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HAL Authorization

1 **Time-series modeling for the quantification of seasonality and forecasting**
2 **antibiotic-resistant episodes: application to carbapenemase-producing**
3 **Enterobacteriaceae episodes in France over 2010-2020**

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14

15 **Running title**

16 Modeling of CPE in France over 2010-2020

17

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29 **Synopsis**

30 **Background** Carbapenemase-producing Enterobacteriaceae (CPE) cause resistant healthcare-associated
31 infections that jeopardize healthcare systems and patient safety worldwide. The number of CPE episodes
32 has been increasing in France since 2009 but the dynamics are still poorly understood.

33 **Objectives** Use time-series modeling to describe the dynamics of CPE episodes from August 2010 to
34 December 2016 and to forecast its evolution for the 2017-2020 period.

35 **Methods** We used time-series to analyze CPE episodes from August 2010 to November 2016 reported to
36 the French national surveillance system. The impact of seasonality was quantified using seasonal-to-
37 irregular ratios. Seven time-series models and three ensemble stacking models (average, convex and linear
38 stacking) were assessed and compared to forecast CPE episodes during 2017-2020.

39 **Results** During 2010-2016, 3559 CPE episodes were observed in France. Compared to the average yearly
40 trend, we observed a 30% increase in the number of CPE episodes in Autumn. We noticed a 1-month
41 lagged seasonality of non-imported episodes compared to imported episodes. Average stacking gave the
42 best forecasts and predicted an increase during 2017-2020 with a peak up to 345 CPE episodes (95%
43 PI[124-1158], 80% PI[171-742]) in September 2020.

44 **Conclusions** The observed seasonality of CPE episodes sheds light on potential factors associated with
45 the increased frequency of episodes which need further investigations. Our model predicts that the number
46 of CPE episodes will continue to rise in the coming years in France, mainly due to local dissemination,
47 associated with bacterial carriage of patients in the community which is becoming an immediate challenge
48 to help controlling the outbreak.

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55 **Introduction**

56 The increasing incidence of healthcare-associated infections caused by carbapenemase-producing
57 Enterobacteriaceae (CPE) jeopardizes healthcare systems and patient safety in Europe,¹ the US, and many
58 countries worldwide.² Because carbapenems remain the main antibiotic for the treatment of multi-resistant
59 bacteria infections, CPE infections are associated with longer hospital stays and an excess risk of death.^{3,4}
60 The primary risk factors of CPE's spread involve consumption of broad-spectrum antibiotics (carbapenems,
61 third and fourth generation cephalosporins and fluoroquinolones), cross-infection during hospital stays, and
62 cross-border transfers of patients in healthcare settings.⁵ In parallel, plasmidic gene transfers between
63 bacteria contribute to the rising number of non-internationally imported cases.⁶
64 Despite reinforced national guidelines and strategies regarding the management and prevention of
65 emerging CPE,^{5,7} the number of episodes in France has risen steadily since 2009.^{8,9} This phenomenon
66 seems to be associated with inter-regional dissemination and importation of international cases as shown
67 in several recent studies.^{1,10-13} Moreover, in France CPE has advanced from its epidemiological stage 3
68 (regional spread) in 2013 to stage 4 (inter-regional spread) in the 2014-2015 period.^{1,14} Despite a growing
69 concern regarding this issue, the majority of studies conducted so far have been limited to the
70 epidemiological description at the national level^{8,9,13} and the reporting of specific local outbreaks,^{10-12,15,16}
71 with especially few information on the seasonality of episodes. Common methods used to understand and
72 predict the dynamics of infectious diseases involve both compartmental and agent-based models.¹⁷ These
73 methods, however, either require a deep knowledge of the transmission pathways used by the pathogens,
74 or rely on assumptions that are difficult to validate. Time-series analysis, on the other hand, appears to be
75 easier to apply and has garnered much interest in the field, especially in modeling influenza dynamics¹⁸⁻²⁰
76 or antimicrobial resistance.²¹ These methods rely on the identification of temporal patterns, with few
77 assumptions modeling the mechanism of how CPE is spread. Time-series analysis can therefore be
78 effectively used to describe and quantify the trend and seasonality of CPE episodes incidence, as currently
79 little is known on the matter. In addition to providing deeper insights into the phenomenon, this approach
80 also allows relatively simple forecasts of the number of cases, which could help public health authorities to
81 better define and evaluate infection control guidelines.

82 Time-series analysis was thus used to firstly describe and quantify the dynamics (trend and seasonality) of
83 CPE episodes from August 2010 to December 2016. The second objective was to identify a methodological
84 process using time-series modeling to forecast the evolution of CPE episodes for the 2017-2020 period.

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86

87 **Materials and methods**

88 **Data sources**

89 Surveillance data of CPE episodes notified between August 2010 and December 2018 were extracted from
90 the French national Healthcare-Associated Infections Early Warning and Response System (HAI-EWRS).²²

91 An episode was defined as a single case or a cluster of cases carrying the same strain of CPE, and known
92 to have been in contact with one another.¹³ A case was defined as a positive CPE diagnosis from sample
93 collected for infection or through systematic screening performed according to standard national
94 recommendations.⁷ Available characteristics on each episode were the occurrence date, the index case
95 status (infected or carrier), and the importation status, i.e. the presence of a direct link with a foreign country
96 for the potential index case (hereafter denominated as imported or in the case of no link, non-imported).
97 Information on the mechanism of CPE resistance confirmed by the national reference center, and the
98 involved bacteria species were also collected. CPE episodes were grouped according to month of
99 occurrence and analyzed together and separately according to their importation status.

100 Since the HAI-EWRS collection system changed in January 2017 (international importation status of the
101 index case not collected in the same way, missing data on the infection status of the index case), we decided
102 not to include the period 2017-2018 in the main analysis but to use it as a control set for the prediction model
103 (Figure 1B). In addition, during the descriptive phase of this work, the number of episodes in December
104 2016 appeared to be an outlier compared to previous months, possibly due to an “end-of-year” reporting
105 issue before the new collection system. The main study period was thus set from August 2010 to November
106 2016. To build and validate the different models, data was split into two datasets: the training set from
107 August 2010 to December 2014 and the test set from January 2015 to November 2016 (Figure 1A).

108

109 **Figure 1 here**

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112 **Statistical analysis**

113 We considered three main time-series in this study: the first was composed of imported episodes, the
114 second one of non-imported episodes and the third of all episodes, whatever their importation status. All
115 considered time-series were multiplicative, a log transformation was thus used in each model built. To
116 quantify the seasonality of episodes in the three time-series on the whole study period (August 2010-
117 November 2016), we used seasonal-to-irregular (SI) ratios.²³ SI ratios were computed based on the de-
118 trended time-series obtained using the X-11 seasonal adjustment method and corresponded to the product
119 of the seasonal and the irregular parts of the multiplicative time series. Time-series were de-trended using
120 moving average²⁴ and trends estimates using time-series linear model.²³ As X-11 seasonal adjustment
121 method required non-zero values; one fictional episode was added each month over the study period for
122 the non-imported time-series.

123 To forecast the evolution of the number of CPE episodes, we considered 10 methods issued from time-
124 series modeling and ensemble methods. We built seven time-series models, hereafter called component
125 models. These included: a seasonal autoregressive integrated moving average (SARIMA) model,²⁵ a time-
126 series linear model (tslm),²³ a X-11 seasonal adjustment method,²⁴ an exponential smoothing state space
127 (ETS) model,^{26,27} a multiplicative Holt-Winters method with multiplicative errors,^{26,27} a neural network
128 autoregression (NNAR),²³ and a TBATS model (exponential smoothing state space model with Box-Cox
129 transformation, ARMA (autoregressive-moving-average) errors, trend and seasonal components).²⁸ All
130 these components models were fitted independently on the training set (August 2010-December 2014) and
131 then used to forecast the number of CPE episodes over the test period (January 2015-November 2016). In
132 addition, we implemented three ensemble stacking methods, which combined the fitted and forecasted
133 values of the seven component models. First, an average stacking model was defined considering all
134 combinations of component models. The retained combination was the one with the best predictive quality
135 on the training set according to the mean absolute error (MAE) quality parameter.²⁹ Next, we used a convex
136 stacking model composed of the best linear combination of the seven component models with non-negative
137 coefficients summing to one.²⁹ Finally, we built a linear stacking model which estimated the best coefficients

138 of the linear combination of all component models.³⁰ Both the convex and the linear stacking model were
139 computed using the square loss as a performance criterion.²⁹ For each component model, 80% and 95%
140 prediction intervals (PIs) were estimated based on the standard deviation of each step forecast.²³ For
141 stacking methods, as no consensus exists to our knowledge, we carried out a linear combination of the PIs
142 by using the stacking coefficients.

143 To select the best model to be used for forecasting, we assessed the quality of each of the 10 models
144 compared to the observed data of training and test sets using MAE, mean absolute percentage error
145 (MAPE), and root mean squared error (RMSE).²³ Forecasts being on the same scale, minimization of MAE
146 was selected as the main selection criterion as suggested by Hyndman.²³ The model with the best
147 forecasting quality on the test set was then trained on all available data (2010-November 2016) and used
148 to predict CPE episodes from December 2016 to December 2020.

149 Analyses were performed using R (3.5.2)³¹ and the packages forecast,³² opera,²⁹ and seasonal.²⁴

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151

152 **Results**

153 **Characteristics of CPE episodes**

154 A total of 3559 CPE episodes – 1473 (41.4%) over the training period and 2086 (58.6%) over the test period
155 – were reported in France between August 2010 and November 2016 (46 episodes occurring in December
156 2016 were excluded from the analyses). Out of these, 1624 (45.6%) episodes were internationally-imported
157 cases and 1935 (54.4%) had no documented link with a foreign country (non-imported episodes). Among
158 the 769 episodes with an infected index case, 280 (36.4%) were imported, whereas 1,350 (49.0%) were
159 imported among the 2753 episodes with a carrier index case ($p < 0.05$) (83 episodes had a missing index
160 case status). The majority of CPE episodes had an OXA-48 (class D beta-lactamases with oxacillinase
161 enzyme activity) mechanism of resistance with a total of 2684 (75.4%) episodes. NDM (New Delhi metallo-
162 beta-lactamase) resistance corresponded to 541 (15.2%) episodes, KPC (Klebsiella pneumoniae
163 Carbapenemase) to 168 (4.7%), and VIM (Verona integron-encoded metallo-beta-lactamase) to 145 (4.1%)
164 episodes. The remaining 21 episodes (0.6%) had no reported resistance mechanism. *Klebsiella*

165 *pneumoniae* and *Escherichia coli* were the two main bacteria species involved in the episodes (1915
166 episodes (53.8%) and 1335 episodes (37.5%), respectively).

167

168 **Quantifying the seasonal effect**

169 The SI ratios chart was obtained using the X-11 seasonal adjustment method, enabling to quantify the
170 impact of seasonality on the number of CPE episodes during the 2010-2016 period (Figure 2). Across the
171 years, the number of episodes reported was higher in Autumn and lower at the beginning of each year. The
172 seasonal increase of the number of CPE episodes was 30% and 29% higher in September and October
173 respectively, as compared to the average trend. In contrast, a 20% decrease in the number of CPE episodes
174 was observed in February compared to the other months.

175 Results of the analysis by importation status using X-11 seasonal adjustment method are presented in
176 Figure 3. The number of non-imported episodes appeared to grow faster than the imported ones. Indeed,
177 we found trends equal to 0.59 and 0.88 for the imported and non-imported episodes, respectively, using the
178 time-series linear model over the whole study period. When only considering data starting from 2012 (no
179 fictional episode added in the non-imported time series), these trends were even higher and respectively
180 equal to 0.67 and 1.01. A decrease in the trend for non-imported episodes was observed at the end of the
181 period mainly due to the low number of episodes reported in November 2016. SI charts highlighted a 1-
182 month lagged seasonal impact of the non-imported compared to imported episodes. Indeed, the number of
183 imported CPE episodes increased by around 33% in August and September, while the peak was observed
184 in October for non-imported episodes with an average rise of 33% compared to other months. We also
185 looked at the seasonality of the two main episodes strains split according to their importation status
186 (Supplementary figure 1). *K. pneumoniae* seemed to drive the seasonality of imported episodes with a 69%
187 increase of the number of episodes in September. On the opposite, *E. coli* drove the non-imported episodes
188 with a 75% increase of the number of episodes related to this strain in October.

189

190 **Figure 2 here**

191

192 **Figure 3 here**

193

194 **Prediction of episodes evolution**

195 Accuracy parameters over the training and test sets of the seven component models and the three stacking
196 methods are presented in Table 1. Aside from the stacking techniques, TBATS appeared to be the best
197 method to model the training set (MAE=3.35), but was less accurate than X-11 seasonal adjustment on the
198 test set (MAE=13.08 versus 12.86 respectively). All three stacking techniques provided better fitted values
199 on the training set, as compared to the component models. Linear stacking had the best adjustment on the
200 training set (MAE=2.65). On the test period, average stacking method based on three component models
201 (X-11 seasonal adjustment, multiplicative Holt-Winters method, and TBATS) produced the most accurate
202 forecasts (MAE=12.65), performing better than X-11 seasonal adjustment alone.

203

204 **Table 1 here**

205

206 Based on its performance on the test set, we used the average stacking method to forecast the number of
207 CPE episodes during 2017-2020. This method was trained on all episodes occurring over the August 2010-
208 November 2016 period, and retained only two component models: X-11 seasonal adjustment method and
209 ETS. The obtained forecasts and PI are presented in Figure 4. The number of CPE episodes was predicted
210 to increase over the next 4 years in France with a peak up to 345 episodes in September 2020 (95% PI
211 [124-1158], 80% PI [171-742]). In addition, the model predicted 177 episodes (95% PI [96-316], 80% PI
212 [118-257]), 225 episodes (95% PI [106-480], 80% PI [136-365]), and 278 episodes (95% PI [1153-733],
213 80% PI [153-514]) in September 2017, September 2018, and September 2019, respectively. The accuracy
214 parameters (RMSE, MAE, and MAPE) comparing the predictions over the 2017-2018 period and the
215 observed values were equal to 25.38, 18.95 and 14.32, respectively. Moreover, the real values observed
216 during control period (2017-2018) were included in the 80% prediction interval (Figure 4).

217

218 **Figure 4 here**

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221 **Discussion**

222 This study is the first, to our knowledge, that investigates the dynamics of the spreading of CPE in France,
223 and deploys time-series analysis for this purpose. Using the exhaustive database of notified cases from the
224 beginning of the epidemic, we showed an ongoing increasing trend of CPE episodes and difference of
225 seasonality according to case importation status. Despite wide prediction intervals, the number of CPE
226 episodes is forecasted to continue to grow for the next 4 years.

227 OXA-48 was the dominant strain of carbapenemase in France, followed by NDM; which differs to what is
228 observed in the US and other European countries.^{1,33} Although France has one of the highest antibiotic
229 consumption rates in Europe, the consumption of carbapenems is lower than average and has not
230 significantly increased during the 2012-2016 period; therefore, antibiotic consumption may not explain the
231 rise in the number of notified episodes we observed.³⁴ While the national public health agency ('Santé
232 publique France') provides a general report on the national epidemiological situation,^{8,9} our analyses
233 enhances the results provided thus far by quantifying the seasonality in the number of episodes. Indeed,
234 we revealed a 30% increase in the number of CPE episodes in Autumn, i.e. September and October,
235 compared to other months. Moreover, when stratifying the dataset according to the origin of the episodes,
236 two separate peaks were observed: a 33%-increase peak in August and September for the internationally-
237 imported episodes and a 33%-increase peak in October for the non-imported ones. The peak of imported
238 cases may be due to summer holidays occurring in July and August in France, and thus a consequence of
239 hospitalizations and repatriations from foreign countries. We cannot, however, rule out the possibility that
240 intra-national variations in patient flows linked to summer holidays tend to increase the population at-risk of
241 infection or CPE carriage. The one-month delay in non-imported cases, causing a peak in October, could
242 be linked to secondary cases occurring in healthcare facilities or communities. These hypotheses, however,
243 require individual patient studies in order to be confirmed. It also appeared that there was a difference in
244 seasonality between bacteria strains. This could be a consequence of the endemic status of *K. pneumoniae*
245 in foreign European countries compared to *E. coli*,³⁵ but this hypothesis may need deeper analyses. In
246 addition, it is more than probable according to national guidelines⁷ that patients having experienced
247 hospitalizations in a CPE-endemic foreign country will be more likely to be screened for CPE carriage and
248 reported; a selection bias that could also explain a delay between imported and non-imported cases. Since

249 2014, the trend of non-imported episodes appeared to grow at a faster rate than that of imported cases.
250 This could be explained by either an increase in community spreading of CPE, or the impossibility of
251 reconstructing chains of episodes between healthcare facilities, which may be due to the inter-regional
252 spread.^{1,14}

253 Using average stacking methodology, our results suggest that the overall number of CPE episodes in
254 France will continue to rise over 2017-2020 with peaks in September each year. This result is consistent
255 with the epidemiological transition of France regarding CPE from stage 3 to 4 in 2014-2015 according to
256 ECDC.^{1,14} Despite the wide prediction intervals of the forecasts, the prediction model seems to be robust.
257 Indeed, we showed that there was a high seasonality in the data and an ongoing trend that may not
258 disappear without implementation of specific control measures or an external event.

259 Regarding statistical analysis, our study relies on a robust methodology aiming at finding the most effective
260 method for prediction. Firstly, seven component models, which are the most frequently used in time-series
261 analysis, were built. Then, three stacking models were implemented based on these component models.
262 These ten methods were compared, to retain the one method that produced predictions, which best fitted
263 the observed data of the test set. The wide variety of models deployed allowed us to consider different
264 underlying generation process of time-series, such as the moving average with SARIMA or the exponential
265 smoothing with ETS or Holt Winter's method. In addition, the use of ensemble techniques improved the
266 quality of predictions, as suggested in the literature,³⁶ supported by the model's better performance on the
267 quality of parameters, when compared to the single component models. The use of such ensemble
268 methods, however, may suffer from an overfitting bias.³⁷ To limit this bias, we chose to split the entire dataset
269 into training and test sets, and to select the best model according to the quality parameters on the test set
270 only. The effective performance of our final model in predicting the final control set (period 2017-2018)
271 indicates that such overfitting is limited. In addition, as shown in the results section, stacking methods rely
272 on component models, which themselves rely on data. Different data may thus lead to a different
273 combination of models retained by the stacking method. Therefore, we looked for a replicable
274 methodological process rather than a model to be replicated in other similar studies.

275 Our study also relies on robust surveillance data. Indeed, due to mandatory reporting of CPE infection and
276 colonization through various healthcare centers and surveillance networks we believe our data accurately

277 reflects the situation of CPE episodes in France over the study period. In addition, the study period stretched
278 over 76 months, leading to training and test sets 53-month and 23-month long, respectively. Because of the
279 seasonality of the data, these lengths were considered long enough to obtain a good fitting of the different
280 models on the data. Moreover, the predictions over 2017-2020 were based on a model trained on the whole
281 dataset, i.e. 76 months. This hypothesis was also confirmed by the control data falling within the prediction
282 intervals. The latter were wide, especially regarding the upper bound, which was mainly due to the ETS
283 component model and the long-term prediction leading to high standard deviations at the end of 3-year
284 forecasting period.

285 Another limit of our study arising from the data is the low number of non-imported episodes, especially at
286 the beginning of the study period where zeroes were frequent. Because some time-series methods cannot
287 deal with such repeated zeroes, we had to modify the non-imported time-series by adding a fictional episode
288 to each month to ensure focus on the seasonality. This is unlikely to impact our findings regarding the
289 seasonality and global trend of this time-series since the addition of an episode was constant through time.
290 However, this low number may be a consequence of the criteria used to classify an episode as imported.
291 Indeed, an episode was considered as internationally-imported if the first patient had been repatriated or
292 hospitalized abroad in the past 12 months. These criteria may therefore underestimate the total number of
293 non-imported episodes which are incorrectly considered as imported ones, but we assume that may
294 correspond to only a few episodes.

295 In conclusion, time-series modeling appears to be a useful tool for the study of the spread of antibiotic
296 resistance in both quantifying the seasonality and forecasting. The seasonality of CPE episodes highlighted
297 in our study need to be further investigated, in order to better account for this phenomenon. Prevention and
298 control efforts should be maintained to better control CPE epidemic including reinforcement of information
299 to healthcare professionals to promptly detect CPE cases, especially in non-imported cases, and dedicated
300 financial and human resources to healthcare facilities. In addition, probable spread of CPE in the community
301 is becoming an immediate challenge to help controlling the outbreak. Infection prevention and control should
302 thus be reinforced to avoid autochthonous cases, which would place undue strain on the French healthcare
303 system.

304

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312

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316 declare.

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393

394 **Table 1** Accuracy parameters of modeling methods of CPE episodes in France during training (2010-2014)
 395 and test (2015-2016) periods.

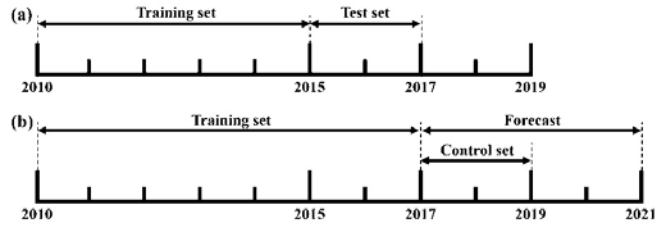
Model	Training set (2010-2014)			Test set (2015-2016)		
	<i>RMSE</i>	<i>MAE</i>	<i>MAPE</i>	<i>RMSE</i>	<i>MAE</i>	<i>MAPE</i>
SARIMA	5.91	4.77	19.23	17.90	13.32	14.99
Tslm	6.72	5.22	17.72	20.54	16.39	18.47
X-11 seasonal adjustment	4.95	4.41	18.08	17.40	12.86	14.06
ETS model	7.11	5.56	20.91	18.45	14.68	17.76
Holt-Winters model	8.09	6.53	21.46	25.16	17.60	20.25
NNAR	4.87	3.93	16.42	32.11	26.59	27.40
TBATS model	4.35	3.35	14.25	16.06	13.08	15.24
Average stacking*	3.72	2.81	11.14	15.92	12.65	14.39
Convex stacking	3.29	2.65	11.70	18.81	14.53	15.60
Linear stacking	3.13	2.55	11.24	20.22	16.08	17.09

396 RMSE: Root mean squared error. MAE: Mean absolute error. MAPE: Mean absolute percentage error.

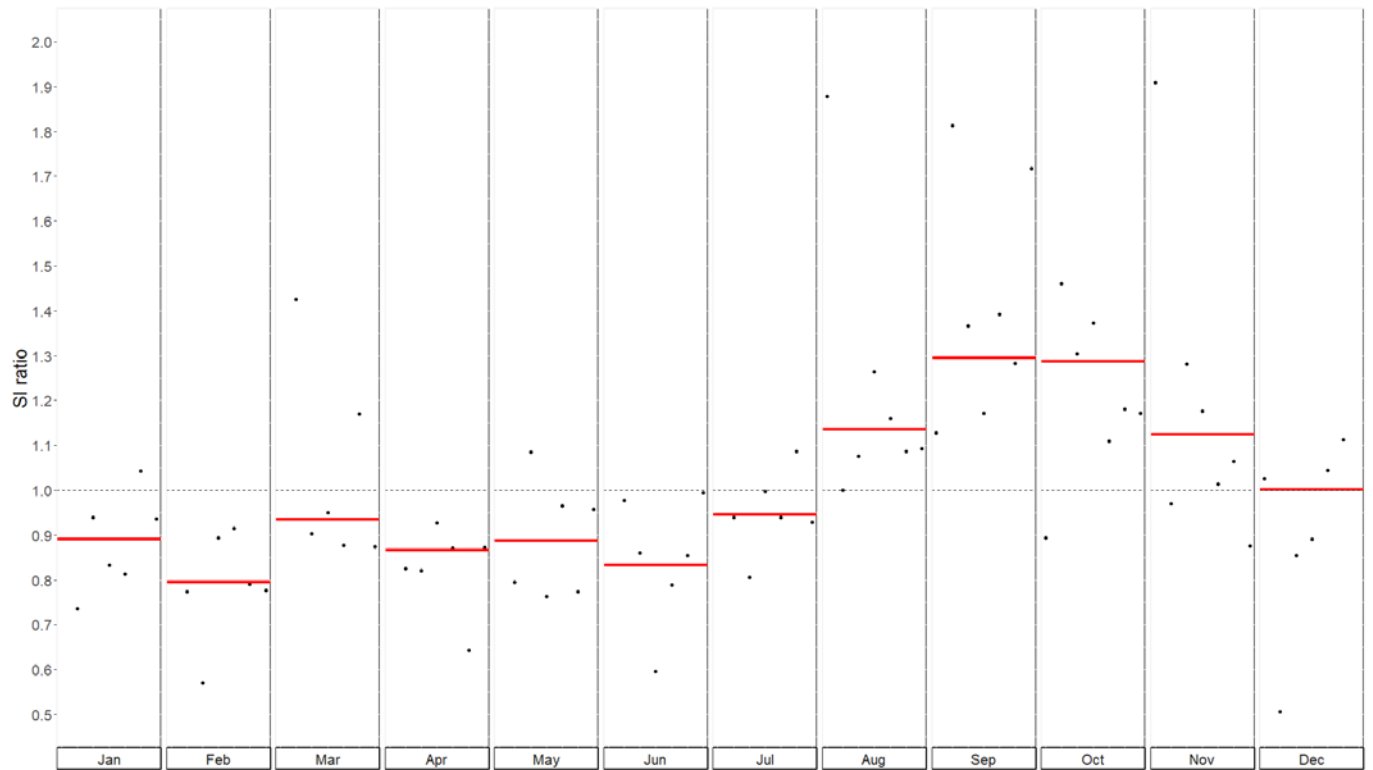
397 * Average stacking based on the three following component models: X-11 seasonal adjustment,
 398 multiplicative Holt-Winters method, and TBATS.

399

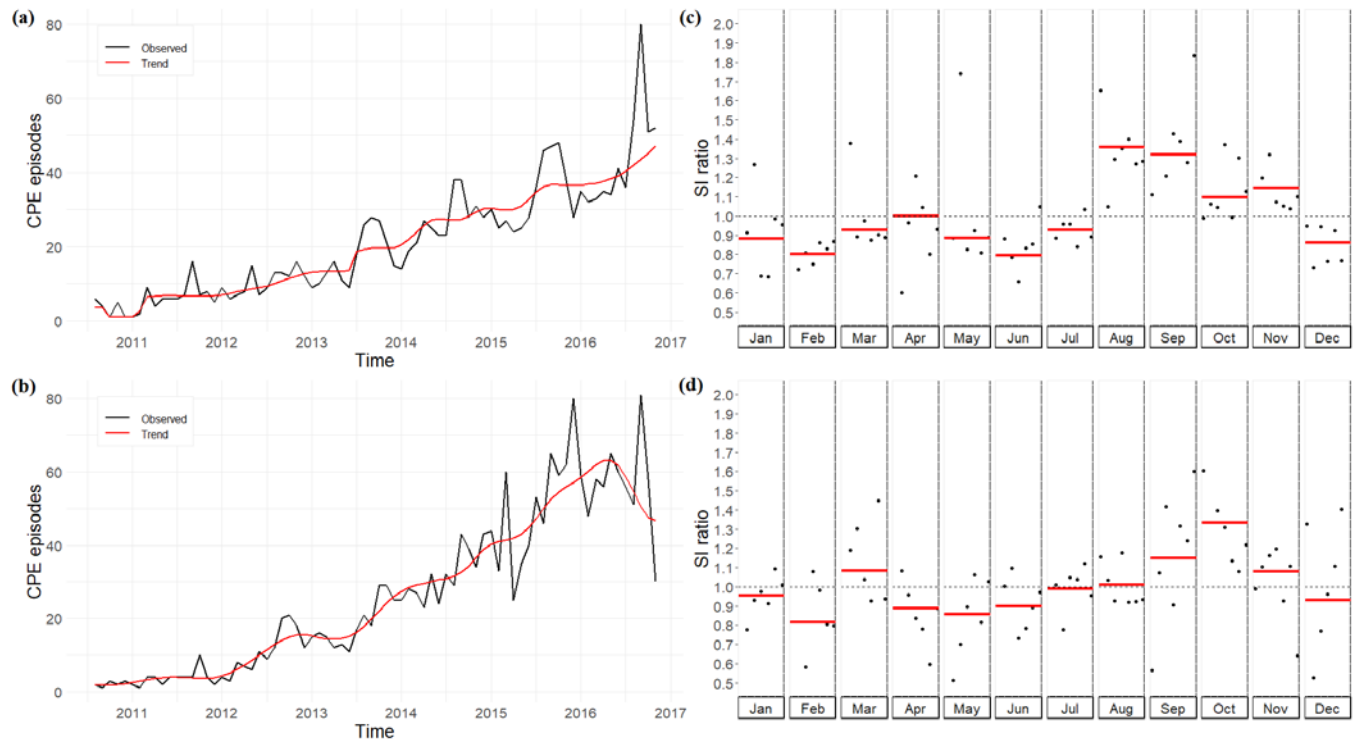
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401
 402 **Figure 1** Summary of time periods used for (a) model building and (b) forecasting of the number of CPE
 403 episodes in France.

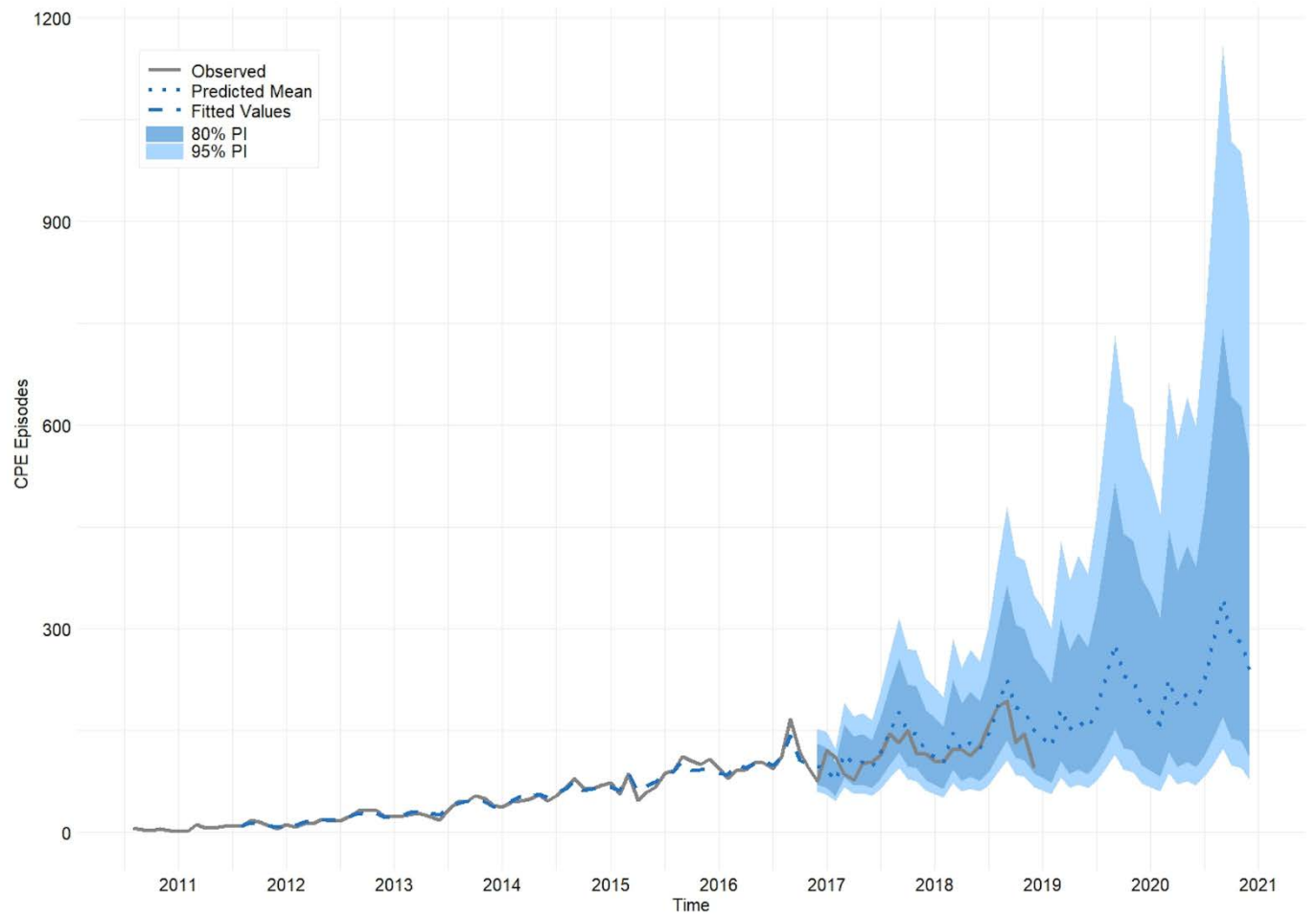


404
 405 **Figure 2** The SI ratios chart of CPE episodes using data on 3,559 episodes in France from August 2010
 406 to November 2016. Average of seasonal factors per month is represented with lines and seasonal-to-
 407 irregular ratios by dots. This figure appears in colour in the online version of JAC and in black and white in
 408 the printed version of JAC.



409

410 **Figure 3** Representation of the number and corresponding trend of (a) imported episodes and (b) non-
 411 imported episodes, and SI ratios chart of (c) imported episodes and (d) non-imported episodes. One fictional
 412 episode was added each month over the study period for the non-imported time-series. Average of seasonal
 413 factors per month is represented with lines and seasonal-to-irregular ratios by dots. This figure appears in
 414 colour in the online version of JAC and in black and white in the printed version of JAC.



415

416 **Figure 4** Prediction over a 4-year period of CPE episodes using data on 3559 episodes in France from
 417 August 2010 to November 2016 and observed number of CPE episodes from December 2016 to December
 418 2018. This figure appears in colour in the online version of JAC and in black and white in the printed version
 419 of JAC.