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A SEASONAL INFLUENZA THEORY AND MATHEMATICAL MODEL INCORPORATING METEOROLOGICAL AND SOCIO- BEHAVIORAL FACTORS

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Abstract: On the basis of a comprehensive literature review and data analysis of global influenza surveillance, a transmission theory based numerical model is developed to understand the causative factors of influenza seasonality and the biodynamical mechanisms of seasonal flu. The model is applied to simulate the seasonality and weekly activity of influenza in different areas across all continents and climate zones around the world. Model solution and the good matches between model output and actual influenza indexes affirm that influenza activity is highly auto-correlative and relies on determinants of a broad spectrum. Internal dynamic resonance; variations of meteorological elements (solar radiation, precipitation and dewpoint); socio-behavioral influences and herd immunity to circulating strains prove to be the critical explanatory factors of the seasonality and weekly activity of influenza. In all climate regions, influenza activity is proportional to the exponential of the number of days with precipitation and to the negative exponential of quarter power of sunny hours. Influenza activity is a negative exponential function of dewpoint in temperate and arctic regions and an exponential function of the absolute deviation of dewpoint from its annual mean in the tropics. Epidemics of seasonal influenza could be deemed as the consequence of the dynamic resonance and interactions of determinants. Early interventions (such as opportune vaccination, prompt social distancing, and maintaining incidence well below a baseline) are key to the control and prevention of seasonal influenza. Moderate amount of sunlight exposure or Vitamin D supplementation during rainy and short-day photoperiod seasons, more outdoor activities, and appropriate indoor dewpoint deserve great attention in influenza prevention. To a considerable degree, the study reveals the mechanism of influenza seasonality, demonstrating a potential for influenza activity projection. The concept and algorithm can be explored for further applications.

Key words: influenza; influenza seasonality; influenza modeling; solar radiation; temperature; precipitation; weather; vitamin D

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1 INTRODUCTION

Epidemic influenza kills approximately 250,000 – 500,000 people around the world each year [1] with millions during pandemic years when a genetic reassortment of influenza viruses results in novel strains, disrupting global economic, social and public health systems.

In recent years, huge amount of budget has been put aside for influenza research, partially due to the scare of a worldwide pandemic and partially due to the cost of experiments and vaccination development. Substantial advances have been made, but the majority of studies merely focus on various DNA and RNA virus species leaving many unknowns about the roles of meteorological, environmental and behavioral elements. To a considerable extent, the mechanism, determinants and dynamics of the seasonality and weekly variations of influenza remain a mystery. This has greatly affected the effectiveness of interventions against the

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disease. On the other hand, influenza modeling, as a relatively thrift means of study, is playing an important role in the quantification and projection of influenza activity and the understanding of these unknowns (e.g. the associations between seasonal influenza and temperature, humidity, and precipitation; the roles of vaccination and social distancing). Because of this, some numerical models of influenza transmission have been developed in recent years. For example, E. Cahill et al.[2] presented a space-time influenza model with demographic, mobility and vaccine parameters, which describes the annual scenarios for the United States quite well. Some models were improved after exploring the importance of social network structure [3-9]. However, blanks still remain: some models are pandemic focused and therefore may not be fully applicable to seasonal and weekly activity of influenza; others are location specific or have tried to induce seasonality as an endogenous property of within-system dynamics, without altering either external seasonal forces or internal strain mutations or multi-strain cross protection, based solely on theories of stochastic processes, the influence of random noise in the system, and cascading local effects [9]. Some models that take account of only one or two variables prove limited. Obviously, models stemming from a more generalized algorithm and transmission pattern are necessary. Such models should be able to incorporate a variety of biological, meteorological, environmental, social and behavioral factors, have clear dynamic properties and clinical significance to explain the seasonality and weekly variations of influenza across different climatic zones, and demonstrate potentials for epidemic projection and other applications of medical and social values. This study is an exploration towards that direction.

2 THE THEORY AND MODEL SCHEME

Traditionally, influenza epidemiology uses a basic reproduction or transmissibility rate R_0 to estimate the average number of secondary cases infected by each primary case. However, such a rate has been found highly variable. For example, the R_0 for the 1918 Pandemic was estimated to be around 1.8 only; whereas a maximum bound for R_0 was obtained by analyzing the case data from an outbreak of the 1978 H1N1 flu in a boys boarding school in England, yielding an upper bound of $R_0 < 21$ [10]. The R_0 may be adjusted to an "actual reproduction rate" for a community based on experience and experiments, but even so the transmissibility is still highly situation specific and greatly affected by a number of factors such as the duration of transmission of infected patients, the infectivity of the virus, and the number of susceptible people in the population that the infected hosts contact, as well as many other environmental and socio-behavioral parameters. Since factors are variable, it would be problematic to use a fixed reproduction rate for incidence projection. Besides secondary cases, the total number of influenza patients in a community is also affected by other elements such as patients' mobility, transmission via those people who carry virus without symptoms, and the number of individuals infected via "non person-to-person contact".

Such being the case, this study does not repeat routine methods, instead, the reproduction rate is set to be a function of determinants that vary with time. The quantitative relationship below lays a foundation for the modeling in this study:

For a given period of time (*Dt*), change in the total number of influenza patients in a community (*DP*) = number of new cases due to "person-to-person" transmission + number of new cases due to "non person-to-person" infection + number of patients entered the community – number of patients recovered – number of patients died – number of patients left the community. Mathematically, this relationship can be expressed as:

$$\Delta P = [\,l\,(t)\cdot R(t) - C(t) - D(t)]\cdot P(t)\cdot \Delta t + [I(t) - O(t) + N(t)]\cdot \Delta t \quad (1)$$

where, *P(t)* denotes the total number of existing patients at time *t*; *R(t)* - the ratio of the number of new cases infected by existing patients to the number of existing patients per unit of time at time *t*; *C(t)* – the ratio of the number of recovered cases from existing patients to the number of existing patients per unit time at time *t*; *D(t)* - the ratio of the number of fatal cases among existing patients to the number of existing patients per unit time at time *t*; *I(t)* – the number of patients entering the community per unit time at time *t*; *O(t)* - the number of patients leaving the community per unit time at time *t*; *N(t)* – the number of new cases from "non person-to-person" infection per unit time at time *t*; and *l(t)* – a revision coefficient for the transmission via those people who carry virus without symptoms. When the increment of *t (Dt)* is small, the above equation becomes a differential equation:

$$\frac{dP}{dt} = a(t)\cdot P(t) + b(t) \quad (2)$$

where,

$$a(t) = l(t)\cdot R(t) - C(t) - D(t) \quad (3)$$

$$b(t) = I(t) - O(t) + N(t) \quad (4)$$

The universal solution to Eq.(2) is:

$$P = e^{\int a(t)dt}\left[\int e^{-\int a(t)dt}\cdot b(t)\cdot dt + C\right] \quad (5)$$

Note that both *a(t)* and *b(t)* are function of time and determinants, which can span from virulence of strains,

herd immunity, temperature, ventilation, interpersonal contacts, social distancing, recovery time to hygiene practice. Because of this, Eq.(5) cannot be integrated unless we know the specific expressions of $a(t)$ and $b(t)$, which is unattainable under most circumstances. Nevertheless, an alternative strategy to overcome this obstacle is to assume $a(t)$ and $b(t)$ take their integration averages (constants) within a short period of time. The errors resulting from such an assumption is expressed as e'. Therefore, an approximate solution of Eq.(5) would be:

$$P(t) = \left(P_0 + \frac{b_0}{a_0} \right) e^{\overline{a(t)} \cdot t} - \frac{\overline{b(t)}}{\overline{a(t)}} + e' \qquad (6)$$

or, in a Taylor expansion form:

$$P(t) = P_0 e^{\overline{a(t)} \cdot t} + \left(\frac{b_0}{a_0} \right) \left[\overline{a(t)} \cdot t + \frac{\left(\overline{a(t)} \cdot t\right)^2}{2!} + \frac{\left(\overline{a(t)} \cdot t\right)^n}{n!} + \ldots \right] \qquad (7)$$
$$+ \left[\frac{b_0}{a_0} - \frac{\overline{b(t)}}{\overline{a(t)}} \right] + e'$$

where P_0, a_0 and b_0 denote their initial values (at time 0) and the quantity under "—" represents integration average during the time period. Eqs.(6) and (7) give the total number of influenza patients in a community/area after a time period of t. They are applied in the modeling and projection of influenza in the study. Since all variables affecting transmission (and thus incidence) can be incorporated into the governing equation and its approximate solution, the hypothesized theory and model is called GR Theory and GR Model respectively, denoting generalized reproduction.

3 MODELING METHODS

Prior to being used for influenza simulation and projection, Eq.(6) needs to be parameterized. This is achieved through four steps:

Step 1. Assume that the net flux of patients is small during a unit time period in a community where public health services are affordably available and that the portion of new cases from "non person-to -person" infection is also small. This gave $\overline{b(t)} \approx 0$ and

$$Ln\left(\frac{P_1 - e^*}{P_0 + \frac{b_0}{a_0}} \right) = \overline{a(t)} \qquad (8)$$

where P_1 denotes the number of influenza patients in the community after a unit time period. e^* denotes total errors (positive or negative) resulting from the approximate solution and the above assumptions.

Step 2. Assume that $\overline{a(t)}$ is a linear combination of explanatory factors (determinants). That is,

$$\overline{a(t)} = a_0 + a_1 f_1 + a_2 f_2 + \ldots . a_n f_n \qquad (9)$$

where, a_0 is a constant. a_1, a_2 and a_n are coefficients. a_0, a_1, a_2 and a_n are all variables of geographic locations and populations. They could also vary over time but are statistically stable for a specific community and population. f_1, f_2 and f_n are the mean values of any explanatory factors for influenza activity in the community during the time period.

Step 3. Screen and choose the explanatory factors based on a comprehensive review of literature [11-25] and statistical correlation analyses. Each potential factor is checked for consistency in correlation with influenza indexes in the different countries/cities listed in Table 1. These countries/cities, as shown in Fig.1, are selected from America, Europe, Asia, Africa and Oceania and distributed across each climate region (arctic, temperate, and tropical) in both hemispheres. These factors are ensured to be etiologically plausible, statistically significant, logically and temporally reasonable; and in accordance with biomedical and social science knowledge.

Table 1 List of the countries/cities selected for the study.

Country	City	° N(S)	° E(W)
Finland	Oulu	64.9 °N	25.4 °E
Kazakhstan	Petropavlovsk	54.8 °N	69.1 °E
USA	Dutch Harbor	53.9 °N	166.5 °W
UK	Nottingham	53.0 °N	1.2 °W
Canada	Vancouver	49.2 °N	123.2 °W
China	Urumqi	43.8 °N	87.6 °W
Japan	Sapporo	43.1 °N	141.0 °W
USA	Boston	42.4 °N	71.0 °W
Italy	Rome	41.8 °N	12.6 °E
Morocco	Rabat	34.0 °N	6.8 °W
USA	Midland	32.0 °N	102.1 °E
Egypt	Cairo (South)	29.9 °N	31.4 °E
China	Hong Kong	22.2 °N	114.2 °E
India	Pune	18.5 °N	73.9 °E
Senegal	Dakar	14.7 °N	17.5 °W
Thailand	Krabi	8.0 °N	98.9 °E
Colombia	Bogota	4.7 °N	74.1 °W
Singapore	Singapore	1.4 °N	104.0 °E
Brazil	Belem	1.5 °S	48.5 °W
Congo	Kinshasa	4.4 °S	15.4 °E
Indonesia	Mataram	8.6 °S	116.1 °E
Brazil	Santa Maria	29.7 °S	53.7 °W
South Africa	Cape Town	34.0 °S	18.6 °E
Australia	Canberra	35.3 °S	149.2 °E
New Zealand	Christchurch	43.5 °S	172.6 °E
Argentina	El Calafate	50.3 °S	72.3 °E

Fig.1 Geographic distribution of the selected cities.

Step 4. Having determined the input explanatory factors, a_0 and coefficients a_1, a_2 and a_n for a specific community/area are obtained by nonlinear regression with historic influenza indexes (e.g. ILI, % of "+" isolates) in a community/area. Initial values for e^* and b_0/a_0 in Eq.(10) are assigned and refined iteratively to achieve least squares.

$$Ln\left(\frac{P_1+e^*}{P_0+\frac{b_0}{a_0}}\right)=a_0+a_1f_1+a_2f_2+....a_nf_n \qquad (10)$$

This gave a parameterized equation for influenza modeling and projection for the community/area:

$$P_1 \approx (P_0+s)\times e^{(a_0+a_1f_1+a_2f_2+...a_nf_n)}+e \qquad (11)$$

where, a_0, a_1, $a_2 \ldots a_n$, s and e are values determined by the nonlinear least squares.

When a coefficient of correlation (R^2) given by Eq.(11) is sufficiently small and the multiple regression is statistically significant at the 0.05 level or less, the influenza activity in the community/area is considered to have been simulated with the variables inputted and Eq.(11) could be applied to influenza projection for the community/area.

Data of influenza activity is obtained from:
1) World Health Organization (WHO) Flu Net
2) Weekly influenza surveillance reports
3) Data from published papers
4) Personal communication with scientists

Environmental data is acquired from:
1) Climate databases from World Meteorological Organization (WMO)
2) Regional Meteorology Organizations
3) Online weather websites
4) Regional Environmental Protection Agencies

4 RESULTS

4.1 *Explanatory factors*

Literature review and correlation analysis identify four significant explanatory factors for influenza seasonality in the countries/areas in Table 1.
1) Sunny hours - S_h
2) Number of rainy days - n_r
3) Dewpoint - T_d (°C) for arctic and temperate regions and the absolute deviation of dewpoint from annual means ($|T_d'|$) for tropical regions (23.5°N – 23.5°S)
4) Socio-behavioral factors - λ, which takes a value between 0.85 and 0.99 for major social events such as school breaks and long public holidays

Significant explanatory factors for weekly influenza activity are similar except that influenza may also relate to change in dewpoint (ΔT_d).

Table 2 summaries the original regression coefficients and correlation coefficients (r) between the explanatory factors and the seasonal influenza indexes in those countries/areas where over 5 years of historical data are available. Indexes of influenza used and the length of data are also listed.

Table 3 gives a perceptible example in the association between percentage of patient visits due to ILI and monthly averaged weather elements observed in a typical temperate area (British Columbia, Canada).

Table 2 Original regression coefficients and correlation coefficients (r) between the explanatory factors and influenza indexes in representative cities.

Country/City	Index	Sh	Nr	Td/|Td'|
Oulu, Finland (64.9 °N 25.4 °E)	No. of case (9 years)	-1.87 (P =0.06) r = -0.55	1.75 (P=0.18) r = 0.41	-1.30 (T_d) (P<0.001) r = -0.89
Nottingham, UK (53.0 °N 1.2 °W)	ILI (8 years)	-4.88 (P<0.001) r = -0.87	2.90 (P=0.002) r = 0.79	-2.03 (T_d) (P=0.002) r = -0.78
BC, Canada 49.2°N 123.2 °W	ILI (6 years)	-0.12 (P<0.001) r = -0.86	0.06 (P<0.001) r = 0.87	-0.07 (P<0.001) r = - 0.89
Rome, Italy (41.8 °N 12.6°E)	ILI (8 years)	-46.17 (P=0.02) r = -0.64	28.33 (P=0.11) r = 0.49	-23.6 (T_d) (P=0.005) r = -0.75
HK, China (22.2 °N 114.2°E)	ILI (12 years)	-0.38 (P=0.002) r = -0.79	0.03 (P=0.68) r = 0.13	0.08 $\|T_d'\|$ (P=0.38) r = 0.28
Bogota, Colombia (4.7 °N 74.1°W)	% of "+" isolates (years)	-3.55 (P<0.001) r = -0.89	1.09 (P<0.001) r = 0.93	2.57 $\|T_d'\|$ (P=0.47) r = 0.23
Singapore (1.4 °N 104.0 °W)	% of "+" isolates (8 years)	1.66 (P=0.199) r = 0.40	-0.27 (P=0.55) r = -0.19	7.39 $\|T_d\|$ (P=0.02) r = 0.63
Belem, Brazil (1.5 °S 48.5 °W)	Res. Dis. Rate (11 years)	-0.02 (P=0.51) r = -0.21	0.03 (P=0.09) r = 0.51	0.75 $\|T_d'\|$ (P=0.06) r = 0.55
Santa, Brazil (29.7 °S 53.7 °W)	Res. Dis. Rate (11 years)	-1.27 (P=0.01) r = -0.71	0.61 (P=0.16) r = 0.43	-0.67 (T_d) (P<0.001) r = -0.92
Canberra, AU (35.3 °S 149.2 °E)	No. of case (13 years)	-87.96 (P=0.22) r = -0.38	162.05 (P=0.006) r = 0.74	-57.3 (T_d) (P=0.02) r = -.067

Table 3 Association between % of patient visits due to ILI and monthly averaged weather elements (BC, Canada).

Month	ILI (%)	Sunny Hours/Day	Rainy Days	Dewpoint
Jan	1.01	2.0	20	2.3
Feb	0.95	3.4	17	2.4
Mar	0.59	4.2	17	3.6
Apr	0.27	6.5	14	5.0
May	0.16	7.5	12	8.5
Jun	0.13	7.7	11	11.4
July	0.08	8.6	7	13.8
Aug	0.04	8.4	8	14.0
Sep	0.11	6.2	9	11.4
Oct	0.27	3.6	16	7.9
Nov	0.52	2.1	19	4.5
Dec	0.88	1.4	22	2.4

Table 4 shows the regression coefficients and correlation coefficients (r) recalculated with the GR Model.

Table 4 Regression coefficients and correlation coefficients (r) recalculated with the GR Model.

Country/City	Index	$S_h^{1/4}$	N_r	$T_d/\lvert T_d'\rvert$
Oulu, Finland 64.9 °N 25.4 °E	log ratio of No. of case	-1.07 (P<0.001) r = -0.74	0.17 (P=0.001) r = 0.81	-0.02 (T_d) (P=0.27) r = -0.35
Nottingham, UK 53.0 °N 1.2 °W	log ratio of ILI	-3.99 (P<0.001) r = -0.86	0.29 (P<0.001) r = 0.89	-0.15 (T_d) (P=0.02) r = -0.64
BC, Canada 49.2°N 123.2 °W	log ratio of ILI	-2.1, r= -.98 (P<0.001) R^2 = 0.96	0.09 (P<0.001) r = 0.93	-0.08 (T_d) (P<0.001) r = -0.83
Rome, Italy 41.8 °N 12.6°E	log ratio of ILI	-6.23 (P<0.001) r = -0.92	0.29 (P<0.001) r = 0.83	-0.14 (T_d) (P=0.005) r = -0.75
HK, China 22.2°N 114.2°E	log ratio of ILI	-1.47 (P=0.02) r = -0.64	0.00 (P=0.89) r = -0.04	0.05 $\lvert T_d'\rvert$ (P=0.12) r = 0.47
Bogota, Colombia 4.7 °N 74.1°W	log ratio of No. of isolates	-10.11 (P<0.001) r = -0.95	0.20 (P=0.001) r = 0.81	0.28 $\lvert T_d'\rvert$ (P=0.71) r = 0.12
Singapore 1.4°N 104.0 °W	log ratio of No. of isolates	-2.50 (P=0.36) r = -0.29	0.14 (P=0.02) r = 0.66	0.12 $\lvert T_d'\rvert$ (P=0.83) r = 0.07
Belem, Brazil 1.5 °S 48.5 °W	log ratio of Res. Dis. Rate	-0.44 (P=0.33) r = -0.31	0.05 (P=0.07) r = 0.54	0.93 $\lvert T_d'\rvert$ (P=0.10) r = 0.50
Santa, Brazil 29.7 °S 53.7 °W	log ratio of Res. Dis. Rate	-1.38 (P<0.001) r = -0.87	0.05 (P=0.02) r = 0.66	-0.04 (T_d) (P<0.001) r = -0.89
Canberra, AU 35.3°S 149.2 °E	log ratio of No. of case	-10.32 (P=0.003) r = -0.78	0.55 (P=0.007) r = 0.73	-0.26 (T_d) (P<0.001) r = -0.88

It can be seen that:

1) In general, seasonal influenza activity is positively correlated to monthly days with precipitation and negatively correlated to monthly sunny hours/day.
2) In temperate and arctic regions, seasonal influenza activity is negatively correlated to dewpoint; while in tropical regions it is positively correlated to the absolute deviation of dewpoint from its annual mean.
3) After applying the GR Model, these correlations remain and become more significant (smaller P values) and consistent.
4) In GR Model, seasonal influenza activity is correlated to negative exponential of quarter (1/4) power of monthly sunny hours/day in all climate zones.
5) Statistical significance of the associations between seasonal influenza activity and the explanatory factors increases in temperate and arctic regions.

4.2 *Modeling of influenza seasonality*

Simulations of influenza seasonality were performed for all countries/cities listed in Table 2.

Table 5 lists the simulation results in terms of value of F, P value, and R^2 obtained from variance analysis and the Pearson correlation coefficient (r) between the actual values of the indexes and model outputs.

Table 5 Simulation results of the seasonality of influenza in different cities.

Country/City	F	P Value	R^2	r
Oulu, Finland	20.98	0.00054	94.0%	0.97
Nottingham, UK	102.75	2.7×10^{-6}	97.1%	0.99
Rome, Italy	25.63	0.00028	94.6%	0.98
HK, China	23.38	0.00038	95.5%	0.97
Bogota, Colombia	21.92	0.00047	92.5%	0.97
Singapore	15.73	0.00130	86.1%	0.93
Belem, Brazil	12.59	0.00260	89.6%	0.97
Santa Maria, Brazil	31.12	0.00015	98.1%	0.99
Canberra, AU	10.03	0.00500	84.1%	0.92

Two typical examples (Finland and Colombia) are given in Fig.2 and Fig.3, representing the situation in an arctic area and a tropical area respectively. Here seasonality is defined as the monthly mean of an influenza activity index (e.g. ILI or total number of flu patients) over years.

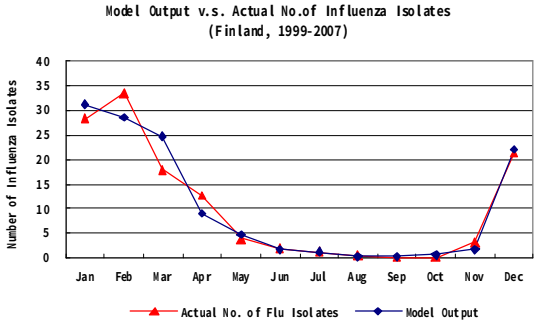

Fig.2 Simulation results of influenza seasonality for Finland.

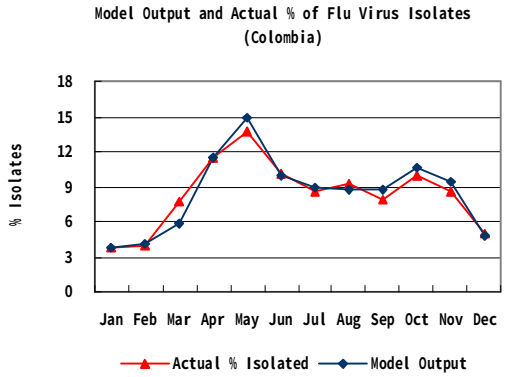

Fig.3 Simulation results of influenza seasonality for Colombia.

The corresponding modeling equations are:

$$P_1 = (P_0 + 3) \cdot e^{(2.22 + 0.07N_r - 0.82S_h^{1/4} + 0.01T_d - 2.31l)} - 3 \quad (12)$$

$$P_1 = (P_0 + 1) \cdot e^{(1.274 - 0.01N_r - 1.031S_h^{1/4} + 0.21|T_d'| - 1.32l)} - 2.9 \quad (13)$$

It can be seen that when the four key explanatory factors are put into the GR model for seasonality modeling,

1) All simulation results have a P value < 0.01 with smaller P values in temperate and arctic regions
2) All simulation results have a coefficient of correlation (R^2) > 0.84
3) All simulation results have a correlation coefficient (r) > 0.92

4.3 *Modeling of weekly influenza activity*

Retrospective simulation and projection of weekly influenza activity were performed for Hong Kong, China and New England Region, USA with the Model and parameter $S_h^{1/4}$, N_r, T_d ($|T_d'|$), and λ.

Fig.4 shows the actual weekly consultation rates of ILI reported by sentinel General Practitioner clinics in Hong Kong in 2006 and the simulation from the GR Model. Fig.5 shows the actual influenza isolates (% Positive) in New England Region of the United States in the 2008-2009 season and the projection from the Model. They represent the weekly projection results in temperate and tropical regions individually.

For comparison, Fig.6 gives the projection result from a simple linear multiple-regression with the same variables. The corresponding equations for the two projection models (GR Model and common multiple regression model) are:

$$P_1 = (P_0 + 9) \cdot e^{(-4.40 + 0.55N_r - 0.05S_h^{1/4} - 0.03T_d + 3.77l)} - 5 \quad (14)$$

$$P = -131.3 - 1.1T_d + 1.1N_r + 11.9S_h^{1/4} + 116.0l \quad (15)$$

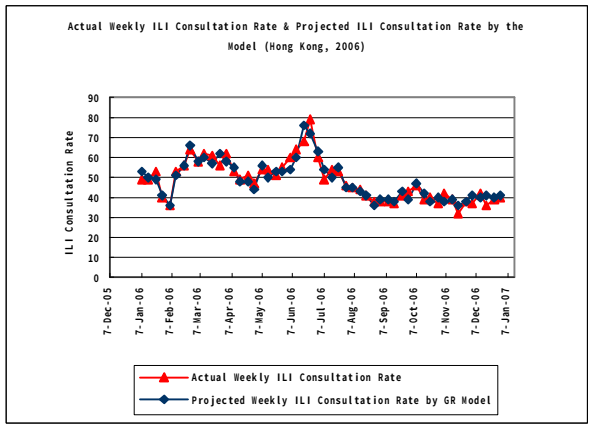

Fig.4 Simulation result of weekly consultation rate of ILI for Hong Kong.

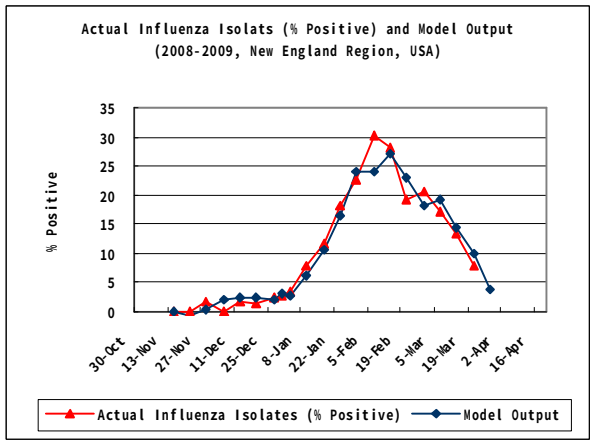

Fig.5 Simulation results of weekly consultation rate of ILI for New England Region, USA.

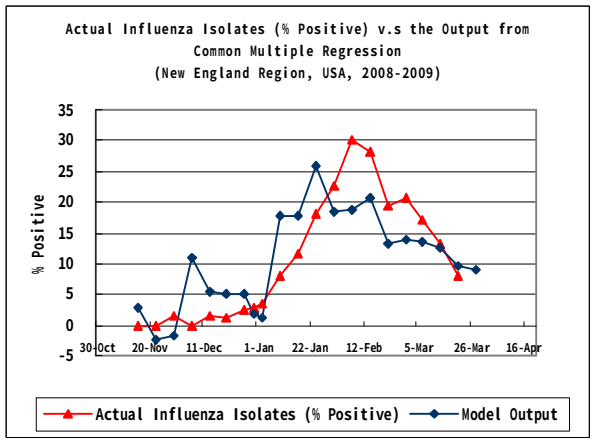

Fig.6 Projection results from the simple linear multiple-regression with the same variables as in Fig.5.

Table 6 summaries these projection results in terms of P value, R^2 and the correlation coefficient r.

Table 6 Projection results of weekly influenza activity.

Region	Model	P Value	R^2	r
Hong Kong	GR	<0.001	90%	0.95
New England	GR	0.001	95%	0.98
New England	Multi Regression	0.003	64%	0.80

Table 7 Weaker annual variations of weather elements lead to weaker seasonality of influenza activity.

Country	Annual Ratio			Annual
	Flu Index	Sunny Hour	Rainy Day	Variation (Td)
Finland	419.5	> 100	1.7	24.3
Italy	49	2.8	11.0	15.7
Australia	20.4	1.8	1.6	11.9
Colombia	3.7	1.7	2.3	1.5

5 DISCUSSIONS AND SUMMARY

For hundreds of years, physicians and scientists have owed people sound answers to such questions as why the flu has seasonality, what are the determinants for weekly variations of influenza activity in a community, and what causes the disease to spread so quickly during epidemics? With a new pandemic being imminent, it is high time we gain a deeper understanding of these in both virology and in epidemiology. To a certain extent, the theory and modeling above shed light on the mystery.

Science solves mysteries. An important mark of science is quantification. Without Newton's 2nd Law ($F=ma$) the specific amount of force required to send a rocket to the sky was unknown although we recognized that speeding up a heavier object needed more force. Similarly, we understand the clinical values of early prevention but planning and control may be blind without quantitative relationships. The approximate solutions in Section 2 quantitatively reveal the following transmission dynamics of influenza for interventions:

(1) The transmission of influenza follows the exponential law ($e^{\overline{a(t)}\cdot t}$ in solution 6). That is, incidence increases or decreases exponentially. This is why the number of ILI patients can dramatically grow in a week, leading to an epidemic. When a novel virus strain emerges, such an exponential growth effect can be easily exaggerated by modern aero vehicles between continents to cause a pandemic.

(2) Incidence of influenza is highly auto-correlative. Specifically, incidence at present (P_1) is proportional to the incidence at a previous moment (P_0). This intra-resonance property together with the exponential response to determinants [$P_1 \propto (P_0 + \frac{b_0}{a_0}) \cdot e^{\overline{a(t)}\cdot t}$] explains why even slight external stimulations can result in a rapid increase of incidence when prevalence is above a critical level. This proves that early interventions such as controlling initial incidence well below a baseline are crucial.

(3) When incidence is small enough its temporal variation is approximately linear, that is, solution (7) can be simplified as:

$$P(t) \approx \left(\frac{b_0}{a_0}\right) \cdot \left[\overline{a(t)} \cdot t.\right] + \left[\frac{b_0}{a_0} - \frac{\overline{b(t)}}{\overline{a(t)}}\right] + e' \qquad (16)$$

This is why small and quasi-linear fluctuations are often observed in weekly ILI graphs during the summer when incidence is very low.

(4) To minimize incidence, solution (6) requires $b_0/a_0 < 0$ and $\overline{b(t)} / \overline{a(t)} > 0$. This means that early quarantine of patients from the community ($b_0 < 0$), promotion of herd immunity with timely vaccination targeting circulating strains (smallest a_0), persistent social distancing [$\overline{b(t)} < 0$], and recovery faster than transmission [$\overline{a(t)} < 0$] are key to the control of flu epidemics.

(5) The exponential and power terms in solution (7) explain why weekly ILI often assumes bell-shaped and/or power law shaped curves.

(6) The simulation and projection based on the quantitative model verify the effects of the identified factors on the seasonality and weekly variations of influenza. The statistically significant P values affirm that the possibility of obtaining these modeling results by chance is extremely low (1/1,0000 ~ 5/1,000).

The identified explanatory variables meet the requirements for potential causative factors:

1) The associations between influenza activity (seasonality and weekly variation) and the explanatory factors are consistent in different climate zones, continents, hemispheres and populations. This is demonstrated by the correlation coefficients and corresponding P values in Tables 2, 4, and 5.
2) The associations are consistent for different indexes of influenza activity, which include the total number of influenza patients in a country/area (Finland, Australia), the ILI consultation rates (UK, Italy, Hong Kong), the percentage of positive influenza isolates (Colombia, Singapore and USA), and respiratory disease morbidity (Rio Grande, Brazil).
3) The associations are consistent for both annual and weekly variations of influenza activity, because the same variables were applied to the simulation of seasonality and the projection of weekly

influenza indexes.

4) The associations have strong (r = 0.5–0.8) to very strong (r = 0.8–0.9) strengths in terms of correlation coefficient (no relative risk or odds ratio was calculated). This is demonstrated in Table 4 and by the high correlation between model output and the actual indexes in Table 6.
5) The associations have reasonable temporal relationships, for variables in the same month were fed in the model during the seasonality simulation and variables in the previous week were the input of the model in the simulation/projection of weekly influenza activity.
6) The associations also show dose-response relationships. This is reflected by the high (0.84-0.98) coefficient of correlation (R^2) in Table 5 and Table 6. Note that these non-linear, good fit dose-response relationships are based on multiple variables. Nevertheless, as shown in Table 3 and further verified by R^2 in Table 4 (BC, Canada) significant dose-response relationship can also exist between influenza indexes and a single variable such as sunny hours per day.
7) Mitigation of annual variations of the variables renders weaker seasonality of the flu (as shown in Table 7), suggesting that removal of the explanatory factors might cause the phenomenon (seasonality of the flu) to disappear.

The identified explanatory factors are biologically plausible and consistent with present microbiology, pathology and epidemiology knowledge:

(1) Temperature and humidity have been reported to have important impacts on the shedding, survival and transport of influenza virus as well as host immunity. Early human experiment to investigate temperature influence on ILI in the Ming Dynasty of China indicated that prisoners who experienced abrupt temperature change were much more likely to develop flu-like symptoms [26]. Using guinea pigs as hosts, Lowen et al [14] found that animals shed more viruses when air temperature dropped to 5°C from 20°C. Studies by Eccles [27], Le Merre et al [28] and Johnson et al. [29] suggested that cold air inhaled can reduce the respiratory defenses such as mucociliary clearance and phagocytic activity of leukocytes and that cooling of the body surface can cause vasoconstriction in the nose, resulting in reduced blood flow and leukocyte supply and increased susceptibility to infection. Cold temperature also influences host behaviors by driving people to stay indoors, increasing the proximity between susceptible individuals and infected hosts. Similar to temperature, humidity has impacts on the airborne length and transport of influenza virus and host immunity. Buckland et al. [30] found that viruses on a glass surface remain viable longer when humidity was low. In a dry atmosphere, virus-carrying droplets expelled from infected hosts can remain suspended in the air for longer period of time due to evaporation, increasing the likelihood of transmission. Williams et al. [31]'s study indicated that inhalation of air with low humidity over hours could dry the mucus, impairing host defenses against infection. Earlier this year, Shaman and Kohn [32] reported a greater association between virus survival and low absolute humidity (AH). The strong correlation between influenza activity and low dewpoint temperature in temperate and arctic regions found in this study supports the above findings from other authors. Because dewpoint is a comprehensive indicator of temperature and humidity, its measurements reflect absolute humidity with less chance for misinterpretation than the effect of pure vapor amount in the air. It is noteworthy that in tropical areas, influenza activity is weakly associated with the absolute deviation of dewpoint from its annual mean. This phenomenon arises because on the one hand lower dewpoint (larger absolute deviation from the mean) still facilitates influenza spread, but on the other hand, high dewpoint (also larger deviation from the mean) is related to hot temperature and rainfall in the tropics, which may encourage people to congregate indoors for shielding, leading to closer contact between susceptible and infected hosts and exposure to re-circulating air and lower dewpoint set by indoor air-conditioning system. High dewpoint can also promote the activity of some other pathogens (such as Rhinovirus [33]). Infections by these pathogens can cause flu-like symptoms. In laboratories, influenza viruses are cultured at 31°C – 38°C to obtain optimal growths. At 24°C or lower temperatures, *in vitro* of viral RNA polymerase decreases by more than 84% [34]. At environmental temperature of 15°C, human nasopharyngeal end inspiratory air temperature drops to 28.1°C [35], which is well below the optimal temperature for virus multiplication. High dewpoint impedes heat and moisture exchanges between the body and the environment, affecting metabolism and immunity [36]. These are very likely to solve the mystery why influenza (including human avian flu cases) tends to peak in hottest months and the rainy season in most tropical countries. If this hypothesis is true, then the transmission efficiency at 30°C and 20°C could be equal (Lowen et al. [37]), for both of temperatures produce larger absolute deviation of T_d from its annual mean. This suggests that in tropics, direct contact or "short-range" transmission indoor may dominate influenza spreading.

In desert areas, flu peaks can occur in cooler, sand-stormy and driest (low dewpoint) months. For example, this study found that most of human avian flu cases in Egypt have been reported from December to

April when temperature and humidity successively reach their minimums.

In most temperate and arctic regions, influenza activity is associated with low dewpoint only, because the sunny days and pleasant temperature (18°C – 24°C) in the summer inhibit virus breeding, promote host immunity and encourage outdoor activities. In the winter of these areas, chilly temperatures near the ground due to net radiation flux from the surface to the space over night often cause an inversion, leading to pollutants / bioaerosols being trapped close to the ground for days, with possible effects on influenza spread. Under such circumstance, a N95 mask will prevent the flu by keeping the respiratory tract warm and humid (higher T_d) in addition to virus filtration.

The fact that influenza peaks when dewpoint significantly deviates from its annual mean in the tropics brings a concern whether the more frequent extreme climate events related to global warming might contribute to the onset of a pandemic.

(2) Solar radiation directly affects virus survival and host immunity. Noteworthily, 13 out of the 18 human avian flu cases in Hong Kong showed up in December 1997 when sunshine was 45% less than normal in the month. Both classic and recent studies by Hollaender et al. [38] and Sagripanti et al. [19] have indicated that the influenza virus is sensitive to the electro magnetic spectrum near 254-nm and can be inactivated by solar radiation. This germicidal effect is unnecessary to be consistent in both indoor and outdoor environments, as indoor conditions involve other confounding variables that may mask the primary effect of UV radiation. In addition to virus inactivation, solar radiation exposure (UVB band in the electro magnetic spectrum) and length of daily photoperiod affect a host's vitamin D level and emotion (mood), which are important to the immune system. Vitamin D modulates the effectiveness of macrophages [39] and induces antimicrobial peptide gene expression [40]. Emotion style can affect the susceptibility to the common cold [41]. Significantly lower vitamin D levels in patients were observed by Cannell et al. [18]. In United Kingdom, the population's vitamin D levels were found to be minimal around January each year, corresponding to the seasonal peak of the flu. In recent years, hypothesis regarding solar radiation and vitamin D roles in influenza seasonality has aroused great attention in scientific circles. To a considerable degree, the simulation and projection results of this study provide a strong, global and quantitative support to the hypothesis in terms of sunny hours (photoperiod). More importantly, this association is quantified by an exponential quarter (1/4) power law of solar radiation ($e^{-S_h^{1/4}}$). Interestingly, from Table 4, it seems that the association (in terms of correlation coefficient - r) is most distinct in middle latitudes and gradually weakens toward both poles and the equator, where precipitation and dewpoint begin to play more crucial roles. The reason for this deserves further study but a plausible explanation could be that the intensity of solar radiation is much more consistent all year in these climate zones than in middle latitude areas. For example, in Longyearbyen, Svalbard (78°13'N) the average monthly UV index varies between 0 and 2 although daily hours of sunshine can increase from 0 in the winter to 9 in May. More extremely, the average monthly UV index is nearly a constant (11) in Singapore (01°17'N). Consequently, populations in these areas receive relatively stable amount (dose) of UVB in different seasons even if they stay outdoors everyday. The net effect of this phenomenon makes the actual amount of solar radiation received in these regions rely more on precipitation and extreme temperatures that encourage lengthy indoor stays.

(3) The positive association between influenza and precipitation found in this study is consistent with the findings from others. The association has been reported more obvious in tropical areas such as Dakar, Senegal [42], Pune, India [43], Colombia [12], and Indonesia [44]. In Thailand, after the hot and dry season, the number of influenza cases rapidly increases at the beginning of rainy season [45]. In the Democratic Republic of the Congo, an epidemic involving influenza virus A (H3N2) had an outbreak in December 2002, infecting more than 31,000 people with a case-fatality rate up to 3.2% [46]. A retrospective study on the weather background of the epidemic indicates that precipitation was excessive in the month, which is the hottest period of a year in the country. In Brazil, a seasonal southward traveling wave of influenza was identified [13]. Interestingly, during the simulation the traveling wave was found coincide with the movement of rainfall pattern. There are a couple of possible explanations for this association: Precipitation is usually correlated to weak solar radiation, reducing germicidal effect and Vitamin D level. It can also affect host behaviors, mainly the frequency of contact between susceptible individuals and infected hosts and the proximity of humans and poultry, for precipitation can "lock" people indoors for days, increasing transmission opportunities. This effect may be exaggerated if poor indoor ventilation or a dirty air conditioner [47] results in high airborne concentration of the virus (transmission of SARS is an example). Human cases of avian influenza in Thailand and Vietnam have been found to peak during both the rainy season and the burning season. The transmission of avian influenza to people during these periods is enhanced by the fact that poultry raised for human consumption are often kept within several meters of

where people live (WHO 2004). Precipitation affects humidity. A considerable portion of ILI is found to be caused by non-influenza pathogens [48], some of which are more active in humid environment related to precipitation. Simply with gray color, a rainy/snowy canopy of the sky may induce negative emotions [49], which can significantly reduce natural killer (NK) cytotoxicity in the immune system [50] and increase the susceptibility to the common cold [51]. In the tropics, pedestrians often get wet in thunderstorms or showers, which may also contribute to ILI especially when people enter an air-conditioned room with wet clothes and experience an abrupt drop of dewpoint. The association between the flu and precipitation might partially explain why human avian flu cases have been concentrated in tropical regions such as Indonesia, Vietnam, Thailand, and south of China where annual rainfall is remarkably higher (with more wet poultry industries) than other countries.

In Table 4 a very weak association between rainfall and ILI is observed in Hong Kong. This is because the effect of precipitation has been masked (confounded) by the first flu peak in the spring when it is often foggy or overcast with less rainfall and lower dewpoint.

(4) Social and behavioral factors have a broad scope. They can include influenza vaccination, diet and nutrition, long public holidays, school breaks, patient mobility, closure of schools or public places, and even time shift for daylight saving. In this study, only long public holidays and major school breaks are taken into account in the simulation and projection. Since the range of variation of λ is set between 0.85 and 0.99 and coefficients of correlation (R^2) of model output are above 0.84, it is estimated that socio-behavioral factors play a role of less than 30% (1- 0.85 $\times$ 0.84) in influenza seasonality. Similar to other variables, socio-behavioral variables could also mask the effect of other determinants. For example, in Thailand, the number of influenza cases begins to decrease in the middle of the rainy season [44] when students take a 3-week school break. This socio-behavioral effect together with other variables could render a distorted (e.g. negative) association between influenza and precipitation. Therefore, in those regions where solar radiation, temperature, precipitation and socio-behavioral factors each has different phase in their annual circles, a combination of the variables can conceal the true effect of a determinant or result in two or more flu peaks (e.g. in Colombia, Thailand and Hong Kong). Under this circumstance, a weak or reverse association is insufficient for removing an explanatory factor, instead, true associations need to be verified by stratification and variables must be put together to achieve a sound explanation for influenza activity.

In sum, the identified explanatory factors are very likely to be the causative factors of the seasonality and weekly variation of influenza. Nevertheless, the Theory and Model neither confine explanatory factors to the parameters used in the study nor suggest other variables are insignificant. In contrast, they have provided a more opened and generalized algorithm [Eq.(9)] that can incorporate any other explanatory factors identified from observations, experiments, literature review, and clinic trials (e.g. circulating strain of virus, effects of vaccination and so on).

The GR Model has demonstrated an ability to produce better modeling results than simple linear multiple-regression. Example in this can be seen from a comparison between Fig.5 and Fig.6.

The fact that only when e^* and b_0/a_0 in Eq.(10) were assigned numerical values could the model achieve the best results suggests that patient mobility and non "person-to-person" cases do contribute to the change in the number of influenza cases in a community. Although the existence of non "person-to-person" cases is controversial, the fact that some sporadic human H5N1 avian flu cases had neither contact with each other nor exposure to infected poultry suggests that similar cases are possible for other influenza virus strains. These cases may carry virus without clinical symptoms for a longer period of time than we currently recognize and could be infectious; the hosts involved might not get sick unless their immunity is weakened and are easily missed by surveillance. If this is true and these cases simultaneously triggered to be sick by some causative factors (e.g. sharp change in temperature, lowered vitamin D level and polluted air) are omitted in the basic reproduction rate, then incidence could be considerably underestimated.

For years, we have tried to verify hypotheses regarding the determinants of influenza seasonality and weekly activity, but confusions resulting from the inconsistent (or even contradictory) findings in different studies, ethic concerns, and shortage of budget for expensive experiments have retarded our progress. The model developed in this study offers an alternative strategy for hypothesis testing, clarifying some inconsistent findings, and narrowing boundless explanatory factors down to some key variables through simulation and projection results of high coefficient of correlations. The study also demonstrates that a single factor is unlikely to explain influenza seasonality and weekly variations; rather, a number of biological, environmental, social and behavioral factors, each playing an essential role, act together in a complex way to produce the seasonal and weekly variations of the flu. This inference agrees with

contemporary epidemiologic concepts and models in regard to the occurrence of a disease.

In additional to hypothesis testing, seasonality simulation and weekly incidence forecast, the established model can be further explored for the study of prevention strategies and analysis of intervention effectiveness. Examples in this aspect could be an estimation of ILI reduction owing to better timing of vaccination, a study on appropriate indoor dewpoint, and an assessment of the effect of vitamin D supplement in rainy and perpetual night seasons. Although the study was focused on seasonal influenza, some findings and principles may also be applicable to pandemics. Other contagious diseases, as long as they have similar transmission mechanisms to influenza, can also be simulated and predicted with the GR Model.

There are a couple of limitations in this study. Modeling was based on an approximate solution to the original governing equation. It was assumed that influenza indexes are proportional to the total number of influenza patients in a community. Such an assumption may not always be true. The insufficient length of data and surveillance unavailability in some countries make it difficult to test the universality and long-term stability of the model. Solar radiation, temperature and precipitation are related to each other with solar radiation being the ultimate energy source, but stratification was not performed to analyze the potential confounding relationships. Alternative explanations for the associations need to be more thoroughly considered. Parameterization of social-behavioral factors contains subjective and experience-based constituents. Finally, more clinical evidence is required before drawing precise conclusions. Despite these limitations, the use of the model does not require a perfect understanding of all determinants and their relationships. The principle and technique can be applied as long as a stable quantitative relation is found.

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