE WORK CONDUCTED

V.1. Scientific articles as first author

Bauzile B, Sicard G, Guinat C, Andraud M, Rose N, Hammami P, Durand, Paul, M., Vergne, T. Unravelling direct and indirect contact patterns between duck farms in France and their association with the 2016–2017 epizootic of Highly Pathogenic Avian Influenza (H5N8). Preventive Veterinary Medicine. 2021;105548. doi:10.1016/J.PREVETMED.2021.105548.

Bauzile B, Durand B, Rautureau S, Andronico, A, Cauchemez, S, Paul, M., Vergne, T. Interplay between duck farm density and the resilience of the poultry sector to highly pathogenic avian influenza H5N8 in France. (in preparation).

Bauzile B, Mugnier A, Lambert S, Durand B, Paul M, Vergne, T. A systematic review of mechanistic models used to study avian influenza virus transmission (in preparation).

V.2. Scientific article as a co-author:

Vergne T, Gubbins S, Guinat C, **Bauzile B**, Delpont M, Chakraborty D, et al. Inferring within-flock transmission dynamics of the highly pathogenic avian influenza H5N8 virus in France, 2020. Transbound Emerg Dis. 2021. doi:10.1111/tbed.14202.

V.3. Oral presentation at international conferences

Bauzile B, Sicard G, Guinat C, Andraud M, Rose N, Hammami P, Durand B, Paul M., Vergne T. Unravelling direct and indirect contact patterns between duck farms in France and their association with the 2016–2017 epidemic of Highly Pathogenic Avian Influenza (H5N8). Society for Veterinary Epidemiology and Preventive Medicine(SVEPM) – Conference and annual meeting, Online March 2021.

Bauzile B, Durand B, Rautureau S, Andronico A, Cauchemez S, Paul M., Vergne T. Interplay between duck farm density and the resilience of the poultry sector to highly pathogenic avian influenza H5N8 in France. Society for Veterinary Epidemiology and Preventive Medicine(SVEPM) – Conference and annual meeting, Belfast, Ireland March 2022.

Annex

VI.1. First article

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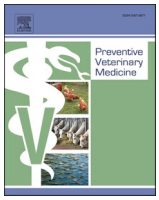



Unravelling direct and indirect contact patterns between duck farms in France and their association with the 2016–2017 epidemic of Highly Pathogenic Avian Influenza (H5N8)

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ABSTRACT

Live animal movements generate direct contacts (via the exchange of live animals) and indirect contacts (via the transit of transport vehicles) between farms, which can contribute to the spread of pathogens. However, most analyses focus solely on direct contacts and can therefore underestimate the contribution of live animal movements in the spread of infectious diseases. Here, we used French live duck movement data (2016–2018) from one of the largest transport companies to compare direct and indirect contact patterns between duck farms and evaluate how these patterns were associated with the French 2016–2017 epidemic of highly pathogenic avian influenza H5N8. A total number of 614 farms were included in the study, and two directed networks were generated: the animal introduction network (exchange of live ducks) and the transit network (transit of transport vehicles). Following descriptive analyses, these two networks were scrutinized in relation to farm infection status during the epidemic. Results showed that farms were substantially more connected in the transit network than in the animal introduction network and that the transit of transport vehicles generated more opportunities for transmission than the exchange of live animals. We also showed that animal introduction and transit networks' statistics decreased substantially during the epidemic (January–March 2017) compared to non-epidemic periods (January–March 2016 and January–March 2018). We estimated a probability of 33.3 % that a farm exposed to the infection through either of the two live duck movement networks (*i.e.* that was in direct or indirect contact with a farm that was reported as infected in the following seven days) becomes infected within seven days after the contact. However, we also demonstrated that the level of exposure of farms by these two contact patterns was low, leading only to a handful of transmission events through these routes. As a consequence, we showed that live animal movement patterns are efficient transmission routes for HPAI but have been efficiently reduced to limit the spread during the French 2020–2021 epidemic. These results underpin the relevance of studying indirect contacts resulting from the movement of animals to understand their transmission potential and the importance of accounting for both routes when designing disease control strategies.

1. Introduction

In 2016–2017, the emergence and spread of highly pathogenic avian influenza (HPAI) H5N8 in Europe resulted in 1,108 poultry outbreaks distributed in 21 countries (Alarcon et al., 2018). With more than 400 farms affected, France was the hardest-hit country in Europe, due to extensive farm-to-farm spread (Guinat et al., 2018). Control measures implemented during the epidemic included culling of infected flocks, movement bans from/to suspected farms and implementation of protection and surveillance zones (3 km and 10 km around infected farms, respectively) in accordance to French and EU regulations (DGAL, 2008; The European Commission, 2019). These measures were reinforced on

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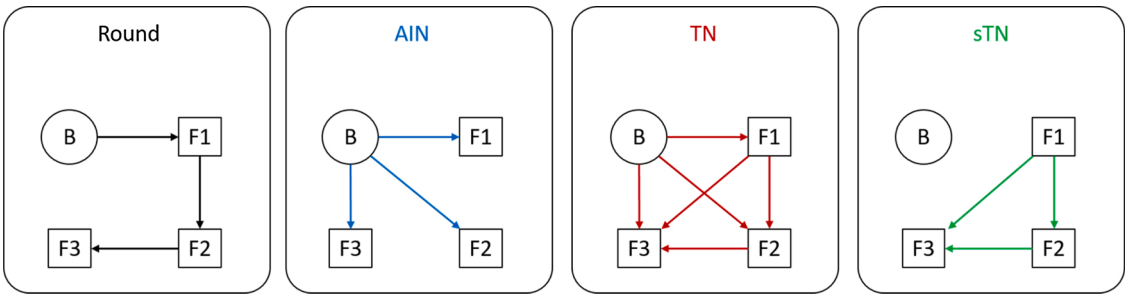

Fig. 1. Illustration of the reconstruction of the different directed networks (AIN: animal introduction network; TN: transit network; sTN: specific transit network) based on a single round. B: breeding farm, FX: fattening farm, with "X" indicating the order in the round (e.g., F1 = first fattening farm visited during the round). The AIN links farms to all those to which it sent live animals; the TN links farms to every single farm located downstream in the round (irrespective of whether there was a live-animal exchange or not); the sTN links farms that did not exchange live-animal but were connected through the transit of transport vehicle.

three occasions with pre-emptive culling of all poultry flocks within 1 km from infected farms and of all duck flocks within 3 km of infected farms (Bronner et al., 2017; DGAL, 2017a, 2017b). This epidemic led to the culling of 6.8 million of birds and induced severe disruptions in the poultry industry, causing important economic losses for local producers and for the whole poultry sector (Guinat et al., 2018). In particular, 81.6 % of H5N8 outbreaks reported in 2016–2017 in France were in farms raising ducks to produce foie gras (hereafter referred to as fattening ducks), mostly located in the southwest region (Guinat et al., 2018). The foie gras sector involves distinct production stages, which may be handled by different farms: rearing (1-day-old ducklings are reared for around three weeks), breeding (1-day to 3-week-old ducks are bred for around 9–12 weeks), and fattening (12-week-old ducks are fattened for around 12 days) (Guinat et al., 2020). Previous studies suggested that trade-related transport of fattening ducks have played a crucial role in the early stages of HPAI H5N8 epidemic (Guinat et al., 2019, 2020).

Network analysis provides a useful analytical framework to study contact patterns between farms generated by animal movements. In addition to the risk posed by movements of potentially infected live animals, contaminated transport vehicles used for these movements can also play a significant role in the transmission process (Lockhart et al., 2010). These contacts are usually defined as indirect, as opposed to exchange of live animal movements which are defined as direct contacts. Investigating these different contacts is key to analyse their respective contribution to a potential spread of pathogens in the duck industry. In recent years, numerous studies have used network analysis to describe potential pathogen spread and inform disease control intervention in various livestock species, including cattle or small ruminants (Kao et al., 2006; Ortiz-Pelaez et al., 2006; Brennan et al., 2008; Dutta et al., 2014; Marquetoux et al., 2016; VanderWaal et al., 2016b; Rossi et al., 2017; Bernini et al., 2019; Büttner and Krieter, 2020), pigs (Bigras-Poulin et al., 2007; Ribbens et al., 2009; Rautureau et al., 2011, 2012; Lentz et al., 2016; Thakur et al., 2016; Salines et al., 2017; Schulz et al., 2017; VanderWaal et al., 2018; Porphyre et al., 2020) and poultry (Soares Magalhães et al., 2010; Kurscheid et al., 2017; Guinat et al., 2020). Most of those studies focused solely on direct contact between farms, but some of them highlighted the potential indirect contact through the transit of contaminated transport vehicles used for the animal movements (Brennan et al., 2008; Ribbens et al., 2009; Thakur et al., 2016; Rossi et al., 2017; Salines et al., 2017; VanderWaal et al., 2018; Bernini et al., 2019; Büttner and Krieter, 2020; Porphyre et al., 2020). Findings suggested that transit of transport vehicles strongly increased the connectivity of farms, and emphasised that focusing only on live animal movements (direct contacts) would likely underestimate the risk of disease transmission.

The objectives of this study were three-fold: (i) to characterise the direct and indirect contact networks resulting from moving fattening ducks between farms in France during a non-epidemic period, (ii) to analyse the impact of the 2016–2017 HPAI H5N8 epidemic on the topology of these two networks and (iii) to analyse the respective contribution of direct and indirect contact networks in the distribution of HPAI H5N8 outbreaks.

2. Materials and methods

2.1. Data processing and network building

The recorded movements were collected from one of the most important French private transport companies. It conveys farm animals all over the country and accounted for around 70 % of live-duck movements between farms in southwest France during the study period. The dataset contained records of fattening duck movements operated from January 2016 to December 2018. It included movement characteristics (number of ducks loaded and unloaded and the vehicle identification that performed the movement) and farm details (identification of the sending and receiving farms, geographical location of sending and receiving farms). Movement of ducks from fattening farms to slaughterhouses was not included in the dataset. A single transport vehicle usually loads ducks from one breeding site and unloads them at several different fattening locations visited successively during the same day (DGAL, 2018). Furthermore, French regulations stipulate that transport vehicles have to be cleaned and disinfected at the end of each round. To do so they have to go to specific cleaning and disinfection stations that are distributed all across the region (DGAL, 2018). Therefore, the dataset was reorganised into transport vehicle round records, defined as the loading of ducks on one farm followed by the unloading of ducks on successive farms by a given transport vehicle on a given day. Farm type was determined based on the type of movements they were involved in, *i.e.* breeding (for farms only sending ducks), fattening (for those only receiving ducks) or mixed (for farms sending and receiving ducks during the study period).

A network analysis approach inspired by Salines et al. (2017) was taken to describe these movements. One-mode directed networks were created: farms were considered as nodes, and directional contacts between two nodes were considered as links. Two types of connections were considered, generating two different networks (Fig. 1): (i) the animal introduction network (AIN) where links represented the movements of live animals being exchanged between breeding and fattening farms; (ii) the transit network (TN) where links represented the contacts between farms based on the successive visits of several farms by a transport vehicle during its round. Since the AIN is embedded in the TN, a subnetwork was created that contained only indirect contacts between farms that did not exchange live animals. Hereafter, this subset will be referred to as the "specific transit network" (sTN). Each network was simplified to remove loops and multiple links between farms for the study period.

Table 1
Network analysis terminology as used in animal movement networks (Lockhart et al., 2010; Büttner et al., 2013; Dutta et al., 2014; Thakur et al., 2016; Salines et al., 2017; Machado et al., 2020).

Term	Level	Definitions
Betweenness	Farm	The frequency at which a farm is located on the shortest path between any two pairs of farms in the network.
Degree	Farm	The number of unique contacts a farm has (sum of unique in- and out-degrees).
In-degree	Farm	The number of different farms from which a farm receives animals.
Link	Farm	The directed contact between two farms (in our case, the movement of live animals or transit of transport vehicles).
Node	Farm	The epidemiological unit of interest in the network. In our case, a farm that was active during the study period.
Out-degree	Farm	The number of different farms to which a farm sent animals.
Assortativity	Network	The Pearson correlation coefficient between the degrees of linked farms.
Average degree	Network	The mean number of unique contacts a farm has
Average path length	Network	The average number of links along the shortest paths between all possible pairs of farms.
Clustering coefficient	Network	The average proportion of neighbours of a farm that are linked to each other. As a global measure, clustering coefficient quantifies 'cliquishness' within the network.
Density	Network	The proportion of actual links present over all possible links in the network.
Diameter	Network	The number of links in the shortest path between the most distant farms of the network for which a path exists.
Strongly Connected Component (SCC)	Network	The subset of networks involving at least two farms in which every farm can be reached from every other farm via one or several directed paths.

2.2. Data analysis

2.2.1. Network description

Both networks were described using the farm-to-farm directed networks generated with the movement data for the period from January 2018 to December 2018. This period corresponded to an interepidemic period for which France did not experience any HPAI epidemic (therefore, the networks were not supposed to be altered by any HPAI-related interventions) and for which the data was available. The movement data was aggregated on a yearly basis to compute both farm and network-level descriptive statistics for each network (Table 1). We also investigated if there was an association between farm types, betweenness and in and out-degree for both networks using Kruskal-Wallis and Wilcoxon test. All networks were generated and analysed using the igraph version 1.2.6 (Csardi and Nepusz, 2006) and tidyverse 1.3.0 (Wickham et al., 2019) packages in R version 4.0.2 (R Core Team, 2020).

Next, we assessed the node *in*-loyalty which measures the tendency of a farmer to purchase animals from the same sellers (for the AIN) and of a transport company to do the same rounds (for the TN) between two consecutive quarters in 2018. To do so, the data was aggregated on a quarterly basis to match the duration between the entry of two successive batches of ducks into a breeding farm. More specifically, the node *in*-loyalty index θ at time t measures the fraction of maintained contacts of a farm between periods $t-1$ and t. Therefore, the *in*-loyalty index varies between zero and one, with zero indicating that all connections were different between the periods, and one indicating that all links were maintained. The *in*-loyalty index for farm i at time t was calculated as follows:

$$\theta_i^{t-1,t} = \frac{\left| Y_i^{t-1} \cap Y_i^t \right|}{\left| Y_i^{t-1} \cup Y_i^t \right|} \quad (1)$$

with Y_i^t being the sets of in-going neighbours for farm i during the quarter t (Schulz et al., 2017).

2.2.2. Impact of the epidemics and related control measures on the topology of the network

We analysed the impact of the H5N8 epidemic and related control measures on the topology of the two networks (AIN and TN) by comparing the network-level statistics defined in Table 1 as well as the distribution of three farm-level statistics, in- and out-degree and betweenness, during the epidemic (January – March 2017) with those of before the epidemic (January – March 2016) and after the epidemic (January – March 2018). To do so, movement data were aggregated for each these three study periods. Statistical comparisons between the periods and the networks were performed with Wilcoxon tests, using the Bonferroni correction to account for multiple comparisons.

2.2.3. Role of direct and indirect contacts in the spread of HPAI H5N8 in France during the 2016–2017 epidemic

We assessed the potential contribution of live animal exchanges in the spread of HPAI H5N8 using a permutation-based approach, referred to as network k-test (VanderWaal et al., 2016a; Guinat et al., 2020), that was applied to the AIN. To assess the contribution of indirect contacts and because the AIN was embedded in the TN, we also applied the k-test to the sTN. The k-test was based upon the calculation of the k-statistic, in our case the number of "infectious" contacts that occurred in the networks. For the AIN, an infectious contact was defined as a live duck movement occurring between two outbreak farms (a breeding and a fattening farms) within t days before the date of suspicion of the most recent outbreak of the two. Similarly, for the sTN, an infectious contact was defined as a specific indirect contact (through the transit of transport vehicle but without live-animal exchange) occurring between two outbreak farms within t days before the date of suspicion of the most recent outbreak of the two. Because recent epidemiological findings suggest that duck mortality is likely to increase rapidly after HPAI (H5N8) virus introduction (Vergne et al., 2021), we considered a time-window of $t = 7$ days, but also tested longer periods of 14 and 21 days, similar to Guinat et al. (2020). The rationale behind the k-test approach was that if the virus spread through the networks, the number of infectious contacts would be significantly greater than expected under the null hypothesis, *i.e.* if infected farms were randomly distributed in the network. The observed value of the k-statistic was then compared to the distribution of the same statistic obtained by randomly reallocating the date of farms' suspicion date, thus simulating a possible pattern of cases under the null hypothesis of an absence of association between HPAI H5N8 infection status and contacts in the network. The empirical p-value of the k-test was calculated as the proportion of permutations for which the simulated k-statistic was greater than the observed one. We ran the permutation test with 10,000 trials to determine the p-value for the AIN and sTN. Finally, we calculated the risk of transmission by live-bird-movement-related direct (respectively indirect) contact, defined as the ratio of (i) the number of infectious direct (resp. indirect) contacts as defined above to (ii) the overall number of "at-risk" direct (resp. indirect) contacts originating from a farm that was reported in the following seven days and that did not necessarily generate a case in the receiving farm.

3. Results

3.1. Data description

There were 614 farms identified in the dataset, with 7,447,838 ducks exchanged through 7,371 movements between January 2016 and December 2018. The year 2018 had the highest recorded number of

Table 2
Number (and %) of live-duck movements operated between the different farm types in the southwest of France, January 2016 to December 2018.

	2016		2017		2018	
	To fattening	*To mixed*	*To fattening*	*To mixed*	*To fattening*	*To mixed*
From breeding	1,445 (60.3)	416 (17.4)	994 (64.8)	218 (14.2)	1,926 (56)	624 (18.1)
From mixed	395 (16.5)	141 (5.9)	225 (14.7)	97 (6.3)	649 (18.9)	241 (7)

Table 3
Descriptive indicators of the animal introduction network (AIN) and transit network (TN) in the duck sector, southwest France, 2018.

Indicators	January – December 2018	
	AIN	TN
No. of active nodes	395	395
No. of active links	2,684	3,664
Average degree	13.6	18.6
Average betweenness	4.0e-4	1.9e-03
Average path length	2.6	3.1
Density	0.02	0.03
Diameter	7	9
Clustering coefficient	0.1	0.3
Assortativity	0.09	0.05
Number of strongly connected components (SCCs)	1	4
Size of the largest SCC (proportion of nodes included in the largest SCC)	19 (4.8 %)	152 (38.5 %)

ducks exchanged (3,451,662) and of movements (3,440). The most common farm production type represented in the data was breeding (278), followed by fattening (225), and then mixed (111). The majority of live animal movements occurred from breeding to fattening farms (59.2 %), followed by mixed to fattening (17.2 %), breeding to mixed (17.1 %) and mixed to mixed farms (6.5 %) (Table 2). For that same period, 103 distinct transport vehicles were used to perform these live animal movements. The transport vehicles completed 7,359 rounds, with an average of 2.9 farms per round.

3.1.1. Comparison of the animal introduction network (AIN) and the transit network (TN)

In 2018, the AIN and the TN contained 395 active farms (Table 3). All statistics used to compare the two networks suggested that the TN was denser than the AIN, forming larger communities of farms with stronger connectivity. The overall number of links was around 1.4 times higher in the TN than in the AIN (3,664 and 2,684 links, respectively). Over 2018, on average in the TN a farm was in contact with 19 other farms (average degree), while in the AIN, a farm was in contact with 14 other farms. One and four strongly connected component (SCC) were identified in the AIN and the TN, respectively. The largest SCC in the TN included 152 active farms (38 %) which is eight times larger than the size of the only SCC identified in the AIN (19 active farms (4.8 %)), suggesting that the TN was less fragmented than the AIN. Moreover, any two given farms located in the largest SCC were separated on average (average path length) by 3.1 links in the TN versus 2.6 links in the AIN. The TN was 45 % denser than the AIN, with density statistics of 0.03 and 0.02, respectively. Due to TN's components greater size, it also had a longer diameter (1.3 times longer) than the AIN (9 versus 7). The clustering coefficients of the network were two times higher in the TN than in the AIN, suggesting that nodes were more tightly connected in the TN than in the AIN. The assortativity was positive for both networks, indicating that farms were more often linked to farms with similar degrees.

The degree distribution in 2018 for both networks was right-skewed (figure not shown), indicating that the majority of the farms had a low degree. Statistically significant differences of centrality values (betweenness, in- and out-degree) were observed between AIN and TN for the different farm types (Fig. 2) with higher values observed in the TN. There were also statistically significant differences of centrality values between farm types for each network (Fig. 2). For in-degree, higher values were observed for fattening as compared to mixed farms in the AIN ($p < 0.0001$) while in the TN, mixed farms had higher values ($p < 0.0001$). Bear in mind that the networks were unidirectional, and as such, the in-degree of breeding farms were equal to zero (Fig. 2) as they did not receive animals from mixed nor from fattening farms. For out-degree, breeding and mixed farms had higher values than fattening farms in the TN ($p < 0.0001$) while no significant difference was observed between mixed and fattening farms. For the TN, no significant difference in the betweenness distribution was observed between fattening and mixed farms (Kruskal-Wallis test: $p = 0.67$).

The distribution of loyalty values computed in both networks showed little variation between quarters (Fig. 3). The average loyalty index was around 15 % in AIN and 16 % in the TN.

3.1.2. Impact of the epidemics and related control measures on the topology of the network

The AIN contained 2.45 times more active nodes (319) during the period before the epidemic (first quarter of 2016) than during the epidemic (130) (Table 4). The number of links in the AIN before the epidemic (808) was 3.7 times higher than during the epidemic (218). On average, a farm exchanged animals with 5.1 different farms before the epidemic, while during the epidemic, this indicator decreased to 3.4 different farms (average degree distribution). The average path length dropped by 43 % during the epidemic from 2.3 to 1, due to a decrease of components size. Indeed, no SCC was detected in the AIN, as each component detected contained less than 1% of active nodes for both periods. The assortativity remained constant (0.2) during both periods. In the AIN, the clustering coefficient decreased from 0.03 to 0 between the period before the epidemic and epidemic period. In the TN, the clustering coefficient remained stable at around 0.16. The size of the largest SCC detected before the epidemic contained 71 active nodes as opposed to two active nodes during the epidemic. After the epidemic (January–March 2018), most network statistics returned to their values close to those before the epidemic. The number of active nodes and links were more than double that of the period during the epidemic. The number of different farms with which a given farm exchanged animals (average degree) was up by 23 % compared to during the epidemic, and the average path length was doubled. In the TN, the size of the largest SCC rose from two during the epidemic to 69 after the epidemic.

Similar to the network statistics, irrespective of the network and the farm type, all centrality measures dropped during the epidemic period and then increased again after, often statistically significantly (Fig. 4). However, in the AIN, the out-degree distributions for breeding and mixed farms did not statistically significantly change between the different periods (Fig. 4). Similarly, in the TN, the out-degree distribution did not drop statistically significantly, except for fattening farms. After the epidemic (January – March 2018), the distributions of the betweenness for all farm types and of the in-degree for mixed farms in the AIN and the TN were not statistically significantly different from the period before the epidemic. Nonetheless, the distributions of the in-degree for fattening farms in the AIN and the TN, despite increasing

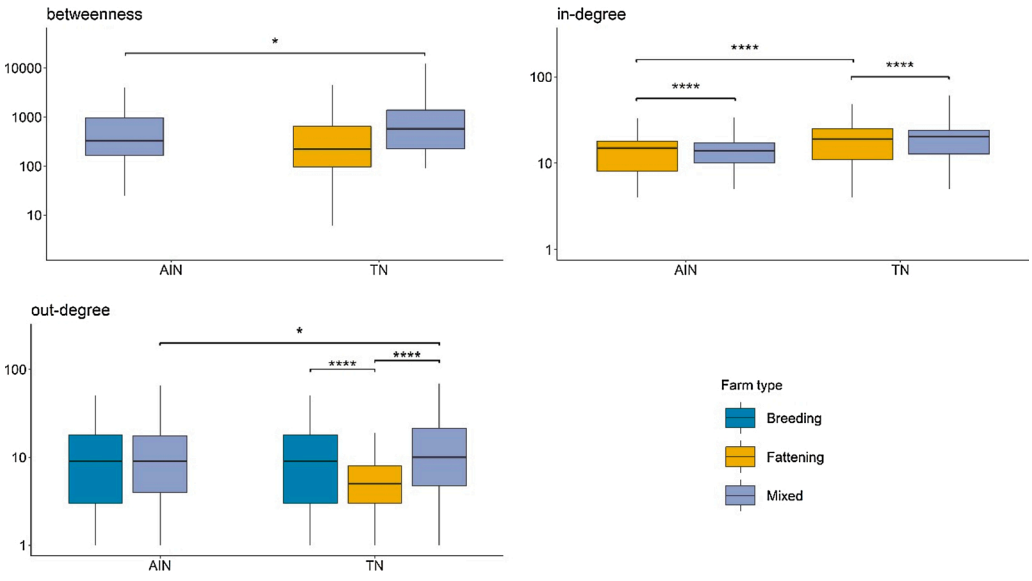

Fig. 2. Distribution of betweenness, in-degree and out-degree centrality measures in southwest France, 2018, according to different duck farm types, for the Animal Introduction Network (AIN) and Transit Network (TN) using a logarithmic scale. For each comparison, the p-value of the Wilcoxon test is shown to indicate whether the difference observed is significant (*: $p \leq 0.05$, **: $p \leq 0.01$, ***: $p \leq 0.001$; ****: $p \leq 0.0001$). Note that breeding and fattening farms are not represented in the betweenness panel for the AIN since they either send or received animals during a round and thus, there is no transit through them; Breeding farms are not represented in the in-degree panel for the AIN and the TN since they do not receive ducks from other farms; similarly, fattening farms are not represented in the out-degree panel for the AIN since they do not send ducks to other farms.

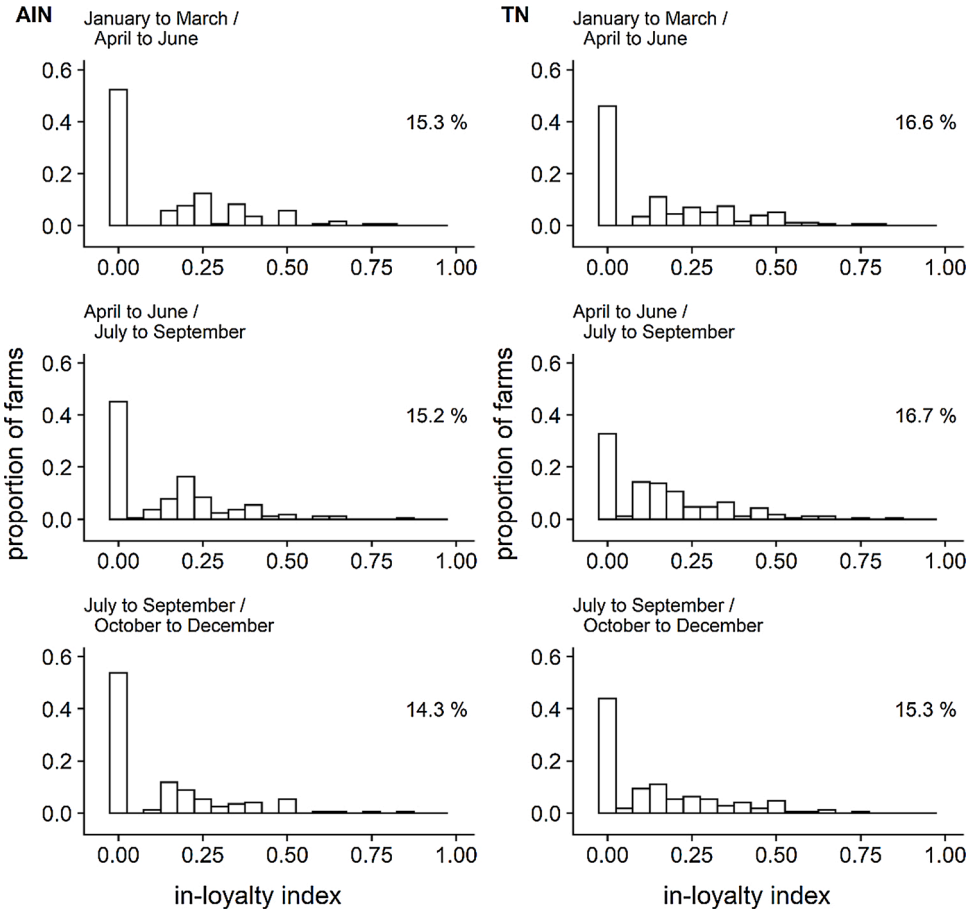

Fig. 3. Node *in*-loyalty distributions in the animal introduction network (AIN) and transit network (TN) from the duck sector in southwest France in 2018. The average percentage of origins maintained from one period to another is shown in the upper right corner.

Table 4
Descriptive indicators of the animal introduction network (AIN) and transit network (TN) of French duck movements for the first quarter (January–March) of 2016, 2017 and 2018 which correspond to the pre-epidemic, epidemic and post-epidemic periods, respectively.

Indicators	AIN			TN		
	2016	2017	2018	2016	2017	2018
No. of active nodes	319	130	310	319	130	310
No. of active links	808	218	676	1055	252	908
Average degree	5.1	3.4	4.4	6.6	3.9	5.9
Average betweenness	10.11	0.02	4.94	260.30	0.99	229.52
Average path length	2.3	1.0	2.0	5.1	1.4	5.0
Density	0.01	0.01	0.01	0.01	0.02	0.01
Diameter	6	2	6	15	4	18
Clustering coefficient	0.03	0	0.02	0.17	0.16	0.16
Assortativity	0.20	0.20	0.05	0.17	0.16	0.16
Number of strongly connected components (SCC)	0	0	1	3	5	3
Size of the largest SCC (proportion of nodes included in the largest SCC)	NA	NA	2 (0.7 %)	71 (22.1 %)	2 (1.5 %)	69 (22.3 %)

again after the epidemic, reached a level that was statistically significantly lower than before the epidemic (Fig. 4).

3.1.3. *Role of direct and indirect contacts in the spread of HPAI H5N8 in France during the 2016–2017 epidemic*

Using a time-window of seven days, we identified two infectious contacts in the AIN out of 7,376 movements (0.03 %). It included two movements from one mixed farm to two distinct fattening farms in early December 2016. This number of infectious contacts was found to be statistically significantly higher than what would be expected under the null hypothesis ($p < 0.0001$). Similarly, using the same time-window, one out of 2,763 contacts was considered infectious in the sTN, which was also statistically significantly higher than what would be expected under the null hypothesis ($p < 0.01$). It corresponded to the transit of a transport vehicle between one fattening and a mixed farm at the end of November 2016. Using the time-window of 14 or 21 days, the number of infectious contacts in each network were still statistically significant greater that what would be observed under the null hypothesis. Finally, the risk of transmission given an at-risk contact was calculated at 33.3 % for both the AIN (2/6) and the sTN (1/3), assuming an at-risk period of seven days prior to the suspicion notification.

4. Discussion

Network analysis has been widely used to investigate the implication of network structure in disease spread for various production systems (Rautureau et al., 2011, 2012; Marquetoux et al., 2016; Porphyre et al., 2020). This study showed that duck farms in southwest France are

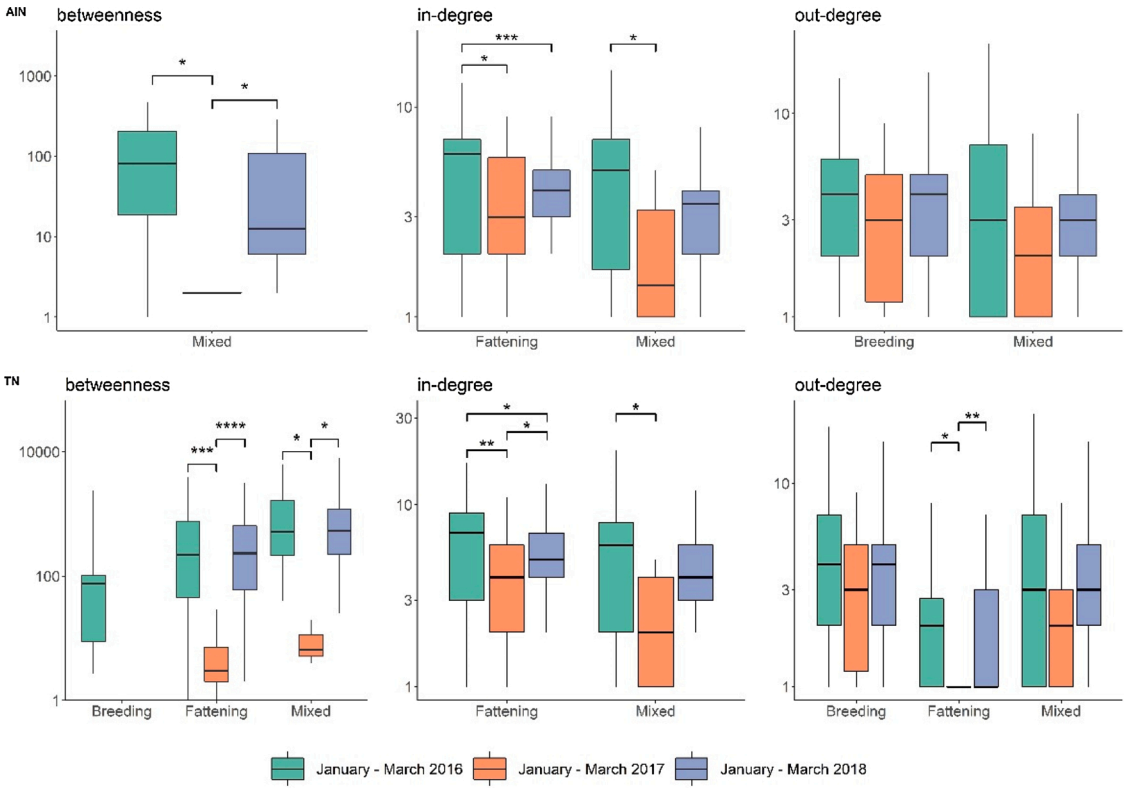

Fig. 4. Centrality indicators for the animal introduction network (AIN) and transit network (TN) in different farm types in the southwest of France before (January – March 2016), during (January – March 2017) and after (January – March 2018) the HPAI H5N8 epidemic using a logarithmic scale for the y-axis. For each comparison, the p-value of the Wilcoxon test is shown to indicate whether the difference observed is significant. Note that breeding and fattening farms are not represented in the betweenness panel for the AIN since they either send or received animals during a round and thus, there is no transit through them; Breeding farms are not represented in the in-degree panel for the AIN and the TN since they do not receive ducks from other farms; similarly, fattening farms are not represented in the out-degree panel for the AIN since they do not send ducks to other farms.

highly connected through the exchange of live birds, which is consistent with a previous analysis (Guinat et al., 2020). Most importantly, it demonstrated that the transport vehicles used to transport live birds were a significant source of inter-farm connectivity through the transit of the same transport vehicles to unload ducks in successive fattening farms. While only one transport company was studied here, this trend is however expected to be the same for other transport companies since the successive unloading of loaded batches of ducks is not specific of a company but is a specificity of the foie gras duck production system. Results showed that the TN connected many more farms than the AIN, as its largest SCC was eight times bigger than the largest SCC in the AIN. These findings are consistent with similar studies focused on transport networks of pig production system (Bigras-Poulin et al., 2007; Thakur et al., 2016; Salines et al., 2017) which is vertically integrated, similar to the foie gras duck production system in France, although the duck production is associated with fewer stages. We need to keep in mind that introducing an infected animal into a farm is expected to be much more effective in spreading a virus than the transit of a contaminated transport vehicle. However, our work highlighted a general need for a deeper knowledge of transmission mediated by fomites, including better ways to properly capture the frequency and probability of contacts due to transport vehicle movements. Consequently, deciphering the contact pattern of these movements could prove essential in constructing fine-tuned epidemiological models, estimating the worst-case scenario in terms of the size of an epidemic (Kao et al., 2006) and bring valuable information for disease management, including contact-tracing and surveillance.

For the French duck industry, our results suggested that mixed farms could be a key production type to consider in order to implement risk-based disease surveillance and to disrupt the contact network between duck farms in case of an epidemic. Indeed, despite their limited number in the dataset, mixed farms appeared more central (higher betweenness and degree values) than specialised breeding or fattening farms, irrespective of the network considered. As such, they present a higher risk to become infected through live-animal movements or the transit of transport vehicles and therefore could be relevant candidates for the implementation of risk-based surveillance approaches. They represent so-called bridges or hubs between different network components, what has been pin-pointed as a potential facilitator of disease spread in the French pig movement network (Rautureau et al., 2011). Therefore, in case of an epidemic, removing these farms through the culling of their flock would decrease theoretically the connection between the network components and limit disease spread through both live-animal movements and the transit of transport vehicles. An alternative to this culling could be to decrease duck farm density by reducing the number of at-risk farms during the high-risk period by forbidding duck placement in these farms and compensating farmers for the production losses. These results also emphasise that strict cleaning and disinfection protocols applied to transport vehicles should be combined with good compliance to external biosecurity measures on farms to limit disease spread. These hypotheses should now be tested by using mechanistic models for simulating disease spread and evaluate targeted control strategies.

Our analysis showed that the live animal movements and the transit of transport vehicles were associated with statistically significantly more infectious contacts than what would be expected if these networks did not contribute to the spread of the virus, suggesting that transmission events were likely to have occurred through these routes. In addition, it was shown that at-risk contacts (direct and indirect) through live-duck movements are relatively efficient at spreading the virus, since around 33 % of them led to an infection event. However, we only identified two and one infectious contacts in the AIN and the sTN, respectively, suggesting that the contribution of direct and indirect contacts to the overall number of transmission events was likely to be very small. The limited number of infectious contacts associated with the networks is likely to be the result of an effective implementation of movement control. These infectious contacts occurred at the very beginning of the epidemic (end of November 2016 and beginning of December 2016) so it is likely that their only contribution was to allow the epidemic to take-off. Then, following the rapid implementation of movement bans and regulations forbidding successive loadings of ducks during a round, the reinforcement of hygiene measures during transport and the systematic virological screening before animals are moved over long distances (more than 20 km) from breeding to fattening farms in early December have likely contributed to curb successfully the importance of these transmission routes in the subsequent phases of the epidemic.

Our results also demonstrated that node loyalty in both networks was highly volatile. On average, node loyalty from one trimester to the next never exceeded 17 %, indicating future contacts might be almost impossible to predict. Even though the AIN and the TN were profoundly impacted by the epidemic (Fig. 4), it is worth noting that most network characteristics after the epidemic returned to values similar to those from before the epidemic (Table 4). The only exception we noted was for the in-degree of fattening farms which were statistically significantly lower than before the epidemic. These two concurring results suggest that the epidemic led fattening farms to reduce the amount of partnering breeding farms and to be more loyal to them. It must however be acknowledged that network topology in early 2016 may have been partially affected by the HPAI outbreaks which occurred during winter 2015.

A limitation to the results presented here is that the data used were collected from a single transport company. Bias in network-level measures (fragmentation and lack of exhaustivity) can thus exist, resulting in a potential underestimation of farms' true connectivity. However, as previously stated the trend observed with this company is not expected to vary by including the other companies, thus our conclusions regarding the respective contribution of direct and indirect contacts in the H5N8 spread should remain valid. The extension of the analytical framework presented here to a broader dataset consisting of all transport companies would be necessary to gain a comprehensive view of farms' connectivity. However, several challenges subsist to reach this goal, including incompleteness and heterogeneity in data recording for the period of interest. Also, our analyses focused on movements operated between farms and did not consider movements to slaughterhouses, since this data was not available. In addition, although movements from and to slaughterhouses could potentially increase farm connectivity and thus facilitate transmission through indirect contact, this transmission route was deemed unlikely as strict cleaning and disinfection procedures were implemented for all transport vehicles leaving slaughterhouses (DGAL, 2017c).

Finally, it must be acknowledged that only a fraction of contacts which are established between farms were captured in the present study. Previous research (Lockhart et al., 2010) highlighted the variety of contact networks – including feed, live birds, poultry products, and manure and waste litter – co-existing in the poultry sector. While our results bring original insights on the respective contribution of direct and indirect contacts related to duck movements in the spread of H5N8 virus, further work is still needed to explore the role of other activities – including management of manure and waste litter, as well as rendering – in infectious contacts which may contribute to disease spread between farms.

Declaration of Competing Interest

The authors report no declarations of interest.

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VIII.2. Second article

Impact of duck farm density on the resilience of the poultry sector to highly pathogenic avian influenza H5N8 in France

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SUMMARY

We analysed the interplay between duck farm density and the vulnerability of the production system to highly pathogenic avian influenza (HPAI) H5N8. To do so, we used a spatial mechanistic model, which was calibrated to reproduce the observed spatio-temporal distribution of outbreaks in France during the 2016-2017 epidemic of HPAI. Six scenarios were investigated, in which the density of duck farms was decreased in the municipalities with the highest duck farm density. For each of the six scenarios, we first calculated the spatial distribution of the basic reproduction number (R_0), *i.e.* the expected number of farms a particular farm would be likely to infect, should all other farms be susceptible. We also ran *in silico* simulations of the adjusted model for each scenario to estimate epidemic sizes and time-varying effective reproduction numbers. We showed that reducing duck farm density in the densest municipalities decreased substantially the size of the areas with high R_0 values (>1.5) but that it would not be sufficient to reduce the transmission rate to levels that would completely prevent the virus from spreading. Our results show that reducing duck farm density in the densest municipalities is expected to decrease substantially the epidemic impact. However, they also suggest that it would not have been sufficient, even in combination with the intervention measures implemented during the 2016-2017 epidemic, to reduce the transmission rate enough to completely prevent the virus from spreading. Therefore, the effectiveness of alternative structural preventive

approaches now needs to be assessed, including flock size reduction, biosecurity compliance improvement and targeted vaccination.

INTRODUCTION

During the winter 2016-2017, France was hit hard by a highly pathogenic avian influenza (HPAI) virus, subtype H5N8, causing almost 500 outbreaks in poultry farms. Outbreaks mostly clustered in the Southwest region of the country, where large numbers of ducks are raised to produce foie-gras. In accordance with European regulations, the French government implemented strict control measures to control virus spread, including the culling of infected flocks, preventive culling of at-risk flocks, movement restrictions in affected zones and pre-movement testing of duck flocks.

Retrospectively, epidemiological studies have highlighted the role of various transmission routes and the factors that influenced the transmission dynamics of HPAI H5N8. Guinat et al. (2019) used a statistical approach to show that HPAI H5N8 outbreaks were much more likely to occur in areas with high density of farms raising ducks. This finding was consistent with findings from a mechanistic modelling study (Andronico et al., 2019) that highlighted the importance of local transmission between poultry farms and the higher susceptibility and infectivity of palmiped farms (e.g. ducks and geese) as compared to galliform farms (e.g. chickens, laying hens, quails, etc.) regarding H5N8 clade 2.3.4.4. Live-duck movements and the transit of vehicles used for these movements seem to have generated only very few transmission events during the 2016-2017 epidemic (Guinat et al., 2020; Bauzile et al., 2021), despite being shown to be an effective transmission route (Bauzile et al., 2021). Important efforts have been devoted in the subsequent years to improve external and internal biosecurity practices in French poultry farms, with the aim of preventing the risk of HPAI occurrence and its negative impacts (Delpont et al., 2021).

While no significant events were reported during the three following winters, France experienced devastating epidemics of HPAI during the winter 2020-2021 (subtype H5N8) and the winter 2021-2022 (subtype H5N1). The repeated occurrence of HPAI epidemics made a wide range of stakeholders of the poultry sector as well as decision-makers face the vulnerability of the French poultry sector with regards to HPAI. Indeed, they demonstrated cruelly that the major improvements on biosecurity implemented all along the poultry chain had remained insufficient to control recent strains of HPAI viruses.

Livestock farm density is regularly emphasised as a key factor driving highly contagious livestock disease transmission dynamic, as was shown for bluetongue (Turner et al., 2019), classical swine fever (Boender et al., 2014) or foot-and-mouth disease (Meadows et al., 2018). Consequently, reducing duck farm density in the areas with the highest densities could be an effective preventive measure to limit the risk of highly pathogenic avian influenza in France. This study aimed at providing

quantitative evidence of the impact a decrease of duck farm density in highly dense areas could have on the resilience of the poultry sector to HPAI outbreaks.

MATERIALS AND METHODS

Underlying mechanistic model

To address this question, we used a farm-based mechanistic spatial model that was calibrated to the observed spatio-temporal distribution of HPAI H5N8 outbreaks in France during the 2016-2017 epidemic wave, and described in detail in (Andronico et al., 2019). Briefly, the model assumed that the force of infection $\lambda_i(t)$ exerted on a given farm *i* at time *t* was given by

$$\lambda_i(t) = \sum_j \lambda_{j\to i}(t).I[j\ infectious\ at\ t] + {\lambda_i}^{ext} \quad (1)$$

where *I* is the indicator function, ${\lambda_i}^{ext}$ is an external force of infection accounting for infection sources other than the infectious farms located at less than 15 km from farm *i* (e.g. infectious wild birds and farms located further away), and $\lambda_{j\to i}(t)$ is a frequency-dependent force of infection exerted by farm *j* on farm *i* at time *t*, given by

$$\lambda_{j\to i}(t) = \psi_j.\varphi_i.\alpha_{SZ}(i,j,t).\frac{\beta(t)}{{N_j}^{15km}}.I\left[d_{ij} < 15km\right] \quad (2)$$

where ψ_j is the relative infectivity of farm *j* (with $\psi_j = 1$ for palmiped farms and $\psi_j = \psi$ for galliform farms), φ_i is the relative susceptibility of farm *i* (with $\varphi_i = 1$ for palmiped farms and $\varphi_i = \varphi$ for galliform farms), $\alpha_{SZ}(i,j,t)$ is a multiplicative term to account for changes in transmission for farms located in the surveillance zones implemented around infected premises (with $\alpha_{SZ}(i,j,t) = 1$ if both farms *i* and *j* do not belong to a surveillance zone at time *t* and $\alpha_{SZ}(i,j,t) = \alpha < 1$ otherwise), $\beta(t)$ is a time-space-varying between-farm transmission rate, ${N_j}^{15km}$ is the number of farms within 15km from farm *j*, and $I[d_{ij} < 15km]$ being an indicator function taking the value 1 if the Euclidean distance between farms *i* and *j* (d_{ij}) was smaller than 15km and 0 otherwise. Andronico et al. (2019) further assumed that the external force of infection, represented by ${\lambda_i}^{ext}$ in Eq.1, was defined as ${\lambda_i}^{ext} = \beta_{ext}.\varphi_i$, with β_{ext} being a constant external force of infection exerted on palmiped farms. Parameters ψ, φ, α_{SZ}, $\beta(t)$ and β_{ext} were estimated by fitting the model to the observed outbreaks during the 2016-2017 epidemic wave and are listed in Table 1. Further details on the model and assumptions can be found in the original paper (Andronico et al., 2019).

Table 1. Inferred model parameter values as estimated in Andronico et al. (2019)

Parameter	Definition	Median (95%CI)
ϕ	Relative susceptibility of galliform farms	0.20 (0.15, 0.27)
ψ	Relative infectivity of galliform farms	0.39 (0.10, 0.85)
β_0	Transmission rate in all departments but Landes	0.23 (0.16, 0.31)
β_1	Transmission rate in Landes before 22 Jan 2017	0.31 (0.20, 0.47)
β_2	Transmission rate in Landes between 22 Jan 2017 and 11 Feb 2017	0.53 (0.37, 0.72)
β_3	Transmission rate in Landes after 11 Feb 2017	0.28 (0.18, 0.40)
β_{ext}	External transmission rate (10^{-4})	0.86 (0.62, 1.15)

Definition of the density scenarios

We defined the study region as the area located within 100 km from any farm that became infected during the 2016-2017 epidemics (Figure 1). In that region, we further defined six scenarios of duck farm density. The baseline scenario considered all 8,379 commercial poultry farms, including 4,188 galliform and 4,191 palmiped farms, as used by Andronico et al. (2019) to estimate transmission parameters. Note that because the vast majority of palmiped farms in the region are farms raising ducks, palmiped farms will be referred to as duck farms hereafter. The five other scenarios simulated a decrease of duck farm density in the densest municipalities (smallest French administrative unit having a median surface of 10 km^2). To do so, we selected the 2, 5, 10, 15 and 20% of the municipalities with the highest duck farm density. Then, for each scenario, we used the lowest duck farm density of these selected municipalities as a threshold to reduce the duck farm density in the municipalities with a higher density, by randomly removing duck farms until the density reached the threshold (Figure 1). These scenarios represented respectively a removal of 62, 188, 477, 648 and 825 duck farms in 33, 80, 174, 256 and 341 municipalities.

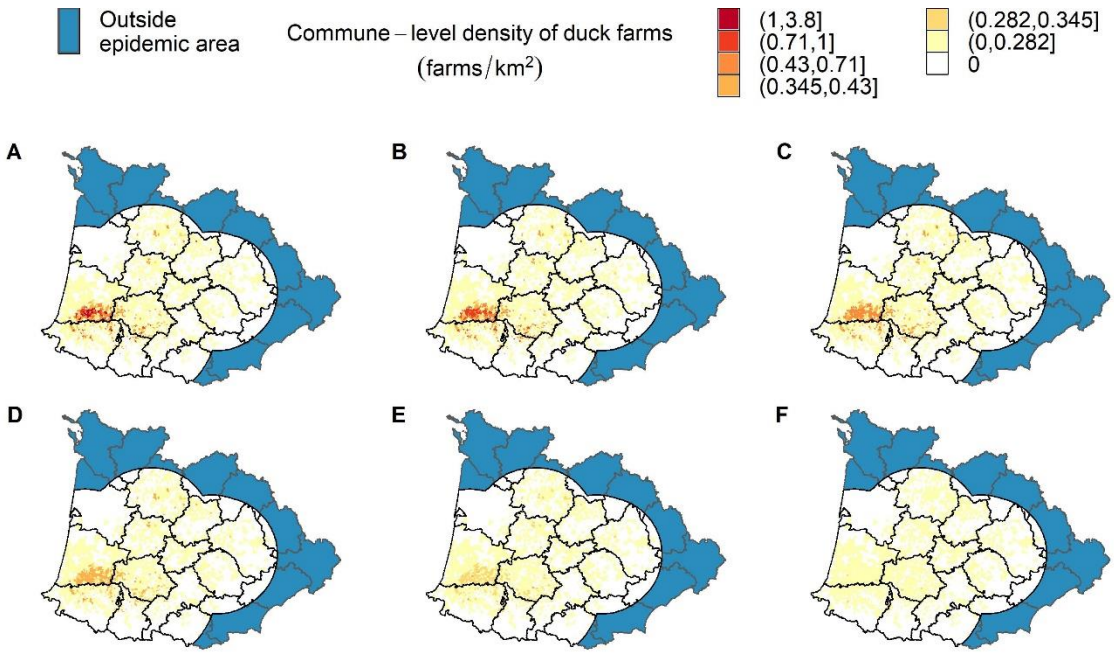

Figure 1. Distribution of duck farm density at municipality level in the Southwest region for each of the six scenarios after a simulated reduction of duck farm density in the 0% (A), 2% (B), 5% (C), 10% (D), 15% (E) and 20% (F) of the municipalities with the highest duck farm density. Note that the category thresholds in the legend correspond to the density thresholds used to define the scenarios. For instance, in scenario B, the densities of the 33 (2%) municipalities with densities between 1 and 3.8 duck farms/km² were all reduced to densities of 1 farm/km². Thus, all municipalities in scenario B had densities below 1 farm/km².

Estimation of the basic reproduction number (R_0)

For each of the six scenarios, we first calculated the basic reproduction number (R_0) for each farm, *i.e.* the expected number of farms a particular farm would be likely to infect, should all other farms be susceptible. For a given farm *j*, R_{0j} was defined as:

$$R0_j = \sum_i \left(1 - exp\left(-\delta * \lambda_{j \to i}\right)\right) \quad (3)$$

where δ is the duration of the infectious period for a farm (in days) and $\lambda_{j \to i}$ is the daily force of infection exerted by an infectious farm *j* on a susceptible farm *i*, as defined in accordance with Andronico et al. (2019) by:

$$\lambda_{j \to i}(t) = \psi_j . \varphi_i . \frac{\beta}{N_j^{15km}} I\left[d_{ij} < 15km\right] \quad (4)$$

where β is a constant β_0 as defined in Table 1. Note that the term $\alpha_{SZ}(i,j,t)$ is no longer part of the expression of $\lambda_{j\to i}(t)$ since the calculation of R_0 assumed that all farms were susceptible and therefore that no surveillance zones were implemented. Also, it is worth noting that R_0 did not integrate the external force of infection, so that, by construction, it only accounted for the infection events occurring within 15km from infected farms. For each scenario, the posterior distribution of R_{0i} was determined by randomly sampling 500 values in the posterior distributions of the parameters, as established in Andronico et al. (2019) and summarised in Table 1. The spatial distribution of R_0 values was smoothed using ordinary kriging method from gstat package (Gräler et al. 2016) to interpolate the R_0 from the data to the rest of the area and displayed using R software version 4.0.2 (R-Core-Team, 2021).

Estimation of the epidemic trajectories and of the effective reproduction number (*Re*)

We then investigated the impact that the reduction in duck farm density would have had on the 2016-2017 epidemic dynamics. To do so, we ran 500 stochastic simulations of the model for each scenario, assuming a force of infection as defined in Eq. (1), the same initial conditions as in the original model, and with parameter values drawn from their posterior distributions (Andronico et al., 2019). Note that the model accounted for the control strategies implemented during the 2016-2017 epidemic, including culling of infected flocks, implementation of surveillance and protection zones (SZ and PZ), enhancement of biosecurity measures in the SZ, and preventive culling of duck flocks in the PZ and of all poultry flocks within 1 km of infected premises starting in early January, as defined in Andronico et al. (2019). For each simulation, we reconstructed the transmission tree of the epidemic (*i.e.* we recorded who infected whom), from which we calculated, for each farm, the number of secondary infections they generated over the course of their infectiousness (i.e. until culling). From this, we calculated, for each day, the mean number of secondary infections generated by farms that became infected on that day and averaged it using a moving seven-day time window. This allowed the estimation of the effective reproduction number (R_e), *i.e.* the time-varying expected number of farms a particular farm would be likely to infect, while accounting for the implementation of control strategies. Similarly to the computation of the R_0, the R_e did not account to the infection events that were due to the external force of infection. For each scenario, the 500 simulated daily incidence and estimated R_e values were summarised using their 50% and 95% prediction intervals.

RESULTS

The spatial distribution of R_0 in the Southwest region of France for the six different scenarios is represented in Figure 2. Our estimates suggest that reducing the density of duck farms in the densest municipalities has a clear impact on the spatial distribution of R_0: the extent of the geographical areas with high R_0 values (>1.5) (in black in Figure 2) decreased as the duck farm density decreased. However, even when the farm density was reduced in the 20% densest municipalities (Figure 2F), *i.e.* when more than 800 duck farms were removed from the baseline population, R_0 remained higher than 1.5 in a relatively wide region, including the municipalities where the density was reduced, suggesting that reducing duck farm density would not prevent viral spread without the implementation of surveillance and intervention strategies.

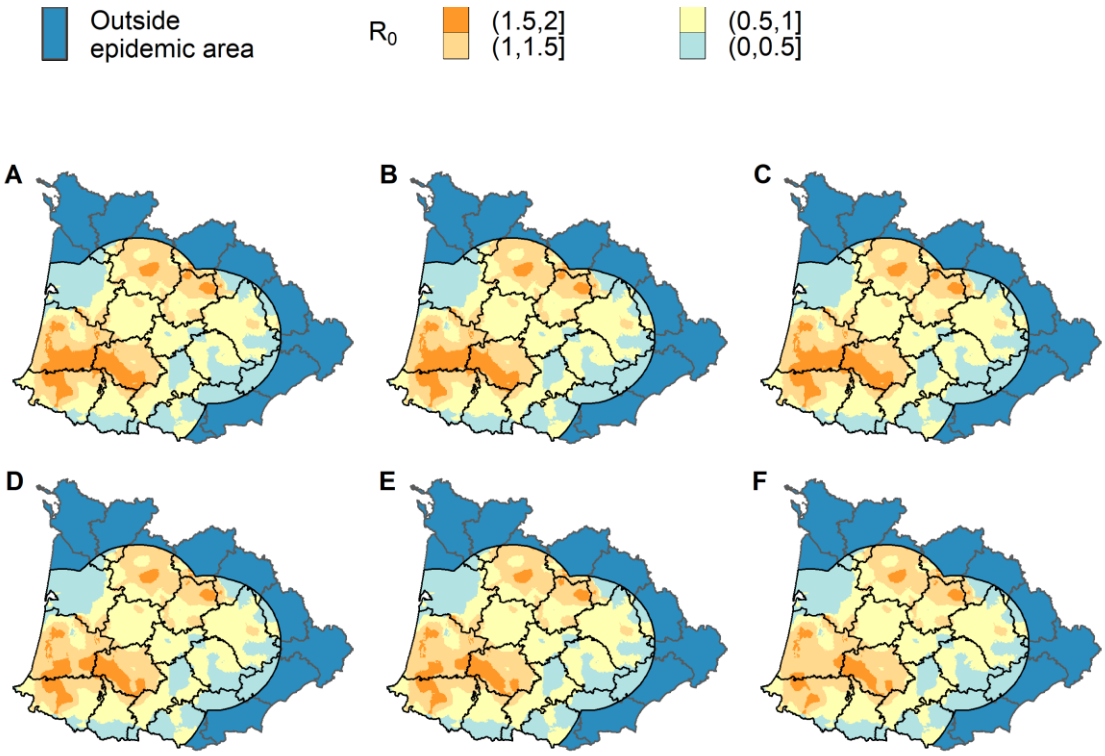

Figure 2. Smoothed spatial distribution of the basic reproduction number (R_0) for each of the six scenarios simulating a reduction of duck farm density in the 0% (A), 2% (B), 5% (C), 10% (D), 15% (E) and 20% (F) of the municipalities with the highest duck farm density.

As illustrated in Figure 3, when accounting for the control strategies implemented during the 2016-2017 epidemic, decreasing duck farm density in the densest municipalities would have had a substantial impact on the epidemic. Indeed, it is expected that reducing the duck farm density in the 20% densest municipalities would have decreased the expected final epidemic size by 66%, but it

would have still led to a total of 150 outbreaks (50% prediction interval: 120-196). Therefore, given the model assumptions, results suggest that none of the investigated scenarios would have totally curbed the epidemic.

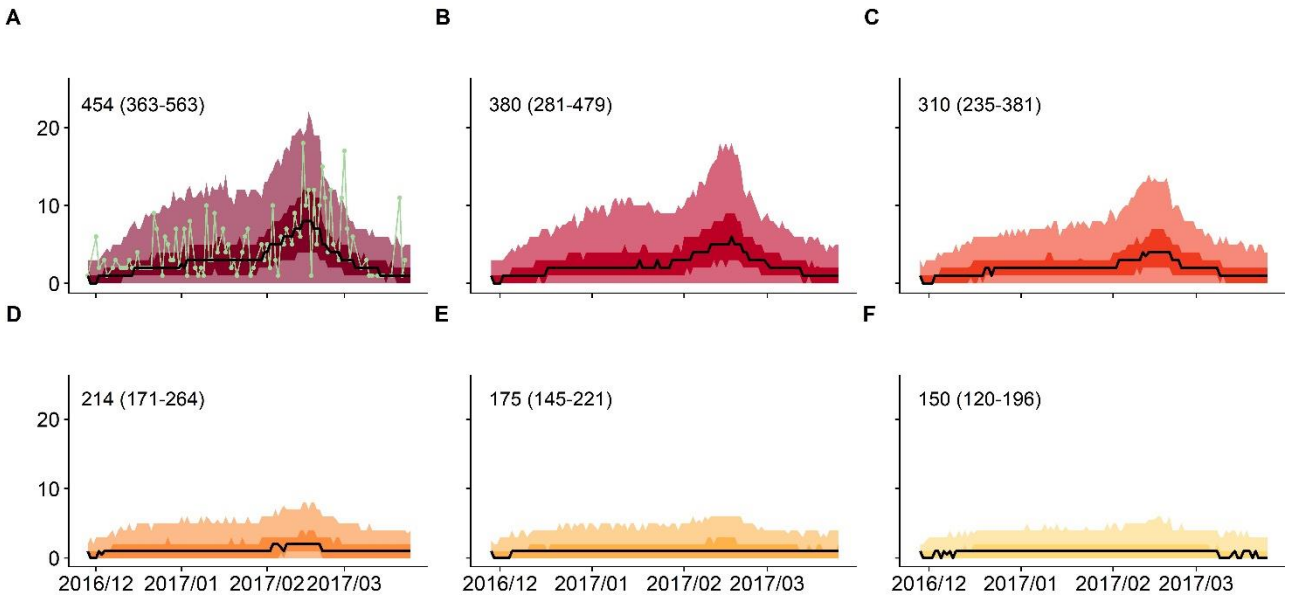

Figure 3. Expected daily incidence of HPAI outbreaks in France during the 2016-2017 epidemic, for each of the six scenarios simulating a reduction of duck farm density in the 0% (A), 2% (B), 5% (C), 10% (D), 15% (E) and 20% (F) of the municipalities with the highest duck farm density. In panel A, the green line shows the observed farm-level daily incidence during the 2016-2017 epidemic. In each panel, solid black lines represent the median daily incidence while the darker and lighter envelopes depict their 50% and 95% prediction intervals, respectively. The numbers inserted in the plot areas represent the expected epidemic size and its 50% prediction interval. This figure was based on 500 stochastic simulations from the model for each scenario with the same initial conditions, with parameter values drawn from their posterior distribution (including the external transmission rate assumed to be the same as during the 2016-2017 epidemic) and with the control strategies implemented during the 2016-2017 epidemic.

The reconstructed transmission trees of the simulated epidemics revealed that every farm that became infected from an external source of infection (*i.e.* either by wild birds or by farms located further than 15 km away) led to an average of 5.7 subsequent farm infections (95%CI: 5.2 – 6.3) in the baseline scenario and that this decreased to 1.8 farm infections (95%CI: 1.5 – 2.5) in the most stringent scenario. Figure 4 demonstrates how the temporal evolution of the *Re* values varied between scenarios. The intermediate scenario (reduction of the duck farm density in the 10% densest

municipalities through the removal of 477 duck farms) led to a 50% confidence that *R*e is below 1 throughout the epidemic (Figure 4D). The most stringent scenario (reduction of the duck farm density in the 20% densest municipalities through the removal of 825 duck farms) led to a 75% confidence that *R*e is below 1 throughout the epidemic (Figure 4F).

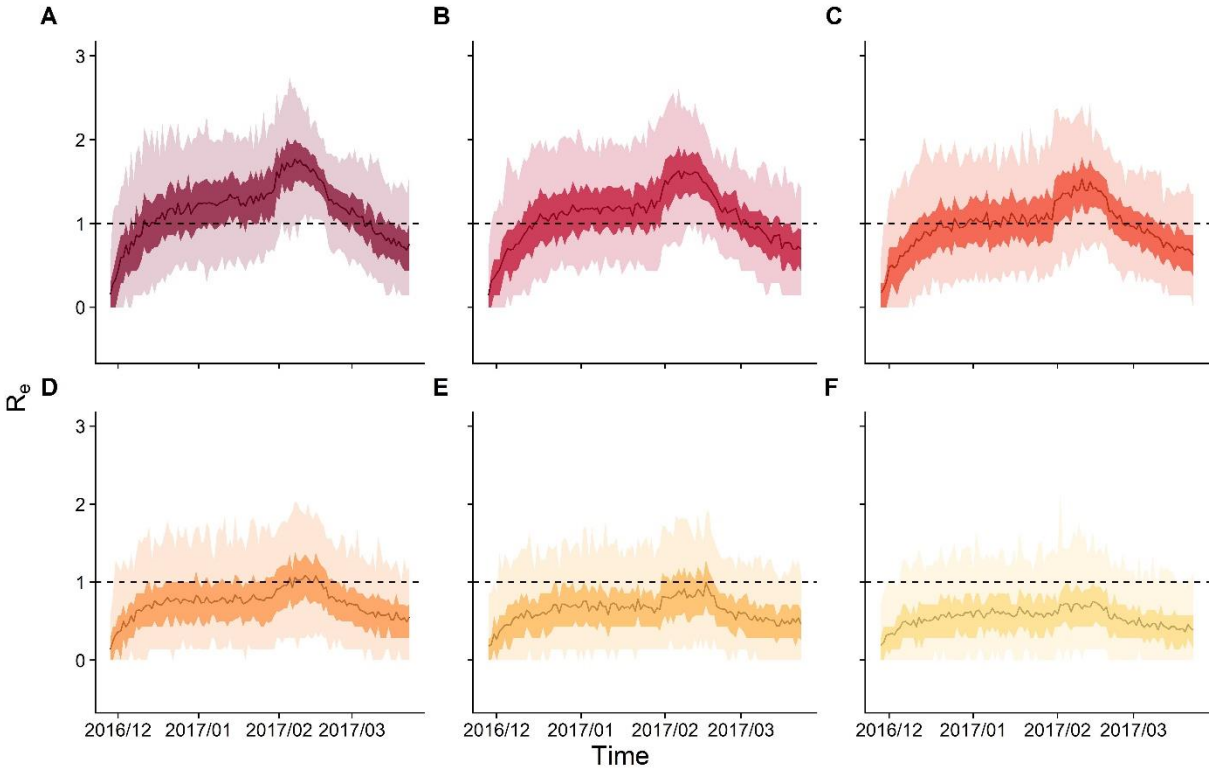

Figure 4. Time-varying effective reproduction numbers (Re) for each of the six scenarios simulating a reduction of duck farm density in the 0% (A), 2% (B), 5% (C), 10% (D), 15% (E) and 20% (F) of the municipalities with the highest duck farm density. In each panel, solid lines represent the mean Re while the darker and lighter envelopes depict their 50% and 95% prediction intervals, respectively.

DISCUSSION

Consistent with the evidence that farm density is a strong determinant of highly contagious disease transmission dynamics (Boender et al., 2014; Meadows et al., 2018; Turner et al., 2019), this modelling study provides quantitative evidence that reducing duck farm density in the densest municipalities would reduce substantially the vulnerability of the whole poultry sector to HPAI outbreaks. Indeed, we demonstrated that having fewer duck farms in the municipalities with the highest duck farm densities would provide intersectoral benefit by decreasing the overall risk to the poultry sector. For instance, reducing the duck farm density in the 20% densest municipalities decreased the number of outbreaks in poultry farms during the whole epidemic by 66%. It is worth noting that these results were obtained for the virus that circulated during the winter 2016-2017 (subtype H5N8), which had the particularity to have impacted more heavily the duck sector (Guinat et al., 2019), due to higher susceptibility and infectivity of duck farms as compared to galliform farms (Andronico et al., 2019). Therefore, reducing duck farm density may be expected to be less effective for other HPAI viruses for which the susceptibility and infectivity of galliform farms may be greater than palmiped farms.

Although it decreased the reproduction numbers and the epidemic size, we showed that decreasing duck farm density, even in combination with the intervention strategies that were implemented in 2016-2017, was not sufficient to reduce the transmission rate to levels that would completely prevent the virus from spreading (Figures 2 and 3). However, it is likely that our approach underestimated this density effect for two reasons. First, it was assumed that the timeliness of the intervention strategies that were implemented following the detection of outbreaks (represented in the model by the delay between the onset of infectiousness and the culling of the flock) was constant across scenarios. However, it is likely that reducing the outbreak incidence would limit the risk that the veterinary services become overwhelmed by the number of farms to depopulate or to control, as was shown to be the case for foot-and-mouth disease in various settings (Halasa and Boklund, 2014; Marschik et al., 2021; Roche et al., 2014). In turn, this could improve the timeliness of their intervention and their ability to communicate to farmers, thus reducing the delay before culling. Therefore, we would expect even lower daily incidence (Figure 3), number of farm-to-farm transmission events and Re values (Figure 4) for scenarios B to F. Second, the external forces of infection for duck or galliform farms (${\lambda_i}^{ext}$) were assumed to be constant across the epidemic and estimated based on the epidemiological context of the 2016-2017 epidemic. These two parameters, already included in the original model, were key to represent the long-distance transmission processes

that were not captured explicitly by the local farm-to-farm force of infection (Andronico et al., 2019). In the scenarios B to F, we used the same external forces of infection than in the baseline scenario, although it is likely that the external forces of infection would be positively correlated with the number of active outbreaks and therefore decrease with decreasing number of outbreaks incurred by the reduced duck farm density. Consequently, we may have overestimated the expected daily incidence (Figure 3) for scenarios B to F, and thus, the final epidemic sizes. It is worth noting that the number of farm-to-farm transmission events and the R_e values are not likely affected by this assumption, since the transmission trees used to calculate these epidemic statistics only focused on farm-to-farm transmission.

Implementing a reduction of duck farm density in the real world might not be easy. However, here are a few insights that could be of interest to reduce the density of duck farms specifically in the densest municipalities, over the short and the long term. On the short term, this effect could be achieved by extending the delay between production cycles (from the fattening or slaughtering of the previous batch of ducks to the installation of the following one) which is usually of around three weeks (DGAL, 2017; INAO, 2026). This would effectively reduce the number of duck farms that are active at a given time point. Such strategy could be applied during the high-risk period of HPAI introduction and spread (i.e. autumn and winter), providing duck breeders receive a financial compensation by the state to account for their production losses.

To further improve the resilience of the poultry sector to HPAI epidemics, given the reduction of duck farm density might not be sufficient and its implementation be likely to raise important socio-economic issues, it is now paramount to further investigate the effect of other strategies on the virus transmission dynamics. Meadows et al. (2018) disentangled the relative impact of farm and livestock density on foot-and-mouth disease epidemic size and showed that increasing livestock density was associated with larger epidemics, and that the effect of farm density on epidemic size increased with livestock density. Therefore, one important question that should now be addressed is related to the impact of duck flock size on virus transmission risk: indeed, instead of requesting some farmers in the densest municipalities to avoid producing during high-risk periods, an appealing alternative would be to ask most farmers to produce fewer ducks. Also, following the HPAI (H5N8) epidemic that occurred in France during the winter 2020-2021, the Ministry of Agriculture mandated large duck flocks (> 3,200 ducks) to be confined during the high-risk periods to avoid exposure to wild birds (DGAL, 2016). Therefore, another important question would be to assess the impact of outdoor farming on virus transmission risk. Unfortunately, the population data that were used to feed the model of the 2016-2017 epidemic were not sufficient to address these challenging questions. However, the relevant data are now available and could be used to reconstruct the 2020-2021

epidemic and assess the impact of these two complementary strategies. Further challenges for modelling studies include the evaluation of alternative preventive methods, including vaccination….

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Titre: Vers une meilleure compréhension des déterminants de la transmission de l'influenza aviaire dans le sud-ouest de la France

Mots clés : épidémiologie, maladies infectieuses, grippe aviaire, modélisation, analyse de réseau, voie de transmission, gestion.

La gestion des crises sanitaires liées aux virus de l'influenza aviaire est devenue un défi crucial pour la viabilité à long terme du secteur avicole européen. Au cours de la dernière décennie, l'Europe a connu quatre épizooties majeures d'influenza aviaire hautement pathogène (IAHP), entraînant de graves conséquences socio-économiques dans le secteur de la volaille. La France a été l'un des pays les plus impactés en Europe, avec environ 500 foyers aviaires déclarés en 2016 – 2017 et en 2020-2021. Ces foyers étaient principalement regroupés dans le sud-ouest de la France, une région où se trouve la plus forte concentration d'élevages de canards du pays. En outre, plus de 80 % des foyers détectés concernaient des élevages de canards, et il a été démontré qu'ils jouaient un rôle essentiel dans l'épidémiologie de l'IAHP.

Cette thèse de doctorat visait à fournir des indices sur les déterminants de la transmission de l'influenza analyses de réseau et des modèles mécanistes, nous avons décrit les schémas de contact direct et indirect des élevages de canards résultant de l'échange de canards vivants, déchiffré le rôle des mouvements d'oiseaux vivants dans la propagation de l'IAHP, et enfin évalué comment la densité des élevages de canards a contribué à la dissémination des virus de l'IAHP dans le sud-ouest de la France.

En utilisant une analyse de réseau des données sur les mouvements de canards vivants (2016 – 2018), nous avons d'abord décrit les patrons de contact entre les fermes, prenant en compte les contacts directs par l'échange de canards vivants et les contacts indirects par le transit des véhicules de transport utilisés pour échanger ces canards vivants. Nous avons estimé qu'une ferme liée épidémiologiquement à un foyer épidémique à travers ces réseaux avait une probabilité de 33 % d'être infectée. Cela indique que les réseaux résultant de ces mouvements étaient des voies de transmission efficaces de l'IAHP. Cependant, leur contribution à l'épizootie a été limitée, comme le soulignent les très rares événements de transmission dus à ces voies de transmission, vraisemblablement en raison des interdictions strictes de mouvements mises en place pour stopper l'épizootie. Ensuite, nous avons exploité un modèle mécaniste individu-centré développé pour évaluer la crise épizootique dans la région du sud-ouest et avons mis en œuvre différents scénarios liés à la réduction de la densité des élevages de canards pour aider à guider la prise de décision en cas de nouvelle épizootie. Nous avons évalué si une réduction de la densité des élevages de canards dans les communes les plus denses aurait amélioré la résilience du secteur face à la propagation du virus IAHP de sous-type H5N8 pendant l'épizootie de 2016 – 2017. Nous avons constaté que l'indice de reproduction de base resterait supérieur à un dans de grandes parties de la région sud-ouest, même avec une forte réduction de la densité des élevages de canards. Sur la base de ces résultats, les stratégies axées uniquement sur la réduction de la densité communale des élevages de canards seraient insuffisantes pour éliminer le risque de propagation de la grippe aviaire. Cependant, la combinaison de la réduction de la densité des élevages de canards et de la mise en œuvre des mesures de contrôle qui étaient en place pendant l'épizootie de 2016 – 2017 aurait permis de réduire de moitié la taille finale de l'épizootie.

En dépit des biais potentiels qu'on a discutés, cette thèse de doctorat améliore notre compréhension des voies de transmission. Au vu de ces résultats, nous encourageons 1) la poursuite de l'étude des schémas de contact dans les élevages afin de déchiffrer leur impact sur la transmission de la grippe aviaire, 2) l'exploration de changements structurels alternatifs du système de production avicole afin d'améliorer sa résilience aux menaces de l'IAHP, et 3) le développement de pipelines analytiques afin de fournir un soutien en temps réel aux décideurs politiques.

Title: Towards a better understanding of transmission determinants of avian influenza in southwest France

Keywords: epidemiology, infectious diseases, avian influenza, modeling, network analysis, transmission route, management

Managing sanitary crises linked to avian influenza viruses has become a crucial challenge for the long-term sustainability of the European poultry sector. In the last decade, Europe has experienced four major epizootics of the highly pathogenic avian influenza (HPAI), resulting in severe socioeconomic consequences in the poultry sector. France was one of the most impacted countries in Europe, with around 500 poultry outbreaks reported in 2016 – 2017. These outbreaks were primarily clustered in southwest France, a region with the country's highest concentration of duck farms. Furthermore, more than 80% of detected outbreaks were in duck farms, and they were shown to play a vital role in HPAI epidemiology.

This Ph.D. thesis aimed to provide insights on transmission determinants of highly pathogenic avian influenza in France. Using various quantitative epidemiological tools, including network analyses and mechanistic modeling, we described direct and indirect contact patterns of duck farms resulting from the exchange of live-duck, untangled the role of live-bird movements in the spread of HPAI, and finally evaluated how duck farm density contributed the dissemination of HPAI viruses in southwest France.

Using network analysis of live duck movement data (2016 – 2018), we first described the contact patterns between farms, including direct contacts through the exchange of live ducks and indirect contacts through transit of transport vehicles used to exchange these live ducks. We estimated that a farm epidemiologically linked with outbreak farms through these networks had a 33% probability of becoming infected. This indicates that networks resulting from these movements were efficient transmission routes for HPAI. However, their contribution to the epidemic has been limited, as highlighted by the very few transmission events that were likely due to these transmission routes, likely due to the stringent movement bans implemented to stop the epizootic. Then, we took advantage of an individual-based model developed to evaluate the epizootic crisis in the southwest region and implemented different scenarios related to the reduction in duck farm density to help guide decision-making in the event of a new epizootic. We assessed whether a reduction in the density of duck farms in the densest communes would have improved the sector's resilience to the spread of the HPAI H5N8 subtype virus during the 2016 – 2017 epizootic. We found that the basic reproduction number would remain higher than one in large parts of the southwest region, even with a strong reduction of duck farm density. Based on these results, strategies focused only on reducing the commune density of duck farms would be insufficient to eliminate the risk of avian influenza propagation. However, the combination of the reduction in duck farm density and the implementation of the control measures that were in place during the 2016 – 2017 epizootic would have halved the final size of the epizootic.

Despite the potential biases discussed, this Ph.D. presents some insights on transmission routes and how that understanding is vital in developing mechanistic models. Considering these results, we encourage 1) the further investigation of farm contact patterns to decipher their impact in avian influenza transmission, 2) the exploration of alternative structural changes of the poultry production system to improve its resilience to HPAI threats, and 3) the development of analytical pipelines to provide real-time support to policy-makers.