

1 **Title:** Two major epidemics of highly pathogenic avian influenza virus H5N8 and H5N1 in  
2 domestic poultry in France, 2020-2022

3

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22

23 **Summary**

24 The spread of highly pathogenic avian influenza (HPAI) viruses worldwide has serious  
25 consequences for animal health and a major economic impact on the poultry production  
26 sector. Since 2014, Europe has been severely hit by several HPAI epidemics, with France  
27 being the most affected country. Most recently, France was again affected by two devastating  
28 highly pathogenic avian influenza epidemics in 2020-21 and 2021-22. We conducted a  
29 descriptive analysis of the 2020-21 and 2021-22 epidemics, in a first step towards identifying  
30 the poultry sector's remaining vulnerabilities regarding HPAI viruses in France. We examined  
31 the spatio-temporal distribution of outbreaks that occurred in France in 2020-21 and 2021-22,  
32 and we assessed the outbreaks' spatial distribution in relation to two High-Risk Zones  
33 recently incorporated into French legislation to strengthen HPAI prevention and control.  
34 There were 468 reported outbreaks during the 2020-21 epidemic, and 1,223 outbreaks during  
35 the 2021-22 epidemic. In both epidemics, most outbreaks (80.6% and 74.0%) were located  
36 into the two High-Risk Zones. The southwestern High-Risk Zone was affected in both  
37 epidemics, while the western High-Risk Zone was affected for the first time in 2021-22,  
38 explaining the extremely high number of outbreaks reported. We showed that the spatial  
39 distribution model used to create the two High-Risk Zones was able to predict the location of  
40 outbreaks for the 2020-21 and 2021-22 epidemics. These zones were characterized by high  
41 poultry farm densities; future efforts should therefore focus on reducing the density of  
42 susceptible poultry in highly dense areas.

43

44 **Keywords:** Influenza A Virus, H5N1 Subtype; Influenza A Virus, H5N8 Subtype; Disease  
45 Outbreaks; Incidence; Basic Reproduction Number; Area Under Curve

46

## 47 **Introduction**

48 Unprecedented spread of highly pathogenic avian influenza (HPAI) viruses was  
49 observed across Europe, Asia, Africa and North America in the winter of 2021-22, infecting  
50 tens of millions of poultry birds and hundreds of thousands of wild birds (Miller, 2022; Wille  
51 and Barr, 2022). These viruses may cause severe clinical signs and high mortality rates in  
52 birds, causing serious economic losses in poultry and raising issues for the conservation of  
53 vulnerable wild bird species (Miller, 2022; Wille and Barr, 2022). HPAI viruses are also  
54 concerning for public health because of their zoonotic potential and the risk of spillover to  
55 people, which increases as the number of bird outbreaks increases (Miller, 2022; Wille and  
56 Barr, 2022).

57 In Europe, several HPAI subtype H5Nx epidemic waves occurred since the emergence  
58 of the current circulating lineage 2.3.4.4 and its introduction by wild migratory birds in late  
59 2014. In particular, during the winter of 2016-17, Europe was affected by an unexpectedly  
60 large HPAI subtype H5N8 epidemic, with 1,218 poultry farm outbreaks reported across 29  
61 countries (EFSA et al., 2022). During this epidemic, France was the most heavily affected  
62 European country, with 464 poultry farm outbreaks (Guinat et al., 2018). The control  
63 measures implemented included culling of infected farms (IFs) and pre-emptive culling of  
64 farms around IFs. These measures led to more than 6.8 million poultry being culled and  
65 caused a substantial economic impact on the French poultry industry (Guinat et al., 2018).  
66 Several studies highlighted the role of biosecurity practices, poultry farm density, and duck  
67 transportation in the spread of HPAI viruses between French farms during the 2016-17  
68 epidemic (Guinat et al., 2019; Guinat, Comin et al., 2020; Guinat, Durand et al., 2020;  
69 Bauzile, Sicard et al., 2022).

70 Following the 2015-16 and 2016-17 HPAI epidemics, new regulations on biosecurity  
71 for poultry farms and live bird transportation came into effect in France (DGAI, 2016, 2018).

72 A national training program was made mandatory for poultry producers, and the French  
73 veterinary authorities performed biosecurity audits on poultry farms between 2016 and 2018  
74 to verify compliance with the new regulations (Delpont et al., 2021). Two “High-Risk Zones”  
75 (HRZ) were also incorporated into French legislation in September 2021 (DGAI, 2021),  
76 where pre-emptive measures (such as confining ducks indoors and timely pre-movement  
77 testing) were implemented in autumn and winter when the risk of HPAI introduction  
78 increased. These two HRZ, located in the southwestern and western parts of France, were  
79 created based on a spatial distribution model of the 2016-17 outbreaks, and were  
80 characterized by high poultry farm densities and high duck movement numbers (Guinat et al.,  
81 2019).

82 In the winters of 2020-21 and 2021-22, France and Europe were affected by two other  
83 major HPAI epidemics (subtypes H5N8 and H5N1, respectively), with the number of poultry  
84 farm outbreaks exceeding those caused by the 2016-17 epidemic. Given the improved  
85 biosecurity and drastic control measures implemented in France, these latest epidemics are  
86 worrying. Our study therefore aimed to characterize the spatio-temporal patterns of the 2020-  
87 21 and 2021-22 epidemics in France and to assess the outbreaks’ spatial distribution in  
88 relation to the two HRZ. This constitutes a first step towards identifying the poultry sector’s  
89 remaining vulnerabilities regarding HPAI viruses in France.

90

## 91 **Materials and Methods**

### 92 *Data collection*

93 We obtained data on the HPAI poultry farm outbreaks for the 2020-21 (December 2,  
94 2020-March 20, 2021) and 2021-22 (November 21, 2021-April 12, 2022) epidemics from the  
95 French General Directorate for Food (DGAI) of the French Ministry of Agriculture. An  
96 outbreak was defined as detection of at least one laboratory confirmed HPAI-infected bird (by

97 virus isolation or polymerase chain reaction) in a commercial poultry farm. Data included the  
98 species involved, type of production, date of suspicion (by clinical or active surveillance) and  
99 geographical location of each outbreak. Spatial data were obtained from DGA1 for the HRZ,  
100 and from Guinat et al. (Guinat et al., 2019) for the predicted probability of having at least one  
101 HPAI outbreak in a commune (the smallest administrative unit in France, corresponding to  
102 Nomenclature of Territorial Units for Statistics level 5).

103

#### 104 *Descriptive analysis*

105 All analyses were conducted using R statistical software version 4.1.1 (R Core Team,  
106 2021). Epidemic curves were plotted using the R package incidence (Kamvar et al., 2019;  
107 Jombart et al., 2020). All maps were produced using the R package tmap (Tennekes, 2018).  
108 Geographic data of all countries and administrative areas were downloaded from the GADM  
109 (<https://gadm.org/>) database using the R package raster (Hijmans, 2021). Outbreaks for which  
110 the precise location was missing were given the coordinates of the centroid of the commune  
111 where they occurred. The coordinates of the communes' centroids were obtained from the  
112 French National Institute of Geographic and Forest Information (IGN) ADMIN EXPRESS  
113 database (<https://geoservices.ign.fr/adminexpress>). To assess the ability of the 2016-17 model  
114 (Guinat et al., 2019) to predict the location of outbreaks for the 2020-21 and 2021-22  
115 epidemics, we calculated the area under the receiver operator characteristic curves (AUC) for  
116 both epidemics using the R package pROC (Robin et al., 2011).

117

118

119 *Transmission dynamics (effective reproduction number)*

120 To study the transmission dynamics, we estimated the effective reproduction number  
121  $R_e$  between farms (i.e., the average number of secondary farms infected by each infectious  
122 farm) using the approach of Wallinga and Teunis (Wallinga and Teunis, 2004). The approach  
123 of Wallinga and Teunis allows estimating  $R_e$  based on the time variations of incidence and on  
124 the distribution of the serial interval (time interval between symptom onset in a farm and that  
125 of its secondary cases). Because the distribution of the serial interval distribution was  
126 unknown, we first used the approach of White and Pagano (White and Pagano, 2008) to  
127 estimate simultaneously the basic reproduction number  $R_0$  and the mean and standard  
128 deviation of the discretized serial interval distribution (assumed to follow a gamma  
129 distribution), based on the initial exponential phase of the epidemic. This approach was  
130 implemented using the R package R0 (Obadia et al., 2012; Boelle and Obadia, 2015). With  
131 the estimates of the serial interval distribution parameters, we were then able to estimate the  
132 effective reproduction number using the approach of Wallinga and Teunis (Wallinga and  
133 Teunis, 2004), implemented in the R package EpiEstim (Cori, 2021).

134 The estimates of the approach of White and Pagano (White and Pagano, 2008)  
135 implemented in the R package R0 can be sensitive to the selected time period over which  
136 epidemic growth is considered exponential (Obadia et al., 2012). By default, the time period  
137 considered is from the date of the first case up to the date of the maximum daily incidence  
138 (Obadia et al., 2012; Boelle and Obadia, 2015). Another possibility is to select the time period  
139 producing the largest R-squared value, corresponding to the period over which the model  
140 fitted the data best (Obadia et al., 2012). To assess the sensitivity of the  $R_e$  estimation to the  
141 parameters of the serial interval distribution, we used the approach of Wallinga and Teunis  
142 (Wallinga and Teunis, 2004) again, this time using the mean and standard deviation of the  
143 serial interval distribution that produced the highest R-squared value.

## 144 **Results and Discussion**

145           The 2020-21 epidemic consisted of a single wave with 468 outbreaks (Figure 1A)  
146 clustered in southwestern France (Figure 2A). In contrast, the 2021-22 epidemic was  
147 characterized by 1,223 outbreaks (as of April 12, 2022) divided into two spatio-temporal  
148 clusters, the first in the southwest and the second in the western part of the country (Figure 1B  
149 and Figure 2B), with a higher incidence during the second wave. Most outbreaks were located  
150 in the HRZ, both in 2020-21 (80.6% of the outbreaks) and 2021-22 (74.0% - Figure 1A and B,  
151 Figure 2). The AUCs of the 2016-17 model were 0.86 (95% confidence interval: 0.83-0.89)  
152 for the 2020-21 epidemic and 0.86 (95%CI: 0.85-0.88) for the 2021-22 epidemic.

153           In both epidemics, the vast majority of farm outbreaks in the southwestern HRZ  
154 (82.7% and 69.9%) were reported in ducks (Table 1), mainly in farms raising ducks for *foie*  
155 *gras* production (breeding and/or force-feeding production stages in Table 1). Conversely, in  
156 the western HRZ in 2021-22, only half of the outbreaks were reported in duck farms, mainly  
157 in breeder and broiler farms (Table 1). Most of the other outbreaks were reported in galliform  
158 farms (mainly chickens and turkeys - Table 1).

159           The estimates of the average serial interval were 4.78 days (standard deviation: 4.63  
160 days) for the 2020-21 epidemic, and 8.9 days (standard deviation: 4.08 days) for the 2021-22  
161 epidemic (Supporting Information Figure S1). In the winter of 2020-21, the  $R_e$  peaked at 2.2  
162 (95%CI: 1.7-2.5) in late December 2020, when the incidence increased in the southwestern  
163 HRZ, then decreased below 1 from mid-January 2021 (Figure 1C). In 2021-22, the  $R_e$  first  
164 peaked at 2.8 (95%CI: 2.5-3.1) in early January 2022, when the virus was mostly circulating  
165 in the southwestern HRZ, and then decreased below 1 in the second half of January 2022  
166 (Figure 1D). At the beginning of February 2022, the  $R_e$  increased again dramatically when the  
167 virus reached the western HRZ, peaked at 3.8 (95%CI: 3.4-4.3) at the end of February 2022  
168 and then decreased below 1 by mid-March 2022 (Figure 1D).

169           The temporal variations of the  $R_e$  estimated using the serial interval distribution  
170 parameters of White and Pagano's default model (Figure 1C-D) matched qualitatively and  
171 quantitatively with the  $R_e$  dynamics estimated using the serial interval distribution parameters  
172 of White and Pagano's model with the highest R-squared value (Supporting Information  
173 Figure S2), although in the latter the  $R_e$  seemed to peak at higher values in 2021-22.

174           During the 2020-21 and 2021-22 epidemics, the virus circulated extensively in the  
175 southwestern HRZ. In that region, where the density of farms raising ducks for *foie gras*  
176 production is extremely high, it is worth noting that the number of reported outbreaks  
177 decreased from 375 to 276 between the two epidemics, likely the result of a higher level of  
178 awareness among farmers, more effective implementation of control strategies and a decrease  
179 of duck flock density. However, in the winter of 2021-22, a second spatio-temporal cluster of  
180 outbreaks occurred in the western HRZ, with no clear epidemiological link with the  
181 southwestern cluster (EFSA et al., 2022). The spread of HPAI within the western HRZ  
182 occurred for the first time during the 2021-22 epidemic and explains the extremely high  
183 number of outbreaks reported. The species composition in poultry farms in this zone,  
184 combined with a higher flock size on average, may have had a significant impact on the  
185 pattern of the epidemic in this area. Why the virus spread in the western HRZ in 2021-22 but  
186 not in the previous epidemics remains to be determined.

187           Biosecurity and control measures were significantly improved after 2016. The  
188 occurrence of these two major epidemics would suggest that these improvements were not  
189 sufficient to prevent the spread of the virus. Interestingly, although the 2016-17 outbreaks  
190 only clustered in the southwest part of France, Guinat et al. (Guinat et al., 2019) identified  
191 two HRZ that predicted with high accuracy the two spatial clusters observed during the 2021-  
192 22 epidemic (Figure 2B). The main risk factors identified were density of poultry farms and  
193 activities related to duck movements. The latter risk factor has already been the target of



194 considerable improvement measures. To increase the resilience of the poultry sector in  
195 France, and other hardly-hit European countries, future efforts should therefore focus on  
196 reducing the density of susceptible poultry farms and the number of susceptible birds on  
197 farms in high-density areas during the high risk periods (Bauzile, Durand et al., 2022).

198         Vaccinating domestic poultry against avian influenza is generally prohibited in the  
199 European Union due to the trade restrictions it would generate (European Commission, 2006).  
200 However, this once-tabooed prevention strategy is currently being given full consideration in  
201 Europe, as it is becoming clear that the accelerating pace of occurrence of devastating HPAI  
202 epidemics is generating new challenges that cannot be addressed with more traditional  
203 prevention and control approaches alone (EFSA et al., 2021; Stokstad, 2022; Wille and Barr,  
204 2022). In the long term, restructuration of the European poultry sector in densely populated  
205 poultry areas, although challenging, may be required alongside vaccination to control HPAI  
206 epidemics (EFSA et al., 2021; Stokstad, 2022). Therefore, further research is needed to devise  
207 new suitable and sustainable HPAI mitigation strategies in Europe.

208

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217

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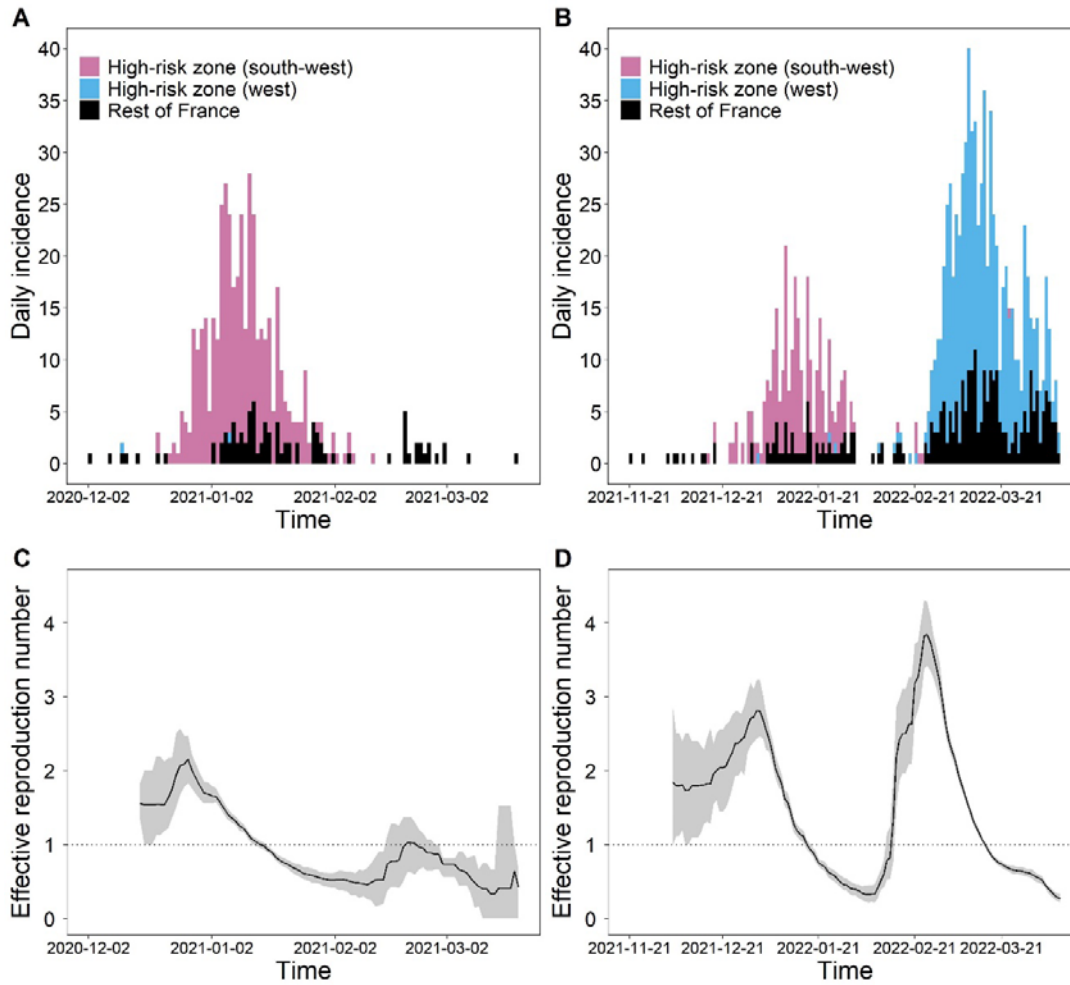
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305 **Table 1: Distribution of HPAI virus outbreaks in commercial poultry farms in France**  
 306 **during the 2020-21 (H5N8) and 2021-22 (H5N1) epidemics**

	2020-21		2021-22			
	South-West*	TOTAL	South-West*	West†	TOTAL	
<b>Type of species</b>						
Duck	310 (82.7%)	389 (83.1%)	193 (69.9%)	315 (50.1%)	711	(58.1%)
Goose	1 (0.3%)	1 (0.2%)	4 (1.4%)	4 (0.6%)	8	(0.7%)
Chicken	34 (9.1%)	42 (9.0%)	45 (16.3%)	172 (27.3%)	287	(23.5%)
Turkey	-	-	-	-	77	(12.2%)
Other galliformes	6 (1.6%)	7 (1.5%)	5 (1.8%)	35 (5.6%)	44	(3.6%)
Multispecies (galliformes)	2 (0.5%)	2 (0.4%)	1 (0.4%)	-	4	(0.3%)
Multispecies (palmipeds + galliformes)	22 (5.9%)	27 (5.8%)	5 (1.8%)	6 (1.0%)	14	(1.1%)
Pigeon	-	-	-	-	2	(0.3%)
Unknown	-	-	23 (8.3%)	18 (2.9%)	52	(4.3%)
<b>TOTAL</b>	<b>375 (100%)</b>	<b>468 (100%)</b>	<b>276 (100%)</b>	<b>629 (100%)</b>	<b>1,223</b>	<b>(100%)</b>
<b>Type of production for duck farms</b>						
Breeding	211 (68.1%)	260 (66.8%)	120 (62.2%)	64 (20.3%)	276	(38.8%)
Force-feeding	76 (24.5%)	97 (24.9%)	52 (26.9%)	40 (12.7%)	132	(18.6%)
Breeding + force-feeding	1 (0.3%)	1 (0.3%)	-	-	-	-
Broiler	2 (0.6%)	7 (1.8%)	6 (3.1%)	126 (40.0%)	178	(25.0%)
Breeder	7 (2.3%)	8 (2.1%)	1 (0.5%)	53 (16.8%)	68	(9.6%)
Other	2 (0.6%)	3 (0.8%)	2 (1.0%)	19 (6.0%)	25	(3.5%)
Unknown	11 (3.5%)	13 (3.3%)	12 (6.2%)	13 (4.1%)	32	(4.5%)
<b>TOTAL</b>	<b>310 (100%)</b>	<b>389 (100%)</b>	<b>193 (100%)</b>	<b>315 (100%)</b>	<b>711</b>	<b>(100%)</b>
<b>Type of production for chicken farms</b>						
Broiler	26 (76.5%)	33 (78.6%)	32 (71.1%)	101 (58.7%)	164	(57.1%)
Layer	4 (11.8%)	5 (11.9%)	7 (15.6%)	32 (18.6%)	65	(22.6%)
Breeder	3 (8.8%)	3 (7.1%)	1 (2.2%)	20 (11.6%)	26	(9.1%)
Other	-	-	-	15 (8.7%)	22	(7.7%)
Unknown	1 (2.9%)	1 (2.4%)	5 (11.1%)	4 (2.3%)	10	(3.5%)
<b>TOTAL</b>	<b>34 (100%)</b>	<b>42 (100%)</b>	<b>45 (100%)</b>	<b>172 (100%)</b>	<b>287</b>	<b>(100%)</b>

307 \* Southwestern high-risk zone,

308 † Western high-risk zone (note that in 2020-21, only two outbreaks were located in the  
 309 western high-risk zone, and were therefore not detailed here).



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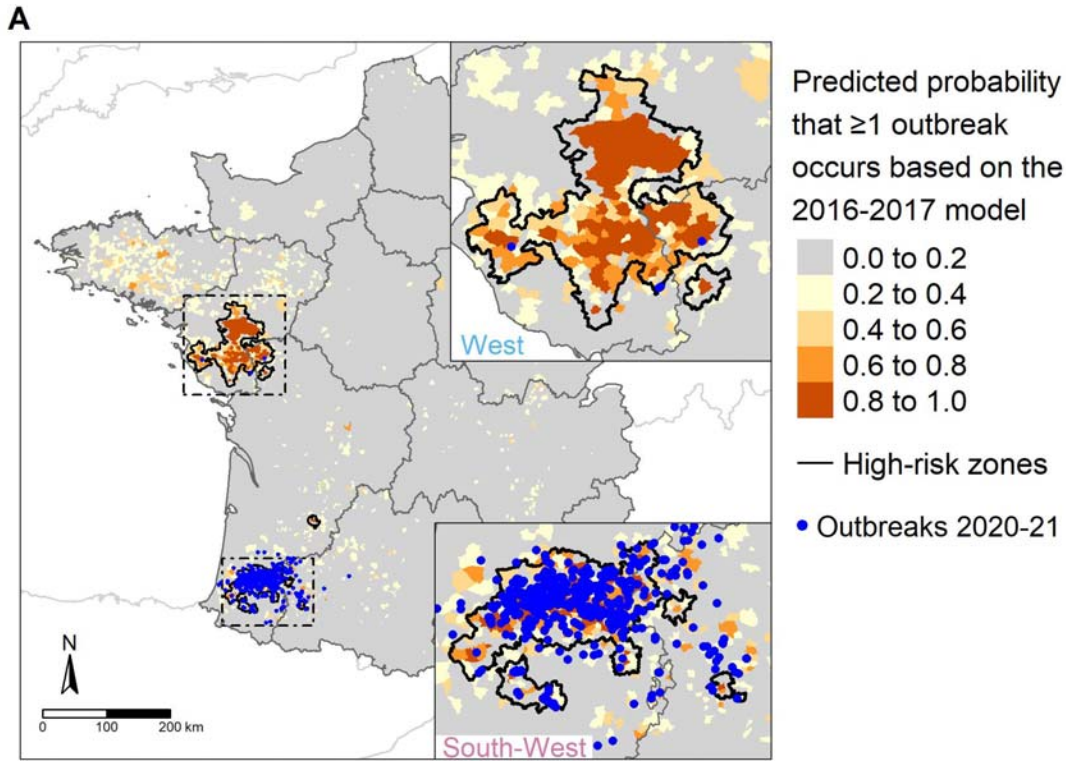
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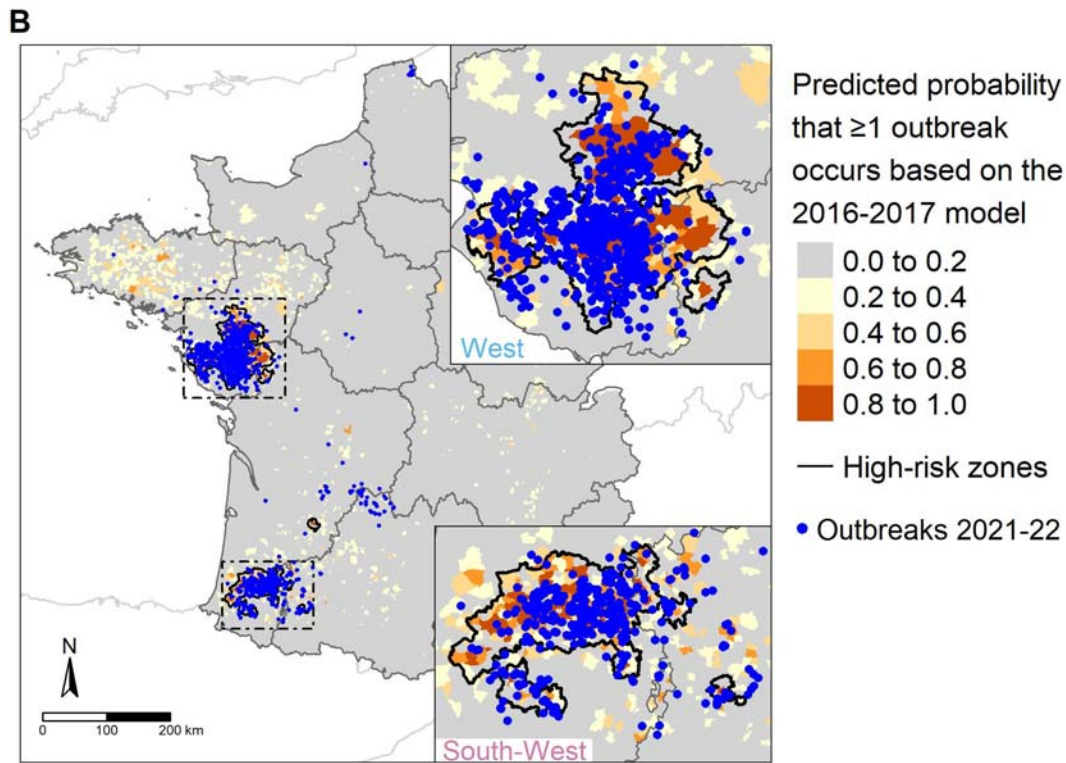
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**Figure 1: Incidence (A, B) and estimated effective reproduction number (C, D) of the 2020-21 (A, C) and 2021-22 (B, D) HPAI virus epidemics in commercial poultry farms in France.** In panels C and D, the graph shows, at each day, the estimate of the effective reproduction number over the 14-day window finishing on that day. The line represents the mean and the grey area represent the 95% confidence interval.



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**Figure 2: HPAI virus outbreaks in commercial poultry farms in France in 2020-21 (A) and 2021-22 (B), and predicted probability of having at least one outbreak in a commune according to the 2016-2017 model of Guinat *et al.* (2019) (2019).**