Monitoring seasonal influenza epidemics by using internet search data with an ensemble penalized regression model

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Seasonal influenza epidemics cause serious public health problems in China. Search queries-based surveillance was recently proposed to complement traditional monitoring approaches of influenza epidemics. However, developing robust techniques of search query selection and enhancing predictability for influenza epidemics remains a challenge. This study aimed to develop a novel ensemble framework to improve penalized regression models for detecting influenza epidemics by using Baidu search engine query data from China. The ensemble framework applied a combination of bootstrap aggregating (bagging) and rank aggregation method to optimize penalized regression models. Different algorithms including lasso, ridge, elastic net and the algorithms in the proposed ensemble framework were compared by using Baidu search engine queries. Most of the selected search terms captured the peaks and troughs of the time series curves of influenza cases. The predictability of the conventional penalized regression models were improved by the proposed ensemble framework. The elastic net regression model outperformed the compared models, with the minimum prediction errors. We established a Baidu search engine queries-based surveillance model for monitoring influenza epidemics, and the proposed model provides a useful tool to support the public health response to influenza and other infectious diseases.

Seasonal influenza is a serious public health problem that causes severe illness and death in the world. According to the World Health Organization (WHO), seasonal influenza occurs with an annual attack rate estimated at 5% to 10% in adults and 20% to 30% in children. The epidemics are estimated to result in about 3 to 5 million cases of severe illness and 250,000 to 500,000 deaths worldwide each year. During 2008–2011, an annual average of 92,677 seasonal influenza cases was reported in China. Overall, the influenza pandemics posed a significant burden of excess influenza-associated mortality in the country. To achieve near real-time surveillance of the spread of infectious diseases, several novel approaches based on online surveillance systems and using informal sources such as news reports, social media data, and search query data have been proposed.

In 2009, Ginsberg, J. et al. first presented a novel method of analyzing large numbers of Google search queries to track influenza-like illness in the United States. The proposed method provided near real-time estimates of seasonal influenza activity each day and overcame the limitation of traditional systems requiring 1–2 weeks to gather and process surveillance data. To estimate the seasonal influenza activity and quickly detect outbreaks in China, several programs were used to predict trends of influenza epidemics. However, these techniques used only influenza-like illness or influenza case data. The robust prediction of influenza epidemics could be improved. In 2013, Yuan, Q. et al. first explored the use of the combination of influenza case data and internet search query data from the search engine Baidu within a linear regression framework to monitor influenza epidemics in China. This provided a new idea to monitor the spread of influenza in the country. To inform the search behavior of users, Baidu released the search volume daily on the Baidu Index website (http://index.baidu.com). The search volume of different search keywords used can be abstracted to assess changes in the search behavior of users.
According to Yuan, Q. et al.\textsuperscript{11}, the construction of the prediction model involved compositing many search keywords into a single index according to different weights. However, in practice, many search keywords are used to construct the prediction model. The direct compositing of all keywords into a single index is not convenient for assessing the contribution of each keyword to the prediction. Developing robust techniques of search keyword selection and enhancing the ability to predict influenza epidemics remains challenging. Beyond the use of a linear regression model for prediction, we explored an ensemble framework that incorporated different penalized regression algorithms including lasso, ridge and elastic net\textsuperscript{12} to avoid the over-fitting problem with various keywords, identify informative predictors from a pool of candidate keywords, and estimate the parameters of the model with low variability.

In our previous study\textsuperscript{13}, use of a penalized regression model based on random bootstrap samples\textsuperscript{14} was able to detect significant variables with better predictive performance. How well a model predicts is practically quantified by performance measures. For example, performance measures such as accuracy, sensitivity, specificity, area under the receiver operating characteristic curve (AUC)\textsuperscript{15} and kappa index of agreement (KIA)\textsuperscript{16} are often used to evaluate performance for classification problems. However, in many settings, the assessment of performance by a single measure has inherent problems\textsuperscript{17}. For example, in disease surveillance applications, to predict periods of high incidence of infectious disease requires large sensitivity and/or specificity rates in addition to prediction accuracy\textsuperscript{18}. Different performance measures reflect different characteristics of the constructed prediction model. Therefore, under many circumstances, several performance measures must be considered simultaneously.

To improve prediction robustness, we sought to develop a Baidu search engine query data-based prediction model whose performance was optimized with respect to a set of measures. A novel ensemble framework was established by combining bootstrap aggregating (bagging) and a multi-objective optimization method in this study. New ensemble penalized regression models using the lasso, ridge and elastic net algorithms were constructed, and applied to predict seasonal influenza activity. Results of this study indicated that the ensemble elastic net regression model outperformed the compared models in monitoring seasonal influenza activity by using Baidu search engine query data.

Material and Methods

Ensemble penalized regression model. Penalized regression model. We first considered the lasso (L1-penalized regression method) linear regression model\textsuperscript{12}. We have an $n \times 1$ response vector $y = (y_1, y_2, \ldots, y_n)^T$ and linearly independent predictors $x = (x_1, x_2, \ldots, x_p)$ ($j = 1, \ldots, p$). Let $X = [x_1, \ldots, x_p]$ be the predictor matrix. We assume that $E[y|x] = \beta_0 + \beta_1 x_1 + \cdots + \beta_p x_p$. The estimates in the lasso linear regression model are defined as (1):

$$
\hat{\beta}_\lambda = \arg\min_\beta \left\{ \sum_{i=1}^{n} (y_i - \sum_{j=1}^{p} \beta_j x_{ij})^2 + \lambda \sum_{j=1}^{p} |\beta_j| \right\}
$$

(1)

where $|\mu|^2$ denotes $\sum_{i}^{p} \mu_i^2$ for vector $\mu \in \mathbb{R}^p$, and $\lambda$ is the nonnegative tuning parameter. This estimation method continuously shrinks the coefficients toward 0 as $\lambda$ increases, and some coefficients are shrunk to exactly 0 if $\lambda$ is sufficiently large\textsuperscript{19}.

Next, we considered the lasso logistic regression setup by using the tuning parameter $\lambda$. The estimates $\hat{\beta}_\lambda$ in the model are given by (2):

$$
\hat{\beta}_\lambda = \arg\min_\beta \left\{ \sum_{i=1}^{n} (-y_i \log(1 + e^{\beta^T x_i}) + \log(1 + e^{\beta^T x_i})) + \lambda \sum_{j=1}^{p} |\beta_j| \right\}
$$

(2)

where $\lambda$ is also the tuning parameter used for shrinking coefficients in the model. Generally, the cross-validation method was proposed to select the optimal $\lambda$\textsuperscript{10}. The ridge and elastic net penalized regression models were established using different penalties\textsuperscript{14, 20}, and the optimal values of tuning parameters were chose by a similar way.

Ensemble penalized regression model built with a bagging strategy. To improve the performance of the conventional penalized regression model, we used a combination of bagging and a rank aggregation\textsuperscript{21} method to develop an ensemble penalized regression model. The architecture of the model consists of a sequence of processing procedures primarily including model training, validation, evaluation and averaging, which are implemented in many random bootstrap samplings (Fig. 1). The details for the methodology are presented below.

According to Breiman, L.\textsuperscript{22}, bagging is a method of generating multiple versions of a prediction model, and these models are used to obtain an aggregated prediction, which gives substantial gains in prediction accuracy. Suppose that a training set $L$ consisting of data $X_{n \times p}$ with known outcomes $y = (y_1, \ldots, y_n)$ that are independently drawn from the probability distribution $P$, then we establish a prediction model $\varphi(X, L)$. Here, $n$ is the number of samples and $p$ is the number of predictors. By taking repeated bootstrap samples $L^{(i)}$ from $L$, we formed a set of new prediction models $\varphi(X, L^{(i)})$. The final prediction of the bagging model denoted by $\varphi_b(x) = E \varphi(X, L^{(i)})$ was obtained by averaging all results for a number of sub-models. The proof of the validity of bagging on improving prediction accuracy is given in the Methods section of the Supplemental Material.

To build the ensemble model, we randomly drew several ($B$) bootstrap samples from the original data $[X_{n \times p}, y_{n \times 1}]$, trained $B$ penalized regression models, $M^1, M^2, \ldots, M^B$, by using the bootstrap samples and combined them to obtain an aggregated prediction. To determine an optimal sub-model in the ensemble penalized regression model according to several performance measures during each random sampling, we used a multi-objective optimization method via the weighted rank aggregation\textsuperscript{21}. First, each model ranked the sub-models according to their performance under that particular measure and generated the ordered lists of sub-models, $R_1, \ldots, R_p$, where
\( K \) is the number of measures used. Second, the weighted rank aggregation approach was used to produce an aggregated list that ranked the sub-models according to their performance under all \( K \) measures simultaneously.

To obtain the optimal ordered list of models, we defined the following objective function:

\[
\Phi(\delta) = \sum_{i=1}^{K} w_i d(\delta, R_i)
\]  

(3)

where \( \delta \) is an ordered list of models of size \( Q \), \( d \) is a distance function that estimates the similarity between any two ordered lists, and \( w_i \) is a weight factor associated with each measure. The Spearman footrule distance function\(^2\) was used to estimate the similarity between any two lists of models.

To determine an optimal model according to all \( K \) measures simultaneously, it is equivalent to seek out an optimal list \( \delta^* \) to minimize the value of the objective function \( \Phi(\delta) \). To determine the optimal parameter \( \delta^* \), the cross-entropy method was used for rank aggregation\(^4\). The algorithm of the ensemble penalized regression model is given as follows:

**Algorithm.** Ensemble penalized regression model.

**Input:**
- \((X, y)\): training set that contains \( n \) samples and a \( p \)-dimensional vector of predictors, and \((X, y) \in \mathbb{R}^{n \times (p+1)}\).
- \( B \): number of random bootstrap samplings.
- \( n_{\text{bootstrap}} \): size of random bootstrap samples with replacement.
- \( Q \): size of an ordered list of sub-models in the ensemble model.
- \( K \): number of performance measures.
- \( RP \): size of random subspace predictor.
- \( \delta \): an initial ordered list of sub-models of size \( L \).
- \( d(.) \): the Spearman footrule distance function.

**Output:** prediction \( \psi_{\text{average}} \) of the ensemble model.

**for** \( b = 1 \) to \( B \) **do**
- generate bootstrap samples \((X^b, y^b) \in \mathbb{R}^{n_{\text{bootstrap}} \times (p+1)}\)
- generate out-of-bag (OOB) samples \( L_{\text{OOB}} = (X_{\text{OOB}}^b, y_{\text{OOB}}^b) \in \mathbb{R}^{n_{\text{OOB}} \times (p+1)}\)
  **for** \( q = 1 \) to \( Q \) **do**
  randomly select \( RP \) predictors as a subset from the original \( P \) predictors

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**Figure 1. Architecture of the ensemble penalized regression model.** A sequence of processing procedures, primarily including model training, validation, evaluation and averaging to be implemented in random bootstrap samplings in this architecture.
Data of influenza cases confirmed by laboratory test for the period January 2010 to May 2015 in China were publicly available from China's Center for Disease Control and Prevention.

| Month      | Cases | Month      | Cases | Month      | Cases | Month      | Cases | Month      | Cases |
|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|-------|
| 2011–01   | 6072  | 2011–12   | 11631 | 2012–11   | 8942  | 2013–10   | 9309  | 2014–09   | 9751  |
| 2011–02   | 5930  | 2012–01   | 10046 | 2012–12   | 12411 | 2013–11   | 12317 | 2014–10   | 8635  |
| 2011–03   | 7299  | 2012–02   | 17421 | 2013–01   | 16012 | 2013–12   | 23894 | 2014–11   | 12043 |
| 2011–04   | 5727  | 2012–03   | 21625 | 2013–02   | 9806  | 2013–03   | 10761 | 2014–02   | 25279 |
| 2011–05   | 4130  | 2012–04   | 6195  | 2013–04   | 9006  | 2013–05   | 14166 | 2014–03   | 19199 |
| 2011–06   | 3065  | 2012–05   | 17421 | 2013–06   | 6254  | 2013–07   | 12317 | 2014–04   | 15063 |
| 2011–07   | 2654  | 2012–06   | 21625 | 2013–08   | 5338  | 2013–09   | 12317 | 2014–05   | 13625 |
| 2011–08   | 3243  | 2012–07   | 9806  | 2013–10   | 6098  | 2013–11   | 12411 | 2014–06   | 12043 |
| 2011–09   | 4360  | 2012–08   | 6793  | 2013–12   | 8635  | 2013–13   | 12685 | 2014–07   | 14056 |
| 2011–10   | 5525  | 2012–09   | 6762  | 2014–01   | 6975  | 2013–14   | 8635  | 2014–08   | 11419 |
| 2011–11   | 7055  | 2012–10   | 7331  | 2014–09   | 7331  | 2013–15   | 12043 | 2014–09   | 7331  |

Model evaluation. To widen the application of the ensemble model, we considered two set-ups of the model including the logistic and linear regression models for monitoring influenza epidemics. For the logistic regression model, we used five performance measures, including accuracy, sensitivity, specificity, AUC15 and KIA16. For the linear regression model, we used relative error (RE), root mean square error (RMSE), mean absolute error (MAE) and symmetric mean absolute percentage error (SMAPE)28 to assess performance.

Application to monitor seasonal influenza activity. Data sources. This study used monthly case counts of influenza occurring from January 2011 to May 2015 in China for testing the model. These laboratory-confirmed cases of influenza were reported by physicians to the notifiable disease-monitoring system managed by China’s Center for Disease Control and Prevention, and the data are publicly available on the official
website (http://www.moh.gov.cn/). The influenza surveillance data for the studied period corresponded to a total of 53 months of influenza cases. Table 1 shows the details of monthly influenza case counts used in this study.

Search query data were obtained from the Baidu Index website, which contains logs of online search query volume for numerous keywords searched by Baidu users. Since the search query data were available on a daily basis, we converted the data to monthly counts over the study period for analysis.

**Keyword selection, crawling and filtering.** Previous studies generally chose the names or clinical symptoms of the studied diseases as the primary terms to find more related keywords. From this idea, we used the term “influenza” (流感 in Chinese) as a primary keyword to search for more keywords associated with the studied disease on a Chinese website (http://tool.chinaz.com/baidu/words.aspx). The recommended keywords were comprehensively extracted from different sources, including Baidu, portal websites, and blogs.

On typing in the primary keyword, a total of 100 related keywords were obtained for further analysis (Table 2). After determining the related keywords, we established an auto-crawler by using Python and used it to collect search volume data for the keywords. The framework of an auto-crawler is depicted in Fig. 2. The Python scripts could be available from the authors for academic usage.

Because some recommended keywords were not necessarily related to influenza epidemics, we further filtered the keywords in three steps: first, the selected search keywords should represent factors that might affect the influenza epidemic; second, the search volume data for each keyword could be presented as a sequential time series with a specific resolution of time (e.g., daily, weekly or monthly); third, the time series of selected keywords should have a maximum cross-correlation coefficient of at least 0.4 with the influenza case data. These filtering approaches were also proposed in previous studies.

We considered two scenarios of model validation. First, the influenza case surveillance data were divided into a fitting and validation dataset. Models were fitted by using data from January 2011 to June 2014, and the remaining part of the data was used for model validation. Second, to compare the models for monitoring a high level of influenza epidemics, we investigated three cases of high incidence thresholds defined as the median, 75th and 90th percentiles of number of influenza cases over the study period, and evaluated their performance. The receiver operating characteristic (ROC) curve was used to assess the predictive ability of the models.

**Results**

On the basis of our filtering steps, 19 of the 100 keywords were not related to influenza epidemics, 8 keywords did not have sequential time series due to low search volume, and a set of only 58 keywords was retained for building the compared models (Table 2). Taking into account the delayed effects of predictors, we considered time lags of 0 to 1 month and the autoregressive term of influenza case number in the previous month. In total, 117 predictors were used for building the prediction models. In this case, the number of predictors was more than the length of time series of influenza cases (117 > 53). Thus, the penalized estimation of parameters in the model was necessary in this study.

In general, influenza causes annual epidemics that peak during the spring and winter in China. Most of our selected search keywords captured the peaks and troughs of the time series curves of influenza cases, so they were good indicators for monitoring influenza epidemics in the country (Figures S1–S5).

Comparison of prediction performance of different penalized regression models and the algorithms in the proposed ensemble framework is shown in Table 3. For the prediction of seasonal influenza case counts in the period between July 2014 and May 2015, the ensemble framework improved the performance of the conventional lasso, ridge and elastic net regression models. Among the models, the ensemble elastic net regression model outperformed the others since it had the smallest prediction errors (Table 3). Regardless of the periods for model fitting and prediction, the ensemble elastic net regression model was able to capture the peaks and troughs of the time series curves of influenza cases (Fig. 3). The forecast intervals given by the ensemble model well covered the actual epidemic curve of influenza cases.

For monitoring a high level of influenza epidemics, this study integrated the set-up of logistic regression models in the ensemble prediction framework. We studied three situations of high incidence thresholds defined as the median, 75th and 90th percentiles of number of influenza cases over the study period. The performance of the models to detect a large number of influenza cases was assessed using the measures including accuracy, sensitivity, specificity, AUC and KIA (Table 4). Overall, the ensemble elastic net regression model had the largest average AUC of 0.97, and thus outperformed the others, irrespectively of thresholds of influenza incidence used. In addition, it suggested that the predictability of the conventional lasso, ridge and elastic net models was consistently improved by the ensemble framework (Fig. 4).

Figure 5 shows the estimated importance score for the top 25 keywords contributing to the prediction of the ensemble model. The keyword, "type a flu" (variable X39), was the most significant factor predicting influenza epidemics over the study period. In addition, the keywords "saying type a h7n9 flu" (variable X99), "the toll of swine flu-related death" (variable X52) and "flu symptom" (variable X47) played important roles in the internet search queries-based surveillance model we established. The ensemble elastic net regression model performed similarly with a large number of random bootstrap samplings, for example, with $B = 100$ (Figure S6). It also guaranteed that the prediction of the ensemble model converged to a stable result.

**Discussion**

We used bagging and a multi-objective optimization technology to establish a novel ensemble elastic net penalized regression model to detect seasonal influenza epidemics in China. The results revealed high performance and small fluctuation of extrapolating ability for the proposed model as a Baidu search engine queries-based surveillance framework. The empirical analysis demonstrated that monitoring seasonal influenza epidemics was better with our ensemble models than the conventional penalized regression models.
| Variable | Chinese name | English name | Include (√) / exclude (×) | Variable | Chinese name | English name | Include (√) / exclude (×) |
|----------|--------------|--------------|--------------------------|----------|--------------|--------------|--------------------------|
| X1       | 香港流感     | Hongkong flu | √                        | X51      | 甲型h1n1流感病毒 | type a h1n1 flu virus   | ×                        |
| X2       | 流感         | Flu          | ×                        | X52      | 流感死亡人数     | the toll of swine flu-related death | √                        |
| X3       | 流感症状     | flu symptom  | ×                        | X53      | 北京流感       | Beijing (space) flu | √                        |
| X4       | 流感疫苗     | flu vaccine  | √                        | X54      | 流感疫苗价格     | flu (space) Korea | √                        |
| X5       | 流感病毒     | swine flu    | ×                        | X55      | 流感的症状       | the symptom of swine flu | √                        |
| X6       | 流感病毒     | flu virus    | √                        | X56      | 流感           | dog flu | ×                        |
| X7       | 流感疫苗有必要打吗 | the flu vaccine is necessary to play | √                        | X57      | 关键字 | Guanyang up flu | ×                        |
| X8       | 甲型流感     | influenza A  | √                        | X58      | 季节性流感       | seasonal influenza | √                        |
| X9       | 流感的症状     | the symptom of flu | √                        | X59      | 流感疫苗价格     | influenza vaccine price | √                        |
| X10      | 西班牙流感  | Spanish flu  | √                        | X60      | 猪流感怎么治疗 | how to treat swine flu | √                        |
| X11      | 美国流感疫苗接种 | US flu spread | ×                        | X61      | 流感疫苗接种时间 | influenza vaccination time | ×                        |
| X12      | 甲型h1n1流感 | type a h1n1 flu | √                        | X62      | h7n9流感症状     | h7n9 flu symptom | √                        |
| X13      | 流感 韩国电影 | flu Korean movies | ×                        | X63      | 甲型h1n1流感不可怕 | type a h1n1 flu is not terrible | √                        |
| X14      | 流感吃什么药 | influenza drugs | √                        | X64      | 流感传播途径 | the routes of flu transmission | ×                        |
| X15      | 流感概念性 | influenza concept stock | ×                        | X65      | 流感的预防       | the prevention of flu | √                        |
| X16      | 流感嗜血杆菌 | haemophilus influenzae | √                        | X66      | 上海流感 | up flu Guanying | ×                        |
| X17      | 預防流感     | prevent flu  | √                        | X67      | 甲型h7n9流感症状 | type a h7n9 flu symptom | √                        |
| X18      | 流感丸     | flu pill     | √                        | X68      | 猪流感疫情       | swine flu epidemic | √                        |
| X19      | 北京流感     | Beijing flu  | √                        | X69      | 4型流感病毒     | type a flu virus | √                        |
| X20      | 情流感     | love flu     | ×                        | X70      | 甲型h1n1流感症状 | type a h1n1 flu symptom | √                        |
| X21      | 情流感     | love flu strain | ×                        | X71      | 甲型h3n2流感病毒 | type 1 h3n2 flu virus | ×                        |
| X22      | 流感疫情     | influenza epidemic | √                        | X72      | 甲型h1n1流感症状 | type a h1n1 flu symptom | ×                        |
| X23      | 超级流感     | super flu   | ×                        | X73      | 流感大流行     | influenza pandemic | √                        |
| X24      | 三月爱情流感 | March love flu | ×                        | X74      | 流感的传播途径 | The route of transmission of flu | √                        |
| X25      | 台湾流感     | Taiwan flu   | √                        | X75      | 流感的预防措施 | the prevention measures of flu | ×                        |
| X26      | 流感疫苗副作用 | side effects of flu vaccine | √                        | X76      | 美国流感 | US (space) flu | √                        |
| X27      | 流感症状     | swine flu symptom | ×                        | X77      | 流感的治疗 | the therapy of swine flu | √                        |
| X28      | 怎样预防流感 | how to prevent flu | √                        | X78      | 猪流感疫苗     | swine flu vaccine | √                        |
| X29      | b7n9流感 | h7n9 flu | √                        | X79      | h3n2流感病毒 | h3n2 flu virus | ×                        |
| X30      | 病毒性流感 | viral flu | √                        | X80      | 甲型流感症状 | type a flu symptom | √                        |
| X31      | 上呼吸道     | Shanghai flu | ×                        | X81      | 甲型流感病毒 | type a flu vaccine | ×                        |
| X32      | 怎样预防流感 | how to prevent flu | √                        | X82      | 怎样预防甲型流感 | how to prevent type a flu | ×                        |
| X33      | 甲型流感病毒 | type a flu virus | ×                        | X83      | 18号欧洲流感 | 18 European flu | √                        |
| X34      | h1n1流感     | h1n1 flu     | ×                        | X84      | 17/18欧洲流感 | 2012 European flu | ×                        |
| X35      | 流感疫苗     | flu prevention | √                        | X85      | 甲型流感     | h1n1 type a flu | √                        |
| X36      | h1n1流感症状 | h1n1 flu symptom | √                        | X86      | 甲型流感症状 | the symptom of h1n1 flu | ×                        |
| X37      | 甲型流感症状 | the symptom of type a flu | √                        | X87      | 甲型流感疫苗 | h1n1 type a flu | ×                        |
| X38      | 情流感的症状 | the symptom of love flu | ×                        | X88      | 甲型流感症状 | what are the symptoms of h1n1 influenza | ×                        |
| X39      | a型流感     | type a flu   | √                        | X89      | 甲型流感预防知识 | what is the knowledge of influenza prevention | √                        |
| X40      | 流感治疗     | flu therapy | √                        | X90      | 甲型流感最新疫情 | the latest outbreak of h1n1 influenza | ×                        |
| X41      | 美国流感     | US flu       | √                        | X91      | 甲型流感 | hini flu | ×                        |
| X42      | 新型流感     | new type flu | ×                        | X92      | 甲型流感症状 | the symptom of hini flu | ×                        |
| X43      | qq流感大亨 | qq flu game | ×                        | X93      | qq流感大亨下载 | qq flu game download | ×                        |
| X44      | 上流感     | up flu       | ×                        | X94      | 北京甲流感 | Beijing influenza a | √                        |
| X45      | 甲流感     | A influenza  | ×                        | X95      | 本山快乐营流感 | Renshan Happy camp swine flu | ×                        |
| X46      | 流感 症状 | flu (space) symptom | √                        | X96      | 没了精流感怎么办 | how to do when having swine flu | ×                        |
| X47      | 香港流感病毒 | Hongkong flu virus | √                        | X97      | 甲型h1n1流感 | about type a h1n1 influenza | ×                        |
| X48      | 新流感     | new flu      | ×                        | X98      | 关于流感的作文 | about the composition of swine flu | ×                        |
| X49      | 羊流感     | goat flu     | ×                        | X99      | 甲型h1n1流感 | saying type a h1n1 flu | ×                        |
| X50      | 副流感病毒 | parainfluenza virus | ×                        | X100     | 季节性流感 | seasonal influenza vaccine | √                        |

Table 2. Search keywords from Baidu search engine used in this study. The search terms in bold were excluded at filtering step (i), search terms in italics were excluded at filtering step (ii) and search terms in bold and italics were excluded at filtering step (iii). Step (i): the selected search terms should represent factors that might influence the influenza epidemics. Step (ii): the search query data for each term was a sequential time series with a daily, weekly or monthly resolution. Step (iii): the time series of selected search terms should have a maximum cross-correlation coefficient of at least 0.4 with the influenza case data.
Recently, Salathé M. et al. discussed the importance of digital disease surveillance for rapid disease outbreak detection and proposed it as a powerful tool to complement traditional approaches. In fact, internet search query data is being explored as a low-cost approach to providing near real-time estimates of disease activity and is becoming widely used for disease surveillance. In China, influenza activity based on routine surveillance data from the ministry of health of China was usually reported with a 1 to 2-week lag. Hence, as a convenient source for timely estimating of influenza activity and detecting an epidemic, search query data can contribute to improve the results of traditional disease surveillance.

### Table 3. Prediction performance of different penalized regression algorithms (lasso, ridge and elastic net) and the algorithms in the proposed ensemble framework was compared using the number of influenza cases during the period of July 2014 to May 2015. Measures including relative error (RE), root mean square error (RMSE), mean absolute error (MAE) and symmetric mean absolute percentage error (SMAPE) were used to assess the predictions.

| Prediction period | Model       | RMSE   | MAE    | RE      | SMAPE  |
|-------------------|-------------|--------|--------|---------|--------|
| 2014/07–2015/05   | ridge       | 5283.87| 4045.57| 26.41%  | 26.53% |
|                   | lasso       | 4702.71| 3419.20| 25.16%  | 23.60% |
|                   | elastic net | 3396.04| 2799.94| 21.29%  | 21.19% |
|                   | ensemble ridge | 4148.28| 3285.35| 22.73%  | 21.74% |
|                   | ensemble lasso | 3756.31| 2897.91| 20.42%  | 19.24% |
|                   | ensemble elastic net | 3488.42| 2650.17| 19.09%  | 17.55% |

Figure 2. Framework of an auto-crawler using Python to collect search query data from the Baidu Index website. The Selenium webdriver was mainly used with Python for automatic crawling of search query data. The software and search engine used for this analysis are in green.
In a newly released report, about 87% of Chinese internet users preferred Baidu to search for any information, so it is the most popular search engine in China. With the wide use of the Baidu search engine, the search volume of Baidu naturally reflects Chinese online behavior. Therefore, data from Baidu are more representative of search queries in China for this analysis. Many search keywords are more likely to be captured with this search engine to build a Baidu search engine queries-based surveillance model.

The data for the surveillance model must be automatically fetched over the internet. To achieve this goal, we established an auto-crawler by using Python to collect search volume data for the keywords obtained. The auto-crawler was mainly completed by using the Selenium package within Python. The framework of the auto-crawler included calling the tool of the Selenium webdriver to start with a browser and open the Baidu Index website, construct a new uniform resource locator (URL) using a keyword, call the Selenium webdriver to open the URL and take screenshots that containing the figures of search volume, and call Tesseract-OCR to extract the data (Fig. 2).

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Table 4. Comparison of different penalized regression algorithms (ridge, lasso and elastic net) and the algorithms in the proposed ensemble framework in predicting influenza epidemics, by using three cases of high incidence thresholds defined as the median, 75th and 90th percentiles of number of influenza cases over the study period. Measures including accuracy (Acc), sensitivity (Sen), specificity (Spe), area under the receiver operating characteristic curve (AUC) and kappa index of agreement (KIA) were used to assess the predictions.

| Percentile cutoff | Model      | Acc | Sen  | Spe  | AUC | KIA |
|-------------------|------------|-----|------|------|-----|-----|
| Median            | ridge      | 0.92| 0.96 | 0.88 | 0.92| 0.85|
|                   | lasso      | 0.92| 0.93 | 0.92 | 0.92| 0.85|
|                   | elastic net| 0.98| 1.00 | 0.96 | 0.98| 0.96|
|                   | ensemble ridge | 0.94| 0.96 | 0.92 | 0.94| 0.88|
|                   | ensemble lasso | 1.00| 1.00 | 1.00 | 1.00| 1.00|
|                   | ensemble elastic net | 1.00| 1.00 | 1.00 | 1.00| 1.00|
| 75th              | ridge      | 0.85| 0.43 | 1.00 | 0.71| 0.52|
|                   | lasso      | 0.96| 0.86 | 1.00 | 0.93| 0.90|
|                   | elastic net| 0.96| 0.86 | 1.00 | 0.93| 0.90|
|                   | ensemble ridge | 0.87| 0.50 | 1.00 | 0.75| 0.59|
|                   | ensemble lasso | 0.98| 0.93 | 1.00 | 0.96| 0.95|
|                   | ensemble elastic net | 1.00| 1.00 | 1.00 | 1.00| 1.00|
| 90th              | ridge      | 0.90| 0.17 | 1.00 | 0.58| 0.26|
|                   | lasso      | 0.92| 0.33 | 1.00 | 0.67| 0.47|
|                   | elastic net| 0.94| 0.50 | 1.00 | 0.75| 0.64|
|                   | ensemble ridge | 0.90| 0.17 | 1.00 | 0.58| 0.26|
|                   | ensemble lasso | 0.96| 0.67 | 1.00 | 0.83| 0.78|
|                   | ensemble elastic net | 0.98| 0.83 | 1.00 | 0.92| 0.90|

Figure 3. Predictions of influenza cases according to the ensemble elastic net regression model for the period of July 2014 to May 2015. Dark-red dots represent the actual counts of influenza case, blue line represents the fitted counts, and the 95% prediction interval is presented, respectively; the grey areas correspond to the periods used for model fitting and the green areas for prediction.
For our empirical analysis, the number of search terms used for predicting influenza epidemics was greater than the sample size (117 > 53) (Table 2). Beyond the use of a linear regression model using a stepwise fashion for significant variable selection and model prediction, this study utilized penalized regression approaches to establish prediction models with various search keywords. With a large number of predictors in the model, we

Figure 4. Performance of different penalized regression algorithms (ridge, lasso and elastic net) and the algorithms in the proposed ensemble framework in predicting influenza epidemics. (A) High incidence threshold defined as the median percentile of influenza case counts over the study period. (B) High incidence threshold defined as the 75th percentile of influenza case counts. (C) High incidence threshold defined as the 90th percentile of influenza case counts. (D) Comparison of performance of the six prediction models using the receiver operating characteristic (ROC) curve. The e-elastic net, e-lasso and e-ridge models represent the ensemble elastic net, lasso and ridge regression models, respectively.

Figure 5. Contribution of each predictor to the prediction in the ensemble elastic net regression model. Only the top 25 significant predictors are shown, and their meanings are described in Table 2. For example, the variable X39 represents the keyword “type a flu” and X99 denotes the keyword “saying type a h1n1 flu.”
would prefer to search for a smaller subset that has the strongest effects. A feature of the penalized regression models is a tuning parameter, $\lambda$, that controls the amount of shrinkage applied to the coefficients. By shrinking variables with very unstable estimates towards zero, the approach can effectively exclude some irrelevant variables and produce a subset of variables with strong effects. Regarding the tuning parameter, the traditional way of choosing the optimal $\lambda$ is to use the cross-validation method. However, the robustness of variable selection is affected by the fold assignment used for cross-validation to some extent. This situation results in estimating the model parameters with a degree of variability. To enhance the predictability of penalized regression models, we combined the methods of bagging and multi-objective optimization to construct the ensemble penalized regression models. Bagging can substantially improve the accuracy of an instable prediction model. Our study suggested that the proposed ensemble framework significantly improved the performance of the conventional lasso, ridge and elastic net regression models, and the ensemble elastic net regression model was optimal in estimating influenza activity.

We found high correlations between specific search terms of Baidu and seasonal influenza incidence. We developed an index of importance score to estimate the contribution of each search term to the prediction of influenza epidemics. Breiman, L. introduced a practical approach to measure variable importance based on computationally intensive permutations. We adopted this idea and assessed the contribution of each predictor in the ensemble model. For the performance, our predictions of time periods with high influenza incidence based on the ensemble elastic net regression model were very accurate, for different thresholds of high incidence (Table 4). Together, these results demonstrate the viability of the presented ensemble model in supporting influenza surveillance. The ensemble model performed similarly when the number of bootstrap replicates was large. The results of the empirical study indicated that the ensemble model was robust. Although China has established a notifiable infectious disease monitoring system nationwide, reported influenza cases are available to the public with a delay of about 1 to 2 weeks. The rapid expansion of the geographical distribution and genetic diversity of novel influenza viruses poses a direct challenge to current disease control systems in China. Potentially, influenza may become a long-term threat to public health in this country. Predictive search term-based models were found to perform better than a model using only reported cases to predict future cases. Specifically, an internet search-term model returns results more quickly and with better performance. Our study also suggested that most of the selected search keywords captured the peaks and troughs of the time series curves of influenza cases. Our ensemble elastic net regression model predicted seasonal influenza epidemics with high performance. Thus, in China, this internet search-based system might be used as a supplement to existing surveillance systems. However, we should note that surveillance models based on internet search query data like Google Flu Trends have substantial flaws including missing the first wave of the 2009 influenza H1N1 pandemic and overestimating the intensity of the H3N2 epidemic during the 2012/2013 season in United States. It means that there is room to improve the performance of surveillance models based on internet search query data and provide reliable surveillance for seasonal or pandemic influenza. In addition, because Google has pulled out of mainland China since 2010, search query data from Google during the study time period of 2011–2013 are not publicly available in mainland China. Therefore, an overall comparison between the algorithm proposed in this study and that of Google Flu Trends cannot be made. All of these drive us to further validate the performance of the proposed algorithm by ongoing studies in the future.

Several limitations of this study should be mentioned. In fact, different people may use different words to search for the same information, especially when searching in Chinese, which has various ways of expression. Thus, search keywords should be carefully selected to reflect terms most likely associated with influenza epidemics. As well, internet searching behavior was susceptible to the impact of media reports, which might affect the performance of the internet search-term-based system. Third, in the empirical study, 100 bootstrap replicates were used for building the ensemble model. With this setting, the ensemble prediction was converged to a stable result but required much time to generate an aggregated prediction. This issue was also discussed by Breiman, L. A procedure for parallel computing integrated into the ensemble model to speed up the analysis would be practical. Hence, the computing efficiency needs to be improved.

In conclusion, this present study developed a novel ensemble elastic net penalized regression model by combining bagging and a multi-objective optimization method to monitor seasonal influenza activity. The approach provided a useful tool in support of the public health response to influenza and other infectious diseases in China.

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Author Contributions

P.G. and Q.Y.Z. conceived and designed the study. P.G., J.J.Z., L.W., S.Y.Y., G.F.L., C.Y.D., Y.W. and Q.Y.Z. collected and cleaned the data. P.G. and Q.Y.Z. analyzed, interpreted the data and wrote the manuscript. All authors read and approved the final manuscript.

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