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Two major epidemics of highly pathogenic avian influenza virus H5N8 and H5N1 in domestic poultry in France, 2020–2022

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13

14 **Authors:** Sébastien Lambert¹, Benoit Durand², Mathieu Andraud³, Roxane Delacourt¹, Axelle
15 Scoizec³, Sophie Le Bouquin³, Séverine Rautureau⁴, Billy Bauzile¹, Claire Guinat^{5,6}, Lisa
16 Fournet¹, Jean-Luc Guérin¹, Mathilde C. Paul¹ and Timothée Vergne¹

17

18 **Affiliations:**

19 ¹ IHAP, Université de Toulouse, INRAE, ENVT, Toulouse, France

20 ² Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail,
21 Université Paris-Est, Maisons-Alfort, France

22 ³ Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail,
23 Ploufragan, France

24 ⁴ Direction Générale de l'Alimentation, Paris, France

25 ⁵ Department of Biosystems Science and Engineering, ETH Zurich, Basel, Switzerland

26 ⁶ Swiss Institute of Bioinformatics, Lausanne, Switzerland

27

28 **Correspondence:** Sébastien Lambert, IHAP, Université de Toulouse, INRAE, ENVT,
29 Toulouse, France

30 Email: sebastien.lambert@envt.fr

31

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34

35 **Summary**

36 The spread of highly pathogenic avian influenza (HPAI) viruses worldwide has serious
37 consequences for animal health and a major economic impact on the poultry production
38 sector. Since 2014, Europe has been severely hit by several HPAI epidemics, with France
39 being the most affected country. Most recently, France was again affected by two devastating
40 highly pathogenic avian influenza epidemics in 2020-21 and 2021-22. We conducted a
41 descriptive analysis of the 2020-21 and 2021-22 epidemics, in a first step towards identifying
42 the poultry sector's remaining vulnerabilities regarding HPAI viruses in France. We examined
43 the spatio-temporal distribution of outbreaks that occurred in France in 2020-21 and 2021-22,
44 and we assessed the outbreaks' spatial distribution in relation to the 2016-17 epidemic and to
45 the two "high-risk zones" recently incorporated into French legislation to strengthen HPAI
46 prevention and control. There were 468 reported outbreaks during the 2020-21 epidemic, and
47 1,375 outbreaks during the 2021-22 epidemic. In both epidemics, the outbreaks' distribution
48 matched extremely well that of 2016-17 and most outbreaks (80.6% and 68.4%) were located
49 into the two high-risk zones. The southwestern high-risk zone was affected in both epidemics,
50 while the western high-risk zone was affected for the first time in 2021-22, explaining the
51 extremely high number of outbreaks reported. As soon as the virus reached the high-risk
52 zones, it started to spread between farms at very high rates, with each infected farm infecting
53 between two and three other farms at the peaks of transmission. We showed that the spatial
54 distribution model used to create the two high-risk zones was able to predict the location of
55 outbreaks for the 2020-21 and 2021-22 epidemics. These zones were characterized by high
56 poultry farm densities; future efforts should therefore focus on reducing the density of
57 susceptible poultry in highly dense areas.

58

59

60 **Introduction**

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

70 In Europe, several HPAI subtype H5Nx epidemic waves occurred since the emergence
71 of the current circulating lineage 2.3.4.4 and its introduction by wild migratory birds in late
72 2014. In particular, during the winter of 2016-17, Europe was affected by an unexpectedly
73 large HPAI subtype H5N8 epidemic, with 1,218 poultry farm outbreaks reported across 29
74 countries (EFSA et al., 2022a). During this epidemic, France was the most heavily affected
75 European country, with 464 poultry farm outbreaks (Guinat et al., 2018). The control
76 measures implemented included culling of infected farms (IFs) and pre-emptive culling of
77 farms around IFs. These measures led to more than 6.8 million poultry being culled and
78 caused a substantial economic impact on the French poultry industry (Guinat et al., 2018).
79 Several studies highlighted the role of biosecurity practices, poultry farm density, and duck
80 transportation in the spread of HPAI viruses between French farms during the 2016-17
81 epidemic (Guinat et al., 2019; Guinat, Comin et al., 2020; Guinat, Durand et al., 2020;
82 Bauzile, Sicard et al., 2022).

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

85 A national training program was made mandatory for poultry producers, and the French
86 veterinary authorities performed biosecurity audits on poultry farms between 2016 and 2018
87 to verify compliance with the new regulations (Delpont et al., 2021). Two “high-risk zones”
88 (HRZ) were also incorporated into French legislation in September 2021 (DGAI, 2021),
89 where pre-emptive measures (such as confining ducks indoors and timely pre-movement
90 testing) were implemented in autumn and winter when the risk of HPAI introduction
91 increased. These two HRZ, located in the southwestern and western parts of France, were
92 created based on a spatial distribution model of the 2016-17 outbreaks, and were
93 characterized by high poultry farm densities and high duck movement numbers (Guinat et al.,
94 2019).

95 In the winters of 2020-21 and 2021-22, France and Europe were affected by two other
96 major HPAI epidemics (subtypes H5N8 and H5N1, respectively), with the number of poultry
97 farm outbreaks exceeding those caused by the 2016-17 epidemic. Given the improved
98 biosecurity and drastic control measures implemented in France, these latest epidemics are
99 worrying. Our study therefore aimed to characterize the spatio-temporal patterns of the 2020-
100 21 and 2021-22 epidemics in France and to assess the outbreaks’ spatial distribution in
101 relation to the 2016-17 model predictions and to the two HRZ. This constitutes a first step
102 towards identifying the poultry sector’s remaining vulnerabilities regarding HPAI viruses in
103 France.

104

105 **Materials and Methods**

106 *Data collection*

107 We obtained data on the HPAI poultry farm outbreaks for the 2020-21 (December 2,
108 2020-March 20, 2021) and 2021-22 (November 21, 2021-August 28, 2022) epidemics from
109 the French General Directorate for Food (DGAI) of the French Ministry of Agriculture. An

110 outbreak was defined as detection of at least one laboratory confirmed HPAI-infected bird (by
111 virus isolation or polymerase chain reaction) in a commercial poultry farm. Data included the
112 species involved, type of production, date of suspicion (by clinical or active surveillance) and
113 geographical location of each outbreak. Spatial data were obtained from DGAI for the HRZ,
114 and from Guinat et al. (2019) for the predicted probability of having at least one HPAI
115 outbreak in a commune (the smallest administrative unit in France, corresponding to
116 Nomenclature of Territorial Units for Statistics level 5).

117

118 *Descriptive analysis*

119 All analyses were conducted using R statistical software version 4.1.1 (R Core Team,
120 2021). Epidemic curves were plotted using the R package incidence (Kamvar et al., 2019;
121 Jombart et al., 2020). All maps were produced using the R package tmap (Tennekes, 2018).
122 Boundaries of all countries (level 0) and French administrative regions (level 1) were
123 downloaded from the GADM (<https://gadm.org/>) database using the R package raster
124 (Hijmans, 2021). Outbreaks for which the precise location was missing were given the
125 coordinates of the centroid of the commune where they occurred. The coordinates of the
126 communes' centroids were obtained from the French National Institute of Geographic and
127 Forest Information (IGN) ADMIN EXPRESS database
128 (<https://geoservices.ign.fr/adminexpress>). To assess the ability of the 2016-17 model (Guinat
129 et al., 2019) to predict the location of outbreaks for the 2020-21 and 2021-22 epidemics, we
130 calculated the area under the receiver operator characteristic curves (AUC) for both epidemics
131 using the R package pROC (Robin et al., 2011).

132

133

134 *Transmission dynamics (effective reproduction number)*

135 To study the transmission dynamics, we estimated the effective reproduction number
136 R_e between farms (i.e., the average number of secondary farms infected by each infectious
137 farm) using the approach of Wallinga and Teunis (Wallinga and Teunis, 2004). The approach
138 of Wallinga and Teunis allows estimating R_e based on the time variations of incidence and on
139 the distribution of the serial interval (time interval between symptom onset in a farm and that
140 of its secondary cases). Because the distribution of the serial interval distribution was
141 unknown, we first used the approach of White and Pagano (White and Pagano, 2008) to
142 estimate simultaneously the basic reproduction number R_0 and the mean and standard
143 deviation of the discretized serial interval distribution (assumed to follow a gamma
144 distribution), based on the initial exponential phase of the epidemic. This approach was
145 implemented using the R package R0 (Obadia et al., 2012; Boelle and Obadia, 2015). With
146 the estimates of the serial interval distribution parameters, we were then able to estimate the
147 effective reproduction number using the approach of Wallinga and Teunis (Wallinga and
148 Teunis, 2004), implemented in the R package EpiEstim (Cori, 2021).

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

159 **Results and Discussion**

160 The 2020-21 epidemic consisted of a single wave with 468 outbreaks (Figure 1A)
161 clustered in southwestern France (Figure 2A). In contrast, the 2021-22 epidemic was
162 characterized by 1,375 outbreaks (as of August 28, 2022) divided into two spatio-temporal
163 clusters, the first in the southwest and the second in the western part of the country (Figure 1B
164 and Figure 2B), with a higher incidence during the second wave. Most outbreaks were located
165 in the HRZ, both in 2020-21 (80.6% of the outbreaks) and 2021-22 (68.4% - Figure 1A and B,
166 Figure 2). The AUCs of the 2016-17 model were 0.86 (95% confidence interval: 0.83-0.89)
167 for the 2020-21 epidemic and 0.85 (95%CI: 0.84-0.87) for the 2021-22 epidemic.

168 In both epidemics, the vast majority of farm outbreaks in the southwestern HRZ
169 (82.7% and 70.8%) were reported in ducks (Table 1), mainly in farms raising ducks for *foie*
170 *gras* production (breeding and/or force-feeding production stages in Table 1). Conversely, in
171 the western HRZ in 2021-22, only half of the outbreaks were reported in duck farms, mainly
172 in breeder and broiler farms (Table 1). Most of the other outbreaks were reported in galliform
173 farms (mainly chickens and turkeys - Table 1).

174 The estimates of the average serial interval were 4.78 days (standard deviation: 4.63
175 days) for the 2020-21 epidemic, and 9.28 days (standard deviation: 7.21 days) for the 2021-22
176 epidemic (Supporting Information Figure S1). In the winter of 2020-21, the R_e peaked at 2.2
177 (95%CI: 1.8-2.5) in late December 2020, when the incidence increased in the southwestern
178 HRZ, then decreased below 1 from mid-January 2021 (Figure 1C). In 2021-22, the R_e first
179 peaked at 2.3 (95%CI: 1.9-2.8) in early January 2022, when the virus was mostly circulating
180 in the southwestern HRZ, and then decreased below 1 in the second half of January 2022
181 (Figure 1D). At the beginning of February 2022, the R_e increased again dramatically when the
182 virus reached the western HRZ, peaked at 2.5 (95%CI: 2.3-2.7) at the end of February 2022
183 and then decreased below 1 by mid-March 2022 (Figure 1D).

184 For the 2020-21 epidemic, the temporal variations of the R_e estimated using the serial
185 interval distribution parameters of White and Pagano's default model (Figure 1C) matched
186 qualitatively and quantitatively with the R_e dynamics estimated using the serial interval
187 distribution parameters of White and Pagano's model with the highest R-squared value
188 (Supporting Information Figure S2). For the 2021-22 epidemic, the default model had the
189 highest R-squared value, and therefore the estimates were the same (Supporting Information
190 Figure S2).

191 During the 2020-21 and 2021-22 epidemics, the virus circulated extensively in the
192 southwestern HRZ. In that region, where the density of farms raising ducks for *foie gras*
193 production is extremely high, it is worth noting that the number of reported outbreaks
194 decreased from 375 to 284 between the two epidemics, likely the result of a higher level of
195 awareness among farmers, more effective implementation of control strategies and a decrease
196 of duck flock density. However, in the winter of 2021-22, a second spatio-temporal cluster of
197 outbreaks occurred in the western HRZ, with no clear epidemiological link with the
198 southwestern cluster (EFSA et al., 2022a). The spread of HPAI within the western HRZ
199 occurred for the first time during the 2021-22 epidemic and explains the extremely high
200 number of outbreaks reported. The species composition in poultry farms in this zone,
201 combined with a higher flock size on average, may have had a significant impact on the
202 pattern of the epidemic in this area. Why the virus spread in the western HRZ in 2021-22 but
203 not in the previous epidemics remains to be determined. Analyses of genotype sequences
204 showed that a single genotype was involved in the western cluster, unrelated to the ones
205 previously detected in the southwestern cluster (EFSA et al., 2022b). The risk posed by wild
206 birds changed and increased in 2021-22, with earlier and higher number of HPAI detections
207 and higher number of species involved (EFSA et al., 2022a), possibly explaining the

208 successful incursion and subsequent spread of the virus in domestic poultry in this zone for
209 the first time in 2021-22.

210 Biosecurity and control measures were significantly improved after 2016. The
211 occurrence of these two major epidemics would suggest that these improvements were not
212 sufficient to prevent the spread of the virus. Interestingly, although the 2016-17 outbreaks
213 only clustered in the southwest part of France, Guinat et al. (2019) identified two HRZ that
214 predicted with high accuracy the two spatial clusters observed during the 2021-22 epidemic
215 (Figure 2B). The main risk factors identified were density of poultry farms and activities
216 related to duck movements. The latter risk factor has already been the target of considerable
217 improvement measures. To increase the resilience of the poultry sector in France, and other
218 hardly-hit European countries, future efforts should therefore focus on reducing the density of
219 susceptible poultry farms and the number of susceptible birds on farms in high-density areas
220 during the high risk periods (Bauzile, Durand et al., 2022).

221 Vaccinating domestic poultry against avian influenza is generally prohibited in the
222 European Union due to the trade restrictions it would generate (European Commission, 2006).
223 However, this once-tabooed prevention strategy is currently being given full consideration in
224 Europe, as it is becoming clear that the accelerating pace of occurrence of devastating HPAI
225 epidemics is generating new challenges that cannot be addressed with more traditional
226 prevention and control approaches alone (EFSA et al., 2021; Stokstad, 2022; Wille and Barr,
227 2022). In the long term, restructuration of the European poultry sector in densely populated
228 poultry areas, although challenging, may be required alongside vaccination to control HPAI
229 epidemics (EFSA et al., 2021; Stokstad, 2022). Therefore, further research is needed to devise
230 new suitable and sustainable HPAI mitigation strategies in Europe.

231

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240

241 **Ethics statements:** The authors confirm that the ethical policies of the journal, as noted on
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243 outbreaks was collated by veterinary authorities as part of their activities to control avian
244 influenza, no ethical approval was required for this study.

245

246 **Data availability statement:** The data that support the findings of this study are available on
247 request from the corresponding author. The data are not publicly available due to privacy or
248 ethical restrictions.

249

250 **Conflict of interest:** The authors declare no conflict of interest.

251

252 **Author contributions:**

253 **Sébastien Lambert:** Conceptualization, Data curation, Formal analysis, Methodology,
254 Software, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing.

255 **Benoit Durand, Mathieu Andraud:** Conceptualization, Formal analysis, Methodology,
256 Writing – Review & Editing. **Roxane Delacourt:** Data curation, Writing – Review & Editing.

257 **Axelle Scoizec:** Conceptualization, Data curation, Writing – Review & Editing. **Sophie Le**
258 **Bouquin:** Conceptualization, Writing – Review & Editing. **Séverine Rautureau:**
259 Investigation, Resources, Writing – Review & Editing. **Billy Bauzile:** Conceptualization,
260 Writing – Review & Editing. **Claire Guinat:** Resources, Writing – Review & Editing. **Lisa**
261 **Fourtune:** Data curation, Formal Analysis, Writing – Review & Editing. **Jean-Luc Guérin,**
262 **Mathilde C. Paul:** Conceptualization, Funding Acquisition, Writing – Review & Editing.
263 **Timothée Vergne:** Conceptualization, Formal analysis, Funding Acquisition, Methodology,
264 Supervision, Writing – Original Draft Preparation, Writing – Review & Editing.

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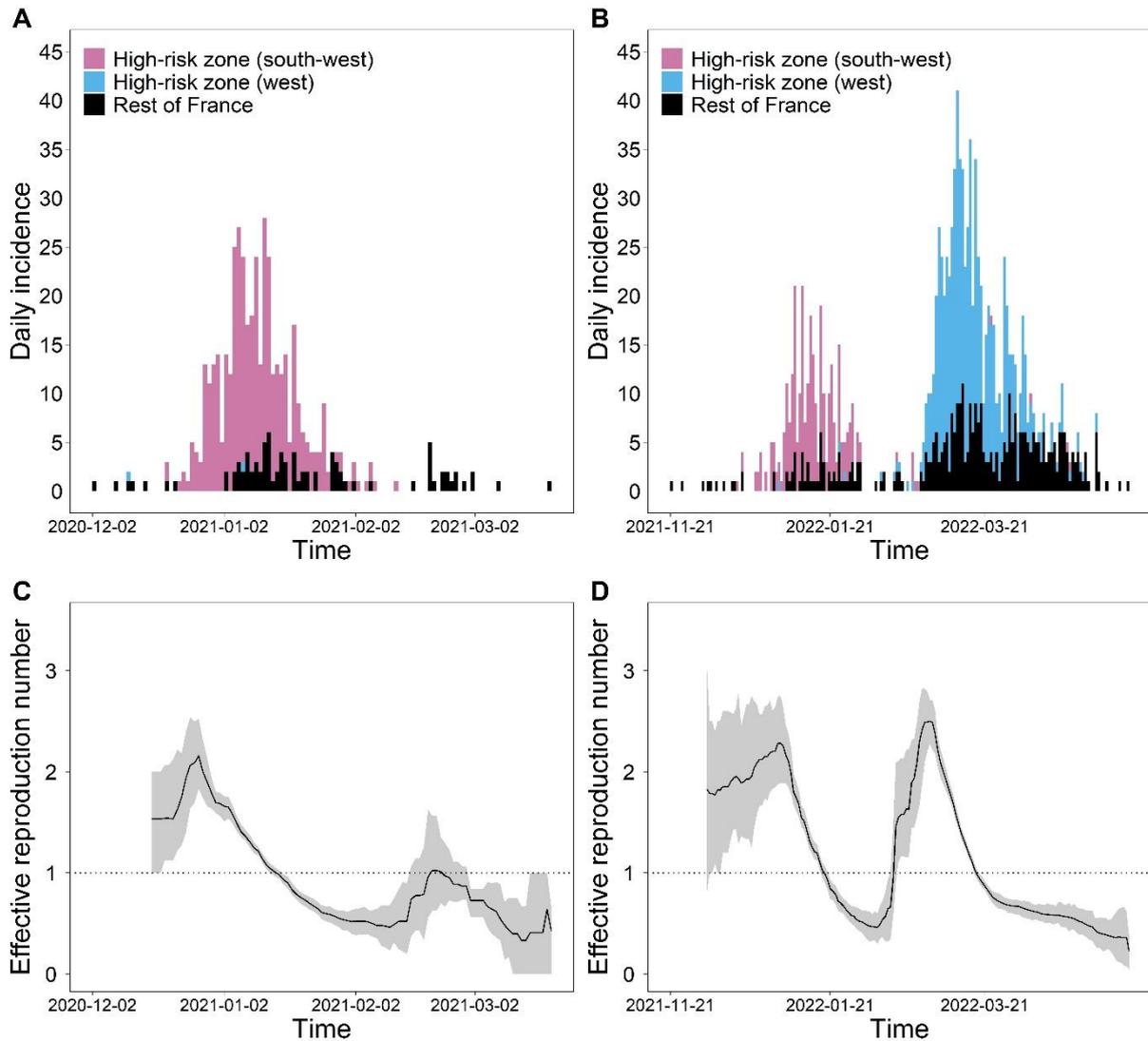
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357 **Table 1: Distribution of HPAI virus outbreaks in commercial poultry farms in France**
 358 **during the 2020-21 (H5N8) and 2021-22 (H5N1) epidemics**

	2020-21		2021-22		TOTAL
	South-West*	TOTAL	South-West*	West†	
Type of species					
Duck	310 (82.7%)	389 (83.1%)	201 (70.8%)	331 (50.4%)	817 (59.4%)
Goose	1 (0.2%)	1 (0.2%)	4 (1.4%)	4 (0.6%)	13 (1.0%)
Chicken	34 (9.1%)	42 (9.0%)	45 (15.8%)	183 (27.8%)	322 (23.4%)
Turkey	-	-	-	78 (11.9%)	104 (7.6%)
Other galliformes	6 (1.6%)	7 (1.5%)	5 (1.8%)	37 (5.6%)	47 (3.4%)
Multispecies (galliformes)	2 (0.5%)	2 (0.4%)	1 (0.3%)	-	4 (0.3%)
Multispecies (palmipeds + galliformes)	22 (5.9%)	27 (5.8%)	5 (1.8%)	7 (1.1%)	18 (1.3%)
Pigeon	-	-	-	2 (0.3%)	2 (0.1%)
Unknown	-	-	23 (8.1%)	15 (2.3%)	48 (3.5%)
TOTAL	375 (100%)	468 (100%)	284 (100%)	657 (100%)	1,375 (100%)
Type of production for duck farms					
Breeding	211 (68.1%)	260 (66.8%)	127 (63.2%)	68 (20.5%)	340 (41.6%)
Force-feeding	76 (24.5%)	97 (24.9%)	53 (26.3%)	42 (12.7%)	149 (18.2%)
Breeding + force-feeding	1 (0.3%)	1 (0.3%)	-	-	-
Broiler	2 (0.6%)	7 (1.8%)	6 (3.0%)	131 (39.6%)	190 (23.3%)
Breeder	7 (2.3%)	8 (2.1%)	1 (0.5%)	62 (18.7%)	83 (10.2%)
Other	2 (0.6%)	3 (0.8%)	2 (1.0%)	21 (6.4%)	28 (3.4%)
Unknown	11 (3.6%)	13 (3.3%)	12 (6.0%)	7 (2.1%)	27 (3.3%)
TOTAL	310 (100%)	389 (100%)	201 (100%)	331 (100%)	817 (100%)
Type of production for chicken farms					
Broiler	26 (76.5%)	33 (78.6%)	32 (71.1%)	109 (59.6%)	184 (57.1%)
Layer	4 (11.8%)	5 (11.9%)	7 (15.6%)	33 (18.0%)	72 (22.4%)
Breeder	3 (8.8%)	3 (7.1%)	1 (2.2%)	21 (11.5%)	31 (9.6%)
Other	-	-	-	17 (9.3%)	26 (8.1%)
Unknown	1 (2.9%)	1 (2.4%)	5 (11.1%)	3 (1.6%)	9 (2.8%)
TOTAL	34 (100%)	42 (100%)	45 (100%)	183 (100%)	322 (100%)

359 * Southwestern high-risk zone,

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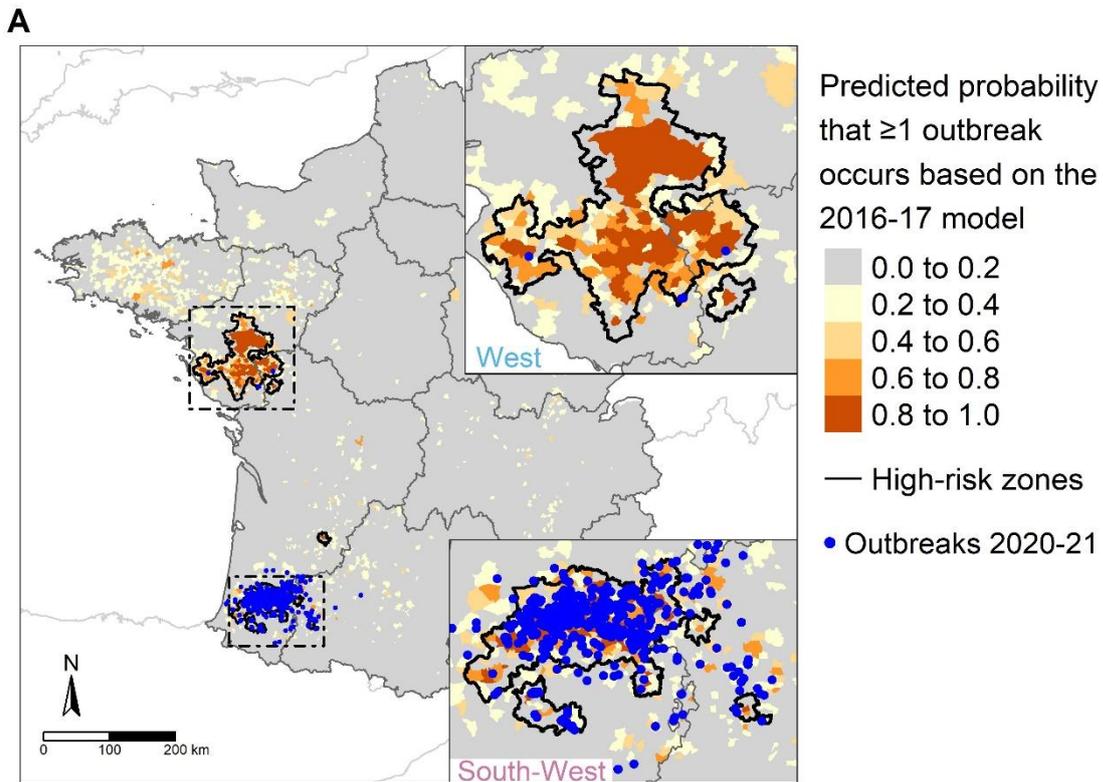


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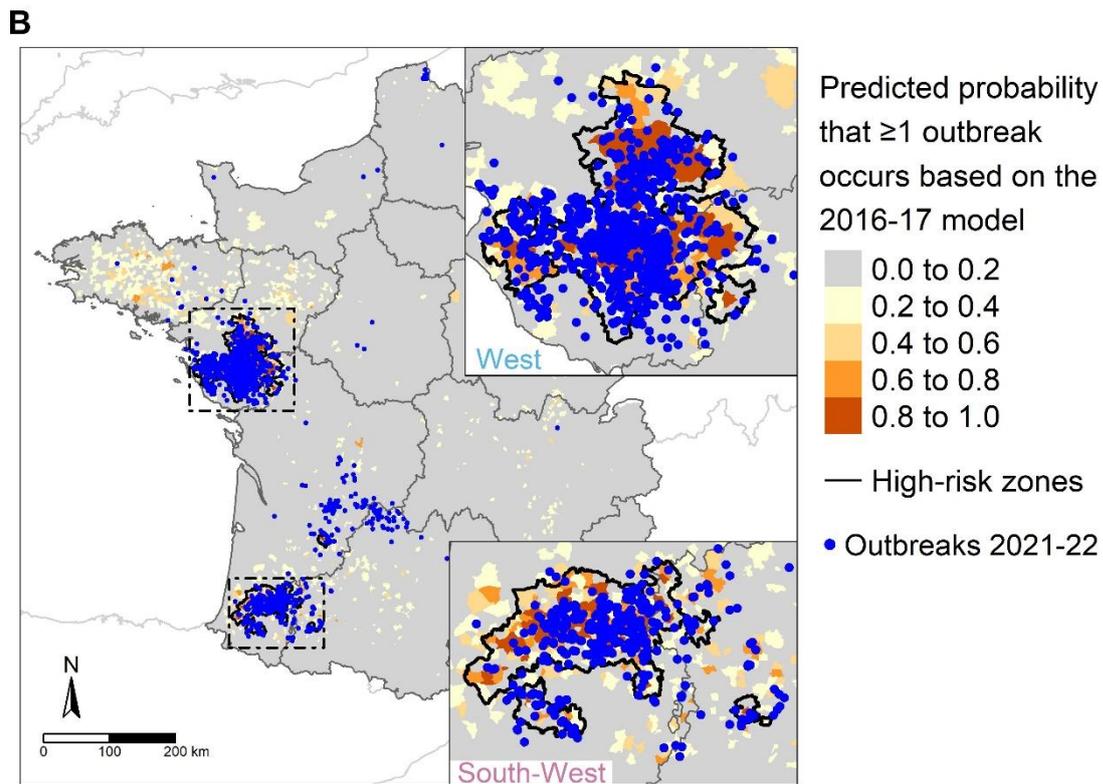
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365 **Figure 1: Incidence (A, B) and estimated effective reproduction number (C, D) of the**
 366 **2020-21 (A, C) and 2021-22 (B, D) HPAI virus epidemics in commercial poultry farms in**
 367 **France.** In panels C and D, the graph shows, at each day, the estimate of the effective
 368 reproduction number over the 14-day window finishing on that day. The line represents the
 369 mean and the grey area represent the 95% confidence interval. In 2021-22 (B, D), incidence
 370 and R_e estimates are shown up to May 15, 2022. Only sporadic cases ($n=7$) occurred between
 371 May 15 and August 28.

372



373



374

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