ORIGINAL ARTICLE

Comparison of methods to Estimate Basic Reproduction Number (R_0) of influenza, Using Canada 2009 and 2017-18 A (H1N1) Data

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Background: The basic reproduction number (R_0) has a key role in epidemics and can be utilized for preventing epidemics. In this study, different methods are used for estimating R_0's and their vaccination coverage to find the formula with the best performance. **Materials and Methods:** We estimated R_0 for cumulative cases count data from April 18 to July 6, 2009 and 35-2017 to 34-2018 weeks in Canada: maximum likelihood (ML), exponential growth rate (EG), time-dependent reproduction numbers (TD), attack rate (AR), gamma-distributed generation time (GT), and the final size of the epidemic. Gamma distribution with mean and standard deviation 3.6 ± 1.4 is used as GT. **Results:** The AR method obtained a R_0 (95% confidence interval [CI]) value of 1.116 (1.1163, 1.1165) and an EG (95%CI) value of 1.46 (1.41, 1.52). The R_0 (95%CI) estimate was 1.42 (1.27, 1.57) for the obtained ML, 1.71 (1.12, 2.03) for the obtained TD, 1.49 (1.0, 1.97) for the gamma-distributed GT, and 1.00 (0.91, 1.09) for the final size of the epidemic. The minimum and maximum vaccination coverage were related to AR and TD methods, respectively, where the TD method has minimum mean squared error (MSE). Finally, the R_0 (95%CI) for 2018 data was 1.52 (1.11, 1.94) by TD method, and vaccination coverage was estimated as 34.2%. **Conclusion:** For the purposes of our study, the estimation of TD was the most useful tool for computing the R_0, because it has the minimum MSE. The estimation $R_0 > 1$ indicating that the epidemic has occurred. Thus, it is required to vaccinate at least 41.5% to prevent and control the next epidemic.

Key words: Basic reproduction number, influenza A virus, vaccination coverage

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INTRODUCTION

Pandemic influenza, a global outbreak, defines as spreading influenza virus between peoples (with little or lack of immunity) over a wide geographic field.[1] In the 20th century, three pandemics of influenza happened which were "Spanish flu," "Asian flu," and "Hong Kong flu" in the years "1918–1919," "1957–1958," and "1968–1969," respectively.[2] In early 2009, H1N1 influenza at first occurred in Mexico and the United States and speared rapidly worldwide (>200 countries involved).[3,4] The influenza virus can spread among people by direct contact (a cough, sneeze or talk), inhalation of virus-laden aerosols, and touch fomites (contaminated objects) that has the flu virus.[5,6] The most affected groups for developing flu-related complications are children, pregnant women, elders (adults older than 64-year-old), and persons with a specific disease (chronic pulmonary disease, chronic heart disease, diabetes, etc.,).[7,8] The mortality and morbidity related to the annual influenza in the worldwide estimated approximately one million people, a considerable number.[9] For example, the number of deaths for "United States flu (2009)" reported 12,469 and

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for "Asian flu" was 1–4 million.[10,11] Therefore, controlling and preventing the epidemic of influenza is an important issue. The basic reproduction number (R_0) is an important metric that used for measuring the vaccination coverage (to prevent epidemic), eradicating an infectious disease, controlling and immunizing the disease which is defined the mean number of secondary infections generated by a single infectious individual in a fully susceptible population without immunity and interventions.[12] In particular, the R_0 determines whether an infection spreads through a population.[13] The basic reproduction number or threshold parameter applied for determining the critical immunity coverage can be a real number greater than, less than, or equal to one. The disease will fade out when $R_0 < 1$ and an epidemic will occur (the infection will grow) if $R_0 \geq 1$, showing an endemic in the population.[13,14]

Since the R_0 has a key role in measuring the transmission of diseases and is crucial in preventing epidemics, thus it is important to know which methods and formulas to apply to estimate R_0 and have better performance. We estimate the R_0 and its related vaccination coverage for Canadian influenza data during 2009 and 2017–2018.

MATERIALS AND METHODS

Objectives

In this study, we reviewed the investigated methods and formulas used for estimating the R_0 of influenza in various published research papers from 1954 to 2017. After a scientific systematic review on R_0, we found out that there are many basic reproduction formula which are applied for determining the vaccination coverage so it is necessary to characterize a formula which gives more accurate result to use in vaccination strategies which leads to optimize the costs. We extracted more commonly-utilized formulas [Appendix Table 1]. We considered six common formulas and applied them to real data to determine which formula most closely approximates the real epidemic threshold parameter with high efficacy.

Then, R_0s and related vaccination coverage of these methods was estimated for a secondary real data of Canadian influenza (2009). The calculated R_0 was compared with R_0 of the Canadian paper[15] and also simulations were performed. Finally, the best method was chosen based on mean squared error (MSE), then R_0 calculated by selected method for the H1N1 Canadian data in the 35th week in 2017–34th week in 2018.

Data

In Canada, circulating of influenza A virus is very common. The data sets in this study were obtained from the Public Health Agency of Canada (PHAC) website[16] and the last FluWatch weekly report of the 2017–2018 influenza surveillance season achieved from the Respiratory Virus Detections in Canada Report website.[17]

The total number of patients was 927 during the 2009 influenza season which were based on month/day and the number of new cases was 1280 for Canada 2017–2018 H1N1 data which report every Thursday in Canada. We fitted all the six models to Canadian 2009 pH 1N1 cumulative cases data.[16] Then, the best model was applied to the data of Canada (34th week in 2017 to 34th week in 2018).[17]

Statistical analysis

The models used in this article included the Richard model, attack rate (AR), exponential growth rate (EG), maximum likelihood (ML), time-dependent reproduction numbers (TD), gamma-distributed generation time (GT), and R_0 using the final size of the epidemic. The above mentioned methods were applied for estimating R_0 using R software (R_0 package and programming). R software was created by Ross Ihaka and Robert Gentleman at the University of Auckland, New Zealand, and is currently developed by the R Development Core Team (of which Chambers is a member).

Generation time

The time-gap between infection of a primary case and infection of a secondary case that is generated by the primary case.[18]

The attack rate

The R_0 can be described by the AR with the following formula:

$$R_0 = -\frac{\log\left(\frac{1-AR}{S_0}\right)}{AR-\left(1-S_0\right)} \quad (1)$$

where AR defines the ratio of the people generating an infection disease and S_0 show the initial susceptible ratio.[19]

The exponential growth rate

The following formula was applied for computing the R:

$$\mu_t = R\left(\sum_{i=1}^{t} N_{t-i} w_i\right) \quad (2)$$

$$R = \frac{1}{M\left(-r\right)} \quad (3)$$

In this formula, M is the moment-generating function of the GT.[20] The parameter r is determined by the Poisson regression. Furthermore, the parameter w is GT.

The maximum likelihood

Let N_0, N_1,...., N_T identify incident cases over sequential time.

The log-likelihood function is:

$$LL(R) = \sum_{t=1}^{T} \frac{\exp(-\mu_t)\mu_t^{N_t}}{N_t!} \quad (4)$$

where

$$\mu_t = R\sum_{i=1}^{t} N_{t-i} w_i \quad (5)$$

and R is the maximum value of the log-likelihood function.[21] Furthermore, the parameter w is estimated by maximizing log-likelihood is GT.

Time-dependent reproduction numbers

In this method, R_t is computed by averaging R_j, which is the mean of all transmission networks corresponding to the cases observed.[22]

$$R_t = \frac{1}{N_t}\sum_{\{t_j = t\}} R_j \quad (6)$$

where

$$R_j = \sum_i p_i \quad (7)$$

And

$$p_{ij} = \frac{N_i w(t_i - t_j)}{\sum_{i \neq k} N_i w(t_i - t_k)} \quad (8)$$

Consider that person i and person j are in times t_i and t_j, respectively, then displays the probability of infection transmission from person j to person i so R_t compute by averaging all R_j which is the mean of all transmission networks correspondent with the cases that observed.

The gamma-distributed generation time

The number of cases on the day "t," denoted by n_t in (t_1, t_2) grows exponentially where

$$n_t = n_{t1} \exp(r[t - t1]) \quad (9)$$

$$r = \frac{cov(\{\log(n_t)\}_{tn[t_1,t_2]}, [t_1, t_2])}{var([t_1, t_2])} \quad (10)$$

And

$$R = (1 + \frac{r}{b})^a \quad (11)$$

The EG denotes by r. The mean and standard deviation of the GT are μ and σ, respectively, where $a = \mu^2/\sigma^2$ and $b = \mu/\sigma^2$.[23]

R_0 using the final size of the epidemic

The R_0 can be estimated with the below formula:

$$R_0 = \frac{N-1}{C}\sum_{i=N-C+1}^{N-1} \frac{1}{i} \quad (12)$$

where the total population at risk and total number of infections are denoted by N and C, respectively.[24]

Vaccination coverage

The vaccination coverage is computed by the basic reproduction number with formula:

$$v = 1 - \frac{1}{R_0} \quad (13)$$

which shows the proportion of peoples who should be received the vaccine.[7]

Comparison of methods

For exploring the closeness of the estimation of the mentioned methods to the actual R_0s and comparing them with each other, we applied 10000 times simulation for each formula based on the Canada data. The epidemics were simulated with the following properties. The distribution of the GT was considered gamma with the mean of 3.6 and standard deviation of 1.4. According to real data (the Canada data), the length of the epidemic was 80 days. Moreover, the peak value (the threshold value for the incidence before epidemics begin decreasing) for the Canada data occurred in the day 54. Therefore, we applied the value equal to 54 for the peak value in the simulation command [For details, see the simulation command under Table 1 in the results section]. Simulation of the basic reproduction number was made with above characteristics and the MSE was calculated for evaluating the performance of models with below formula. The lowest MSE value corresponds to the method which fitted the data best.

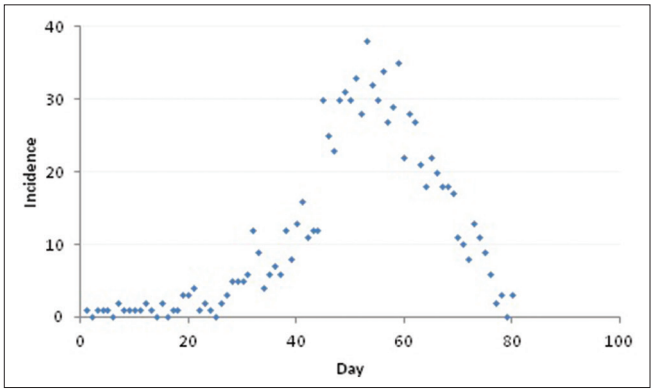

Figure 1: The incidence case counts influenza data of Canada during 18 April, 2009–6 July, 2009

Table 1: The simulated R_0s and their 95% confidence interval for each method

Actual R_0	R_0 (95% CI)					
	ML	EG	TD	AR	Gamma-distributed generation time	R_0 using the final size of the epidemic
1	1.23 (1.03, 1.47)	1.26 (1.19, 1.34)	1.17 (0.93, 1.42)	1.000003 (1.000003, 1.000004)	1.25 (0.98, 1.52)	0.91 (0.23, 1.58)
1.116	1.27 (1.08, 1.49)	1.33 (1.26, 1.40)	1.24 (1.0, 1.47)	1.000004 (1.000004, 1.000005)	1.30 (1.03, 1.57)	0.93 (0.39, 1.46)
1.42	1.43 (1.28, 1.61)	1.54 (1.48, 1.61)	1.47 (1.29, 1.65)	1.000009 (1.000008, 1.000009)	1.48 (1.21, 1.75)	0.97 (0.71, 1.23)
1.46	1.47 (1.32, 1.63)	1.59 (1.53, 1.66)	1.51 (1.34, 1.69)	1.000007 (1.000007, 1.000009)	1.52 (1.26, 1.79)	0.98 (0.75, 1.20)
1.49	1.48 (1.33, 1.64)	1.59 (1.53, 1.65)	1.51 (1.33, 1.69)	1.000008 (1.000008, 1.000009)	1.54 (1.27, 1.81)	0.98 (0.75, 1.21)
1.68	1.60 (1.47, 1.73)	1.75 (1.69, 1.81)	1.64 (1.44, 1.84)	1.000006 (1.000006, 1.000007)	1.64 (1.37, 1.91)	0.99 (0.80, 1.73)
1.71	1.60 (1.48, 1.73)	1.76 (1.71, 1.83)	1.66 (1.44, 1.88)	1.000006 (1.000005, 1.000006)	1.64 (1.38, 1.91)	0.99 (0.81, 1.17)
2	1.56 (1.47, 1.66)	1.80 (1.76, 1.85)	1.83 (1.53, 2.13)	1.000005 (1.000005, 1.000006)	1.67 (1.41, 1.94)	0.99 (0.83, 1.16)
2.5	1.36 (1.29, 1.42)	1.6 (1.57, 1.63)	2.16 (1.71, 2.60)	1.000004 (1.000003, 1.000004)	1.62 (1.35, 1.89)	1 (0.82, 1.17)
3	1.26 (1.21, 1.33)	1.46 (1.43, 1.48)	2.47 (1.87, 3.06)	1.000003 (1.000003, 1.000004)	1.56 (1.29, 1.82)	1 (0.81, 1.18)

Sim.epid (epid.n b=10000, GT=Generation.time ("gamma", c [3, 1.4]), R0 =r0, epid.length=80, family="poisson", peak.value=54). AR=Attack rate; R0 =Reproduction number; CI=Confidence interval; EG=Exponential growth rate; TD=Time dependent reproduction numbers; ML=Maximum likelihood; This is simulation command in R_0 package of R software

$$MSE = \frac{\sum_{i=1}^{n}(r_{0i} - R0)^2}{n-1} \quad (14)$$

RESULTS

Canadian 2009 H1N1 influenza data

We fitted the six models to the daily dataset of Canada, throughout the 80-day period of the studies. All dates of the Canada data were based on month/day form 18 April, 2009 to 6 July, 2009. Moreover, the number of infected people was plotted as frequency [Figure 1].

In order to demonstrate the difference in modeling with various formulas, the result of the Richard model (presented in Hsieh's study)[15] as well as the results of the other six models are presented in Table 2. The reported R_0 (95% confidence interval [CI]) (vaccination coverage%) using the Richard model was 1.68 (1.45, 1.91) (40.47) that means every person infected 1.68 other people on average during the infection period. Note that, R_0 (95%CI) (vaccination coverage%) for the estimation of TD (1.71 [1.12, 2.03] [41.52]) was clearly close to R_0 for the Richard model. The second method with the closest R_0 (95%CI) to that of the Richard model was the gamma-distributed GT (1.49 [1.0, 1.97] [32.88]). On the other hand, the computed R_0 (95%CI) using the EG was 1.46 (1.41, 1.52) (31.51). The ML method revealed that the calculated R_0 (95% CI) for this model was different from that for the Richard model (1.42 [1.27, 1.57] [29.58]). In addition, the estimated R_0 (95% CI) (vaccination coverage%) by the AR with two approaches was 1.000388 (1.000383, 1.000392) (0.04) and 1.1164 (1.1163, 1.1165) (10.43). The minimum computed R_0 (95% CI) was related to the estimation of the final size of the epidemic obtained as 1.0 (0.91, 1.09). The estimates of vaccination coverage for the six methods were vary. The lowest and highest vaccination coverage values in this setting were associated with AR and TD methods, respectively.

In order to compare the mentioned models to find the formula with better fit to the actual values, we conducted a simulation with R software and calculated R_0 based on the six models reported in Table 2. We used gamma distribution for the GT with the mean of 3.6 and standard deviation of 1.4. The peak value determined right over the original data were equal to 54. Then, using the above parameters, the simulation was implemented and R_0 was computed for each method. The simulation results for comparing the quality of the six methods are represented in Table 1 and Figure 2. In order to carry out the simulation, the number of runs to achieve the R_0 was 10000.

The results, given in Table 1, indicated that there were differences between the actual and simulated R_0; however, the TD method had the closest value to the R_0 calculated from the simulation compared to the other methods. Surprisingly, some variation was considered for the ML estimations when the actual values were equal to one, between one and two and greater than two. In the ML method, we found that the simulated R_0 for small values was very close to that for the actual values when the actual values were between 1.42 and 1.71; while the simulated R_0 for large values was very different from that for the actual values. For the gamma-distributed GT approach, the simulated R_0 grew out of the actual values for values close to one. In contrast, the results showed that the computed values for R_0 in the simulated system were slightly greater than the actual values when we applied R_0 between 1.42 and 2. By following the same interpretation, we can infer that the EG method had a small variation for small R_0 values ($1.4 < R_0 < 2$). On the other hand, the R_0 estimations using the EG diverged from the actual R_0 but was not significant. Finally, the computed R_0 by the AR and final size of the epidemic methods seemed likely to reflect stability for all R_0s. In particular, for the latest assumed R_0s, the estimated R_0 was equal to one.

We also plotted [Figure 2] the actual R_0 and simulated R_0 based on six methods with the parameters described in Table1. For evaluating the performance of models, we computed MSE for all methods [Table 3]. The TD method had the lowest MSE value in comparison to other methods. The MSE of AR and final size of the epidemic methods was very varied. In addition, MSE of ML, EG, and gamma-distributed GT methods were also calculated. For ML, EG, and gamma-distributed GT, the mean of MSE of all points were 4.85, 3.81, and 3.31, respectively. As noted above, the TD introduced the approach with the nearest estimation to the actual R_0 based on MSE criterion.

We also performed a sensitivity analysis with the incidence data of Canada on the GT with the gamma distribution [Figure 3]. The sensitivity analysis demonstrated that R_0 (95% CI) for the mean GT (days) of 3.6 and 4.9 was estimated as 1.47 (1.41, 1.53) and 1.67 (1.58, 1.76). Thus, the computed R_0 was approximately near that of the Richard and TD methods when the mean GT was equal to 4.9.

Canadian 2017–2018 H1N1 influenza data

The incidence data are reported based on week/year from the 35th week in 2017 to the 34th week in 2018. Peak value for this data has occurred in the 12th week in 2018 after starting the epidemics. The number of infected cases is plotted in Figure 4.

For the given data, R_0 (95% CI) and vaccination coverage based on TD method was computed. Indeed, we found that the estimated R_0 by TD method was (1.52 95% CI: 1.11, 1.94). In addition, the estimates of vaccination coverage were 34.2% for 2017–2018.

Table 2: The Reproduction number estimation by the different methods for the Canada data (2009)

Method	R_0 (95% CI for R_0)	Vaccination coverage (%)
Richard model	1.68 (1.45, 1.91)	40.47
AR	1.000388 (1.000383, 1.000392)[a]	0.04
	1.1164 (1.1163, 1.1165)[b]	10.43
EG	1.46 (1.41, 1.52)	31.51
ML	1.42 (1.27, 1.57)	29.58
TD	1.71 (1.12, 2.03)	41.52
Gamma-distributed generation time	1.49 (1.0, 1.97)	32.88
R_0 using the final size of the epidemic	1.0 (0.91, 1.09)	0

[a]AR based on incidence (n=33,630,000), [b]AR based on reported AR=0.201. R_0: Reproduction number; TD=Time-dependent reproduction numbers; ML=Maximum likelihood; EG=Exponential growth rate; AR=Attack rate, CI=Confidence interval

DISCUSSION

We implemented six methods (the ML, EG, TD, AR, gamma-distributed and final size of the epidemic), which permitted the estimation of the R_0 as key parameters of the epidemic based on the A/H1N1 Influenza cumulative case counts data in Canada (2009). The R_0 for the ML, EG, TD, AR, gamma-distributed and final size of the epidemic methods were estimated 1.42, 1.46, 1.71, 1.116, 1.49, and 1.0, respectively. In most cases, the R_0 was greater than unity; hence, the epidemic outbreak was observed. In addition, the computed R_0 for Canadian data (2018) by TD method was greater than one indicating that an epidemic occurred in Canada ($R_0 > 1$). Thus, it seems necessary to consider appropriate solutions in order to control, decrease and prevent the epidemic or pandemic of influenza. One of the most effective methods to protect people against

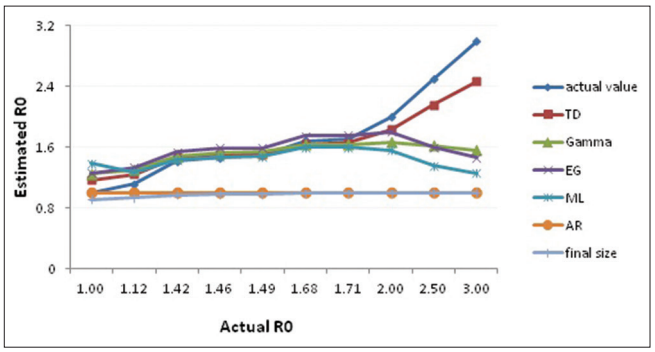

Figure 2: The plots of the actual and simulated R_0 compared for each method

Table 3: Mean squared error of reproduction number estimation for each method

R_0	Method					
	ML	EG	TD	AR	Gamma-distributed generation time	The final size of the epidemic
1	0.061	0.090	0.042	1.036e-11	0.080	0.015
1.116	0.038	0.072	0.030	0.014	0.055	0.043
1.42	0.027	0.064	0.025	0.178	0.043	0.207
1.46	0.027	0.065	0.022	0.212	0.041	0.236
1.49	0.027	0.059	0.022	0.240	0.040	0.266
1.68	0.035	0.050	0.014	0.046	0.026	0.482
1.71	0.042	0.050	0.016	0.505	0.028	0.524
2.0	0.242	0.089	0.043	1.001	0.118	1.014
2.5	1.345	0.862	0.141	2.252	0.784	2.267
3.0	3.011	2.405	0.321	4.004	2.097	4.022
Total mean	4.855	3.806	0.676	8.452	3.312	9.076

R_0=Reproduction number; TD=Time-dependent reproduction numbers; ML=Maximum likelihood; EG=Exponential growth rate; AR=Attack rate

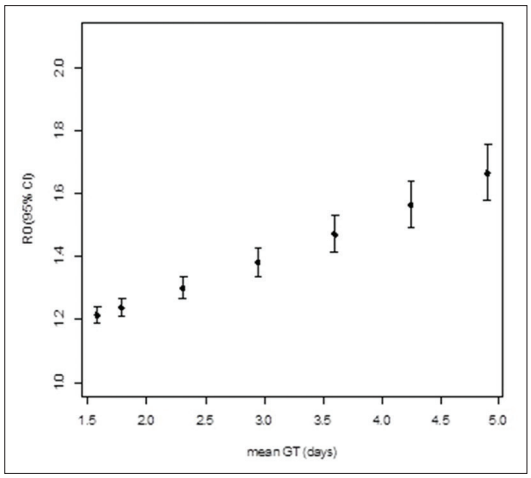

Figure 3: Sensitivity of R_0 to mean generation time to select the generation time

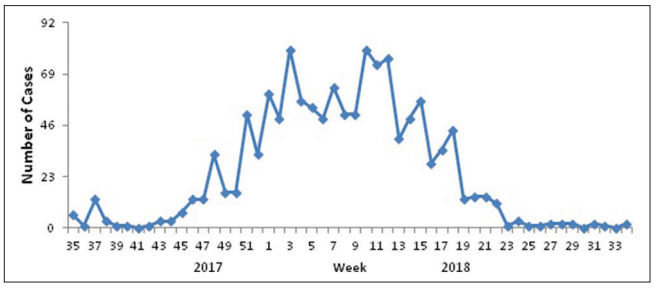

Figure 4: The incidence case counts influenza data of Canada from the 35th week in 2017 to the 34th week in 2018

influenza is vaccination that can be determined by using R_0 (vaccination coverage = $1 - 1/R_0$). On the other hand, annual influenza vaccination in the high-risk groups such as elderly people, ill person, pregnant woman, and children can reduce mortality rate. In addition, vaccination can also reduce the incidence of disease, cost, exacerbations of the disease, and hospitalizations. The vaccination coverage for Canada (2009) ranged between 10.43 and 41.52 using various methods and this value was 34.2% for 2017–2018 influenza Canada data.

Moreover, we performed a simulation using R software for several R_0 and obtained their estimates based on the epidemic data of Canada (2009) for the six methods. The computed R_0 in the TD method was nearly the same as the actual R_0 based on MSE criterion. Comparing the simulation results from the ML, gamma-distributed GT and EG methods showed variation for different values of the actual R_0; however, some of the calculated R_0s applying the simulation were close to the actual values. For the most actual R_0, the simulated R_0 by the AR and final size of the epidemic methods was equal to one. Whereas these type of modeling approaches are not able to differentiate between various R_0. We believe that this may correspond to the small number of the infected cases compared to the susceptible cases.

Note that, our basic reproduction number estimated using the TD method was consistent with that derived from the Richard model in the Canadian papers.[15] Not only the simulated R_0 for the value 1.68 almost agreed with that of the TD approach but also the other simulated R_0 by the TD method was nearly consistent with the actual R_0. In other words, the lowest MSE values were obtained for TD method.

From the methods reviewed in Appendix Table 2, which can be applied to estimate the R_0, the approaches presented in Table 1 fitted to the cumulative cases data. All the methods reviewed in this paper, as any modeling techniques, had advantageous and disadvantageous. One of the strengths of this study is to review all studies done related to influenza and then selected some of the frequently used model and determine their strengths and weaknesses; seven of them used for the R_0 estimation in the Canada data, as shown in Table 1, are explained in details in Table 4.

Regarding Table 4, it seemed that the TD, ML and EG methods had superiority compared to the other methods. These models were used by researchers to estimate R_0 of influenza.

Some studies estimated the R_0 from influenza data using different models and compared the results. Obadia *et al*. obtained estimates of R_0 from the "Germany 1918" epidemic data based on five approaches which including the AR, ML, sequential Bayesian and TD methods. In addition, comparing results from different methods showed that the biased ML and TD methods were least.[30] Another study applied four different methods (the EG, simple susceptible-exposed-infectious-recovered [SEIR], more complex SEIR-type model, and ML model) in order to compare these estimation approaches. The EG had large uncertainty while ML had a consistent estimate with the estimate of the autumn wave.[20] In general, the TD had a good fit on the data as confirmed with the Richard model and MSE criterion.

A weakness of this study is that the 2009 Canada data have been used for comparing methods, which looks old. The reason for this, is comparing R_0 with pervious article[15] and comparing the methods with the actual values which are exist on this data in the mentioned paper. Finally, a more comprehensive study for influenza as an annual national disaster using new method such as Bayesian is needed that we are going to do in the future research.

CONCLUSION

Awareness of the basic reproduction number of influenza is useful for calculating vaccination coverage and then applying vaccine strategy. Therefore, it is necessary to know the method which has better performance for influenza data that our results showed the TD method is preferred.

Table 4: Limitation and power of the methods used for the cumulative case counts data

Models	Advantageous	Disadvantageous
The Richard model	For cumulative case count, it gives simple means of fitting For modeling, it only needs cumulative case counts Initial estimation of R_0 is fairly stable and credible	Missing data provide problems (which may be nonrandom) Data quality (real-time modeling) is important
ML	Serial interval estimates by this formulation and then details of the disease dynamics can be characterized The MLE and posterior mode (with uninformative gamma prior distribution) are equal when the serial interval is known[25] The MLE approach is the least biased The approach used for missing data in the ML method is similar to McBryde in Bayesian[26]	Some of the assumptions of the models are: no imported cases, no missing data and uniformly-mixed population. Violation of any of these assumptions changes the results[27] In the long period for the aggregated data, the estimation of the reproduction number tends to be increasingly underestimated
EG	Aggregated data and dispersion are least impressed on the estimation of reproduction	For the initial phase of the epidemic, this simple method may not be always powerful The assumptions should be checked and the method should be used with caution[28]
TD	It is the least biased Importation of the cases can be accounted within the epidemic	In the long period for the aggregated data, the estimation of the reproduction number tends to be increasingly underestimated In the TD approach, the R_0 depends on time and changes with it and no solution exists for correcting this method
AR	The least information is needed for this approach[28] The AR method, unlike the other models, does not require the GT distribution (there may be no prior knowledge about the GT distribution)	It is useful when the epidemic ends No intervention is required to set up during outbreak This method is applied in particular limited settings such as army and schools[29] It does not require the GT distribution
The gamma-distributed generation time	Only the number of cases on each day and generation time distribution are needed for modeling	The growth in case number over time should be specified; the violation of this condition can be problematic
R_0 using the final size of the epidemic	For modeling, the total population at risk and total number of infections for a fully susceptible population are only required	It is useful when the epidemic ends It does not require the generation time distribution

GT=Generation time; R_0=Reproduction number; TD=Time-dependent reproduction numbers; ML=Maximum likelihood; MLE=ML estimation; EG=Exponential growth rate; AR=Attack rate

One advantage of the TD method in compared to the other methods was that it was useful for computing the R_0 regarding the real cumulative case count data. Another advantage of the mentioned modeling was that it did not require extensive, detailed data as well as more parameters to calculate the basic reproduction number. Therefore, we recommend using this method in order to estimate the basic reproduction number.

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Conflicts of interest

There are no conflicts of interest.

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APPENDIX

SEARCH STRATEGY

In order to review the literature on basic reproduction number of influenza, we searched in the electronic databases such as the web of knowledge, PubMed, EMBASE, and Google Scholar to find published papers between 1954 and 2017. The medical subject heading was applied to find a wide range of keywords that had a maximum sensitivity. The following keywords were searched: influenza, human, and reproduction number. In detail searched keywords were ("influenza, human"[MeSH Terms] OR ("influenza"[All Fields] AND "human"[All Fields]) OR "human influenza"[All Fields] OR "influenza"[All Fields]) AND (("reproduction"[MeSH Terms] OR "reproduction"[All Fields]) AND number [All Fields]).

STUDY SELECTION

Two reviewers independently extracted relevant studies from the keywords search. All types of original articles were investigated. The studies which included "influenza reproduction number" in their titles or abstracts were included. The irrelevant articles, based on the title and abstract evaluation, were excluded. Moreover, we eliminated the duplicated articles to determine unique studies. Animal studies and human studies that included special populations such as pregnant women and schizophrenia were excluded. We then extracted data and formulas from the full text of the included studies.

Figure 1 shows the search strategy, through which 1213 papers were obtained in the initial round. The number of the retained papers was 910, which estimated R_0 for epidemic or pandemic influenza with A/H1N1, A/H1N5, H1N2, H1N3, H5N1, pH 1N1, A/H3N2, influenza B, A (H7N9), Spanish flu, H2N2, H3N2, AH1, AH3, A (H5N1), and Asian flu. The number of papers identified through other sources was 5. Overall, 89 papers presented the basic reproduction number estimation and its formula, as summarized in Table 1.

In addition, detailed information of the study characteristics provided in the systematic review is given in Table 2, of which 10 studies were taken into consideration. In some of the studies, p-H1N1, A (H1N1), A (H3N2), type B, and A (H7N9) were reported as types of influenza. The models used for estimating R_0 in these 8 studies were the multi-control measure, growth rate of exponential, and multi-phase Richards. In several of the studies, laboratory-confirmed cases were investigated for determining the reproduction number of influenza. Maximum, minimum and median of the reproduction number were 10.03 (in Mainland China), 0.08 (in China) and 1.39, respectively. The reproduction number of the influenza type A (H1N1) in Taiwan (2013) and Mexico was reported 1.54 (95% confidence interval [CI]: 0.22–8.88) and 1.69 (95% CI: 1.65–1.73), respectively. For A (H7N9), the reproduction number and its 95% CI in China for the first wave was estimated 0.27 (0.14, 0.44).

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Appendix Table 1: The formula which applied for calculating reproduction number in different studies

Id	Formula	Reference	Id	Formula	Reference
1	$R_0 = \frac{1}{\int_{t=0}^{\infty} e^{-\pi} w(\tau) d\tau}$	Ajelli and Merler, 2012	2	$R = \left(1+\frac{r}{b_1}\right)\left(1+\frac{r}{b_2}\right)$	Ajelli and Merler, 2012, Chowell *et al.*, 2008, Chowell *et al.*, 2012, Chowell *et al.*, 2011, Pamaran *et al.*, 2013
3	$\lambda_i(t) = \frac{\beta\rho(a_i) I_{hi}(t)}{N_{hi}(t)}$	Ajelli *et al.*, 2014	4	$R_0 = \frac{mc^2 \beta_{\vartheta h} \beta_{h\vartheta}}{\mu_\vartheta \gamma_\vartheta} \left(\frac{e_\vartheta k_\vartheta}{e_\vartheta k_\vartheta + \mu_\vartheta}\right)^{e_\vartheta}$	Chowell *et al.*, 2007b
5	$R_0 = (n-1)\left\{1-\exp\left\{\left[1-\frac{V}{Qt}\right]\left\{1-\exp\left[\left(-\frac{Qt}{V}\right)\right]\right\}\left(-\frac{q_{max}p_t}{Q}\right)\right\}\right\}$ $R_0 = [(1 - \varepsilon_1) + \varepsilon_1\theta)^{-1}$	Chen and Liao, 2010, Chen and Liao, 2013, Chong *et al.*, 2016	6	$R = \frac{\beta k}{k+\mu}\left\{\rho\left(\frac{1}{\gamma_1+\alpha+\mu} + \frac{\alpha}{(\gamma_1+\alpha+\mu)(\gamma_2+\delta+\mu)}\right) + (1-\rho)\left(\frac{q}{\gamma_1+\mu}\right)\right\}$ $R = 1 + V_r + f(1 - f)(Vr)^2 + O[(Vr)^3]$	Chowell *et al.*, 2007c
7	$R_0 = \frac{N-1}{C}\sum_{i=S_T+1}^{S_0}\frac{1}{i}$	Andreasen *et al.*, 2008, Haghdoost *et al.*, 2012, Jackson *et al.*, 2009	8	$P[R\|C(t+\tau) \leftarrow C(t)] = \frac{P[C(t+\tau) \leftarrow C(t)\|R]P[R]}{P[C(t+\tau) \leftarrow C(t)]}$	Chowell *et al.*, 2013
9	$R_0 = (1+\hat{r}\mu k^2)^{1/k^2}$	Andreasen *et al.*, 2008, Barakat *et al.*, 2012, Buckley and Bulger, 2011, Jackson *et al.*, 2009	10	$R = \frac{\beta}{\gamma+\delta}$	Chowell *et al.*, 2010
11	$R_A(t) = R_0\sigma(t) = \frac{R(t)}{s(t)}$	Caley *et al.*, 2008	12	$R_\Delta = \frac{\sum_{t\in\Delta} X_t}{\sum_{t\in\Delta} n_t}$	Cowling *et al.*, 2010
13	$R_0 = \frac{\beta_i \times N}{\mu+\vartheta}$	Chen *et al.*, 2009	14	$R_0 = \frac{ps(h_1+h_2)}{\gamma}$	Dorigatti *et al.*, 2012
15	$R_0 = \frac{\beta_M}{\vartheta}$	Chen *et al.*, 2015	16	$f_p = (1-p).1 + p.f_i = 1 + p(f_i - 1)$ $R = S_{init} \times R_0$	Earn *et al.*, 2014
17	$R_t = \frac{I_t}{\sum_{k=0}^{n} w_k I_{t-k}}$	Sheikh Taslim *et al.*, 2013	18	$R_0 = kR_3 + (1-k)R_4$ $R_0 = R_1 + \alpha R_2$	Ejima *et al.*, 2013
19	$R_t = \beta S_0\left(\frac{1-p}{\gamma} + \frac{kp}{\gamma}\right)$	Chen *et al.*, 2016	20	$R_e = \sum p_i \frac{\beta_i}{\gamma_i} = \sum p_i \frac{\theta\mu_i}{\gamma_i}$	Fielding *et al.*, 2015
21	$R = 1 + rT_c$	Chen *et al.*, 2017	22	$R = \frac{r}{\sum_{i=1}^{n} g_i\left(e^{-r\theta_{i-1}} - e^{-r\theta_i}\right)}$	Fierro and Liccardo, 2011
23	$R_0 = \frac{\alpha\rho N\pi}{\gamma(\rho N+\mu)}$	Cheng *et al.*, 2016	24	$R_A = (n-1)P$	Furuya, 2007
25	$I(R_t) = constant + \sum^{t}[I_t \ln \left(R_t\sum_{s=1}^{t} I_{t-s}\omega_s\right) - R_t\sum_{s=1}^{t} I_{t-s}\omega_s$	Fraser *et al.*, 2011	26	$R_0 = -det\begin{pmatrix} R_{11}-1 & R_{12} \\ R_{21} & R_{22}-1 \end{pmatrix} + 1 = R_{11} + R_{22\_}R_{11}R_{22} + R_{12}R_{21}$	Hsieh, 2010a
27	$\lambda_H(t) = \frac{\beta S(t) I(t)}{N} \approx \gamma R I(t)$	Chong *et al.*, 2016	28	$L = constant \times \prod_{j=0}^{N-1}\left(C_j R_j\right)^{C_{j+1}} \exp\left(-C_j R_j\right)$	Nishiura, 2007

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Appendix Table 1: Contd...

Id	Formula	Reference	Id	Formula	Reference
29	$I(t)=I(0)\exp\left[(\beta-\gamma)t\right]$ $=\exp\left[(R_0-1)\gamma t\right]$	Chong *et al*., 2017	30	$M=\begin{bmatrix} m_{CC} & m_{CA} \\ m_{AC} & m_{AA} \end{bmatrix}$	Glass *et al*., 2011
31	$R_i=R_i^{infectious}$ $+R_i^{hospitalized}+R_i^{asymptom}$	Chowell *et al*., 2007a	32	$R=1+\frac{r^2+(k+\gamma)r}{k\gamma}$ $R=(1-p)R_0$	Gran *et al*., 2010
33	$R=n\left(1+\frac{r}{a}\right)\left(1+\frac{r}{k}\right)$	Gurav *et al*., 2017	34	$zR_0=\ln\left(\frac{1}{1-z}\right)$	Meeyai *et al*., 2012
35	$R_t=\sum_j\sum_{i=2}p_{ij}(\vartheta,w,\theta)$ $p_{ij}\left(\vartheta,w,\theta\right)=$ $\frac{g\left(t_i-t_j\vert\theta\right)\times\pi_{ij}(\vartheta,w)}{\sum_{k\neq i}g\left(t_i-t_j\vert\theta\right)\times\pi_{ij}(\vartheta,w)}$	Hens *et al*., 2012	36	$R_0=\frac{R(t\approx0)}{S(t\approx0)}=\frac{1+Vr+f(1-f)(Vr)^2}{S(t\approx0)}$ $\approx1+Vr+f(1-f)(Vr)^2$	Modchang *et al*., 2012
37	$_t\quad R_t\left(\sum p_sM_{t\ s}\right)$	Hens *et al*., 2011	38	$I(t)\approx I_0e^{\frac{1}{2}\left[\sqrt{4(R_0-1)\sigma\gamma+(\sigma+\gamma)^2}-(\sigma+\gamma)\right]t}$	Mostaco-Guidolin *et al*., 2012
39	$R_0=\exp(rT)$	Hsieh, 2010b, Hsieh *et al*., 2011a, Hsieh *et al*., 2010, Hsieh *et al*., 2016, Hsieh *et al*., 2011b, Liu *et al*., 2015b, Mostaco-Guidolin *et al*., 2012	40	$R_{ij}=Rs_im_{ij}$ R is defined as the dominant eigenvalue of the next-generation matrix	Nishiura *et al*., 2010
41	$\frac{1}{R_0}=\int_0^\infty e^{-\lambda t}y(\tau)d\tau$	Inaba and Nishiura, 2008	42	$C_{hh}=k\left(\sum_{n=0}^{\infty}f_n\frac{1-R^n}{1-R}-1\right)$	Nishiura *et al*., 2013
43	$\propto_t=R\left(\sum_{i=1}^{t}N_{t-j}w_i\right)$ $R=\frac{1}{M(-r)}$ $P(R\vert N_0,\ldots,N_{t+1})=$ $P(N_{t+1}\vert R,N_0,\ldots,N_t)$ $\frac{P(R\vert N_0,\ldots,N_t)}{P(N_0,\ldots,N_{t+1})}$ $R_t=\frac{1}{N_t}\sum_{\{t_j=t\}}R_j$	Obadia *et al*., 2012	44	$R_{0Yamagata}(t)=\frac{SS+\alpha_{Victoria\rightarrow Yamagata}RS}{N}$ $\times\int_{\tau=t}^{\infty}\gamma\left[1+\exp\left(a_{Yamagata}-b_{Yamagata}h(\tau)\right)\right]$ $exp(-\gamma\tau)d\tau$	Nyirenda *et al*., 2016
45	$\pi\left(\frac{1}{R_0}\right)=\frac{1}{\beta(a,b)}$ $(\frac{1}{R_0})^{a-1}(1-\frac{1}{R_0})^{b-1}$	Kadi and Avaradi, 2015	46	$P_{trans}=\beta\times Inf\left(I_i\right)\times Susc\left(I_s\right)$ $\times AVF\left(I_i,I_s\right)$	Kelso *et al*., 2013
47	$R_0=\left[\frac{\lambda_1\gamma}{\alpha_1}+\frac{\lambda_2(1-\gamma)}{\alpha_2}\right]\frac{k^2}{k}$	Lin *et al*., 2016	48	$R_0=\left(1+rT_I\right)\left(1+rT_L\right)$	Rizzo *et al*., 2011
49	$R_0=\frac{\beta N}{\gamma}$	Kim *et al*., 2017	50	$\hat{R}=\frac{1}{M(-r)+\mathrm{n}_0^{-1}e^{-rt}\int_0^\infty c(t-\tau)g(t)d\tau}$	Roberts and Nishiura, 2011

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Appendix Table 1: Contd...

Id	Formula	Reference	Id	Formula	Reference
51	$R=\begin{pmatrix} R_{11} & R_{12} \\ R_{21} & R_{22} \end{pmatrix}$ $R_{ij}=\begin{cases} \frac{qm_{ij}}{\lambda} & if\ i=1 \\ \frac{qSm_{ij}}{\lambda} & if\ i=2 \end{cases}$	Kucharski and Edmunds, 2015	52	$\hat{R}_e=\frac{\sum_{t=d+1}^{T} i(t)}{\sum_{\tau=d+1}^{T}\sum_{\tau=1}^{d} P_\tau\left[i(t-\tau)+i^o(t-\tau)\right]}$	Roll *et al*., 2011
53	$R_0=\frac{h}{I\times\gamma}$	Liu *et al*., 2015a	54	$R_0=\frac{\beta}{\gamma}$	Sattenspiel, 2011, Sertsou *et al*., 2006
55	$R_0=1+\frac{\lambda}{\gamma}=1+\lambda\times T$	Marquetoux *et al*., 2012	56	$R_0=\left(1+\frac{r}{a}\right)\left(1+\frac{r}{k}\right)$	Shil *et al*., 2011
57	$R_0=\frac{\beta(\mu+\alpha+\gamma+\sigma)}{\left[(\mu+\sigma+k)(\mu+\alpha+\gamma)\right]}$	Massad *et al*., 2007	58	$R_0=\beta(q/\delta+p/\gamma_1+\frac{1-p}{\gamma_2}$	Tan *et al*., 2013
59	$R=Z(t)R_0$	Mathews *et al*., 2010	60	$L(R_c,p\mid N)=\prod_{t=1}^{T}\frac{\exp(-\Phi_t)\Phi_t^{N_t}}{\Gamma(N_t+1)}$	Tang *et al*., 2012
61	$R_0=r\overline{R_0}$ and $S_0=\frac{\overline{S_0}}{r}$	Truscott *et al*., 2009	62	$C_i(t)=\sum_t R_{ij}\int_0^\infty C_i(t-s)g(s)ds$	Tsukui, 2012
63	$\eta=\frac{\sum G^A\vartheta^{mixed}}{\sum G^A\vartheta^{mixed}+\hat{\varphi}\sum G^S\vartheta^{mixed}}$	Van Kerckhove *et al*., 2013	64	$R_i=a+\frac{b}{1+\exp\{c(i-d)\}}$	Ward *et al*., 2009
65	$\varphi_t=R_0\sum_{j=1}^{k}p_jN_{t-j}$	White *et al*., 2009	66	$R_0=\frac{\beta_h}{\gamma+\alpha}$	Xiao *et al*., 2014
67	$\hat{\pi}_j=\frac{N_je^{\hat{\beta}_j}}{\sum_i N_ie^{\hat{\beta}_i}}$	Yang *et al*., 2015	68	$R=(1+\frac{r}{b})^a$	Yu *et al*., 2012
69	$R_0=1+\frac{\hat{\beta}}{\gamma}$	Zhang *et al*., 2010	70	$P(z,\theta\mid y)\propto P(y\mid z)P(z\mid\theta)P(\theta)$	Cauchemez *et al*., 2011
71	$b(R)=\exp(\tau\gamma(R-1))$	Kelly *et al*., 2010	72	$R_c=\frac{\delta_1(1-\varphi)}{(\delta_1+q_c)(\delta_2+q_p)}\left(\frac{\beta\delta_2}{\delta_3+\gamma_1}+\varepsilon\beta\right)$	Tang *et al*., 2010

Appendix Table 2: Characteristics of several included studies

Id	Author (published date)	Place of study	Subject	Type of influenza	R0 (95% CI)	Formula	Method	Model	Refrence
1	Y. H. Cheng (2013)	Taiwan	Elementary school	p-H1N1 A (H1N1) A (H3N2) Type B	3.30 (0.75, 11.47) 1.54 (0.22, 8.88) 1.11 (0.18, 6.20) 1.11 (0.12, 8.52)	$R_0=(n-1)\left\{1-\exp\left\{\frac{-qpt}{Q}\left[1-\frac{V}{Qt}\left(1-\exp\left(\frac{-Qt}{V}\right)\right)\right]\right\}\right\}$	Branching process	Multi-control measure model	Cheng and Liao, 2013
2	K. C. Chong (2016)	Zhejiang Province, China	Laboratory-confirmed patients	A (H7N9) first wave A (H7N9) second wave A (H7N9) third wave	0.27 (0.14, 0.44) 0.15 (0.09, 0.24) 0.15 (0.06, 0.26)	$\lambda_H(t)=\frac{\beta S(t)I(t)}{N}\approx\gamma RI(t)$	MCMC	Susceptible (S [t]), infectious (I [t]), or recovered	Chong *et al.*, 2016
3	K. C. Chong (2017)	Mexico	New influenza pandemic	A/H1N1	1.69 (1.65, 1.73)	$I(t)=I(0)\exp\left[(\beta-\gamma)t\right]=\exp\left[(R_0-1)\gamma t\right]$	A likelihood-based method	SIR	Chong *et al.*, 2017
5	G. Chowell (2012)	Chile-Northern area	All hospitalizations	A/H1N1	1.19 (1.13, 1.24) 1.25 (1.18, 1.32) 1.32 (1.27, 1.37) 1.43 (1.36, 1.50) 1.58 (1.45, 1.72) 1.81 (1.62, 2.0)	$R=\left(1+\frac{r}{b_1}\right)\left(1+\frac{r}{b_2}\right)$	Maximum likelihood	Growth rate of the exponential pandemic	Chowell *et al.*, 2012
6	I. Dorigatti (2012)	Italy	Surveillance data	A/H1N1	1.42 (1.41, 1.424) 1.38 (1.37, 1.39) 1.32 (1.30, 1.34) 1.31 (1.282, 1.35)	$R_0=\frac{ps(C)(h_1+h_2)}{\gamma}$	MCMC, Bayesian	SEIR	Dorigatti *et al.*, 2012
7	Y. H. Hsieh (2011)	Taiwan	Confirmed cases and hospitalizations	pH1N1	1.14 (1.04, 1.25) 1.02 (1.01, 1.02)	$R_0=\exp(rT)$	-	The multi-phase Richards model	Hsieh *et al.*, 2011a

CI=Confidence interval; MCMC=Monte carlo markov chain; SEIR=Susceptible-exposed-infectious-recovered; SIR=Susceptible-infectious-recovered

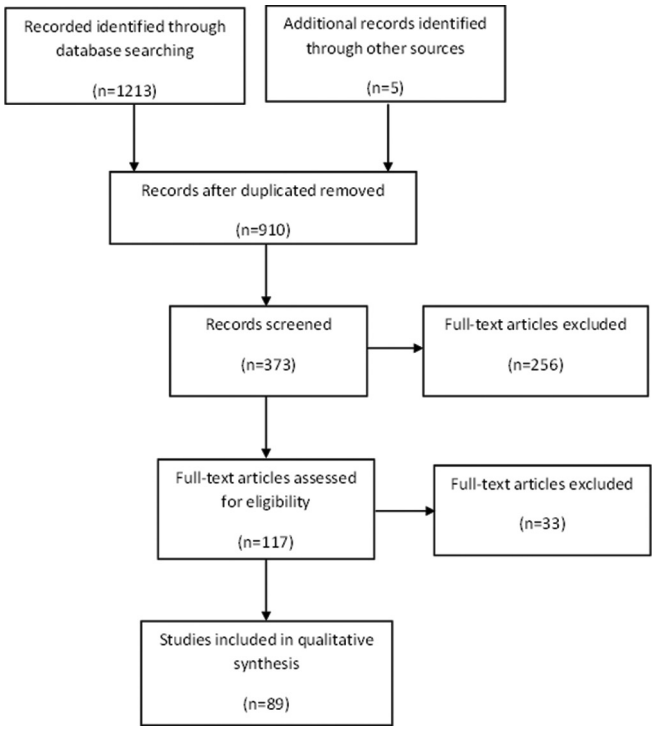

Figure 1: The PRISMA flowchart of the article selection for the reproduction number and influenza literature review