Computational Biology and Chemistry 33 (2009) 339–343

Contents lists available at ScienceDirect

Computational Biology and Chemistry

journal homepage: www.elsevier.com/locate/compbiolchem

Brief Communication

Probabilistic model of influenza virus transmissibility at various temperature and humidity conditions

Tomasz Żuk*, Franciszek Rakowski, Jan P. Radomski

Interdisciplinary Center for Mathematical and Computational Modeling, University of Warsaw, Pawinskiego 5A, bldg. D, 02-106 Warsaw, Poland

ARTICLE INFO

Article history:
Received 7 April 2009
Received in revised form 2 July 2009
Accepted 5 July 2009

Keywords:
Influenza
Influenza epidemiology
Influenza infectivity
Influenza transmission

ABSTRACT

The spread efficiency of influenza virus is significantly affected by several environmental parameters. However, neither the underlying reasons, nor the exact character and magnitude of the phenomena involved are sufficiently well understood. Here we present a probabilistic approach to the virus transmission events. For a sample ensemble, we construct a model of the infectivity as a function of the ambient conditions, and we determine its parameter values on the basis of the available experimental data.

1. Introduction

Among the viruses that are spread efficiently by air, the influenza A virus causes one of the highest worldwide morbidity and mortality rates. However, there are still some factors related to its spread that have not been thoroughly examined and understood. In particular, the influence of weather conditions, such as air temperature and humidity, on the between-host transmission of this virus is not understood clearly, although many studies were carried out in the past (Brankston et al., 2007; Weber and Stilianakis, 2008; Mäkinen et al., 2009). Thus far, the underlying reasons for the predominantly wintertime spread of influenza, significant for the understanding of its epidemiology and evolution, are still unexplained. Nonetheless, the seasonality of influenza epidemics is well characterized. In temperate regions influenza epidemics recur with marked regularity: in the northern hemisphere the influenza season spans period from November to March, while in the southern hemisphere epidemics last from May until September. Many theories have been proposed to explain this seasonal variation (Lofgren et al., 2007; Lipsitch and Viboud, 2009). Markedly different is influenza's virus behavior in the tropics (Viboud et al., 2006; Lowen et al., 2008). Recently some results have provided direct experimental evidence of the major role of weather conditions in the dynamics of influenza transmission. Lowen et al. (2007), using the guinea pig as a model host, have shown that the efficiency of airborne influenza spreading depends upon both ambient relative humidity and temperature, and that both cold and dry conditions strongly favor transmission. Shaman and Kohn (2009) analyzed the effects of the absolute humidity on the influenza virus transmissibility (IVT) and its survival rates (IVS), and found that absolute humidity constrains both these effects much more significantly than the relative humidity does. Their study shows 50% of IVT variability, and 90% of IVS variability can be explained by the absolute humidity, whereas, respectively, only 12% and 36% could be explained by the relative humidity. In temperate regions, both outdoor and indoor, the absolute humidity possesses a strong seasonal cycle that minimizes in winter, which is consistent with a wintertime increase in IVS and IVT, and may explain the seasonality of influenza. The stability of the virus in aerosols, and the size range of aerosol droplets, are supposedly the most significant factors influencing the influenza virus spread. Some studies of the possible effects they might have were carried out, although they are neither numerous nor conclusive. Wang et al. (2005) studied the case of SARS; Tellier (2006) reported on influenza A aerosol spread. Lai and Cheng (2007) modeled expiratory droplets dispersion transport using Eulerian approach. Quantification of the routes of influenza transmission was attempted by Atkinson and Wein (2008).

Recently we have presented a simple model of influenza transmission (Żuk et al., 2009), which included some environmental variables, based on the experimental results of the work of Lowen et al. (2007), involving guinea pigs. The transmissibility parameter occurring in that model was approximated for given conditions by comparing results of pseudo-simulations with the actual experimental data. That approach had, however, quite substantial limitations regarding rather small size of the data set available. Consequently, the results were to some extent not entirely satisfying. In particular, the following problems were encountered while

* Corresponding author. Tel.: +48 22 55 40 800; fax: +48 22 55 40 801.
E-mail addresses: tzuk@icm.edu.pl (T. Żuk), rakowski@icm.edu.pl (F. Rakowski), janr@icm.edu.pl (J.P. Radomski).

1476-9271/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.compbiolchem.2009.07.005

analyzing the model behavior at 20 °C:

1. The model failed to produce any statistically representative output that would be similar to the experimental results obtained for 35% humidity. The same concerns also the case of 20% humidity—unless we assume an unexpectedly high and otherwise improper value of a certain ensemble-dependent parameter.
2. The case of 50% humidity, for which a small infection rate occurred, was assigned the highest transmissibility.

In addition, that model provided ranges, rather than exact values, of parameters.

In this work we propose yet another model, based on a different approach, which seems to be less sensitive to the size of the data set available.

2. Theoretical background

2.1. Available data

No additional experimental data of kind necessary here were published yet, as far as were able to ascertain. Therefore, we again make use of the data set of Lowen et al. (2007), who conducted several trials, putting four infected and four healthy (and susceptible) guinea pigs together in a four-shelf chamber such that there were one healthy and one infected animal on each shelf. Besides, the infected individuals were all placed on the one side of the ensemble, and the healthy ones, on the other. Afterward a steady stream of air was blown from the former side toward the latter. Every 2 days the experimenters measured the nasal wash titer in each animal in order to control the infection course or occurrence. This procedure were repeated two times for every set of environmental parameters, namely, for 20%, 35%, 50%, and 65% humidity at 20 ° C and 35%, 50%, 65%, and 80% humidity at 5 °C. There were also two trials conducted at 30 °C, but no infections were observed at this temperature. The results revealed a somewhat complex dependency relationship between the infection rate and the environmental conditions (Lowen et al., 2007).

2.2. Probabilistic framework

We propose a stochastic approach to model phenomena related to infection and subsequent illness development. In particular, we describe each act of infection in terms of the three consecutive random events: (a) inhalation of a biologically active virion, (b) virion entering into a host cell, and (c) the cell survival over a timeframe sufficient for the virion to produce, and to release, its descendants, not being destroyed by the host's immune system. If any of the virions in the ensemble succeeds in each of those three stages, infection develops, and the host gets ill. Our basic premise is:

1. All these random events, taken for all virions separately, are mutually independent in the probabilistic terms, i.e., successes or failures of any number of virions at any of these three steps does not affect the success/failure probability of any other virion at any step.
2. Those probabilities are independent of the total number of virions that are present in the ensemble or have passed the preceding step.

In other words, we assume that all virions contribute to the infection on their own merits, and do not act synergistically or directly affect the host's state. This single assumption implies the neglect of some otherwise important phenomena, e.g., the fact that a contact with a pathogen leads to an increased immune response at the later time. However, we will show that such a model is accurate enough for the purpose of analyzing results of short-lasting infection-rate-related experiments with average virus concentration levels.

Let p_0 denote the probability that a virion will pass through both steps (b) and (c) after being inhaled, thus leading to infection. This quantity may more or less depend on the environmental conditions, but except for this fact, it should be constant following the above assumptions (and particularly, it should be constant within a single experiment). If the total number of inhaled virions is N, the probability of infection equals

$$P = 1 - (1 - p_0)^N$$

as the subtracted term is the probability that none of the N virions will succeed. We expect p_0 to be small (a single virion is not very likely to cause a disease), so it will be possible and convenient to use a Poisson-like formula instead:

$$P = 1 - e^{-p_0 N}.$$

If there are several sources of virions (infected hosts) in the ensemble, the jth source has released M_j virions, and the probability of inhalation of a still active virion from source j by host i is φ_{ij}, the infection probability for host i then equals

$$P_i = 1 - \exp\left(-p_0 \sum_j \varphi_{ij} M_j\right).$$

The probabilities φ_{ij} serve as coefficients carrying the information about geometrical and mechanical properties of the ensemble, as well as about virus stability. The latter feature implies an explicit dependency on temperature and humidity. However, it seems reasonable to assume that the transport-related phenomena and those affecting stability are independent of each other. This enables us to separate $\varphi_{ij}(T, H)$ into two factors: position-dependent α_{ij} and weather-dependent $g_0(T, H)$. We also assume a direct proportionality between the number of virions released by an individual per unit time and the virus titer in its nasal wash (β_j). We then put $M_j = \lambda \langle \beta_j \rangle \Delta t$, where Δt is the relevant period of time and $\langle \beta_j \rangle$ is the mean titer over that period. The coefficient λ may also slightly depend on temperature. However, we may put it together with p_0 and g_0 into a single weather-dependent parameter $\gamma_0(T, H)$; thus finally

$$P_i = 1 - \exp\left(-\gamma_0(T, H) \Delta t \sum_j \alpha_{ij} \langle \beta_j \rangle\right). \quad (1)$$

The parameter γ_0, which relative values for different T and H are to be calculated from the experimental results, contains all the relevant ensemble-independent information about the influence of environmental conditions on influenza transmissibility, such as those related to viral aerosol release and stability, relative cell infectivity potential, or mucous membranes vulnerability. What it does *not* incorporate is issues directly related to the disease course, e.g., the mean virus titer, or the duration of infectious period. That is they are treated rather as variables than as parameters in this model, which is geared to quantify transmissibility as a phenomenon, normalized to the unitary viral load.

Table 1
Decimal logarithms of the mean nasal wash titer values in pre-infected guinea pigs on day 2 ($\log \beta_{ref}$) in each experimental case.

	Case							
	A	B	C	D	E	F	G	H
20 °C	6.9	6.2	7.9	7.5	7.1	6.8	7.2	7.1
5 °C	6.9	7.2	7.1	6.9	6.4	6.9	6.1	6.9

3. Methods

3.1. Infections in our ensemble

In each experiment there are two ways of getting infected: by a pre-infected individual, or by one that was healthy at the beginning, but became infected in the first manner (secondary infections). We assume that these two possibilities do not co-exist at the same time, i.e., the pre-infected animals recover before any of the other starts to be infectious. This seems reasonable if one looks at the graph showing the average nasal wash titer in pre-infected animals (Lowen et al., 2007) and note the logarithmic scale. Only a minor viral load is released after day 4 (at 20 °C), or 5 (at 5 °C). On the other hand, as the incubation period lasts for 2 days and the peak infectiousness occurs 2–4 more days afterwards, the infectious periods of the pre-infected and the non-pre-infected hosts generally do not intersect. Thus, we classify the infections occurring up to day 5 to the first phase, and the rest of them, to the second one. When the titer is at first non-zero on day t, we take day $t-2$ as the infection moment if $\beta < 10^3$ or $t-3$ otherwise.

Thus, having the infection rates for particular T, H from the experiment, we might calculate $\gamma_0(T,H)$ from Eq. (1) although approximation of the α_{ij} coefficients would be a challenge even should we knew all the relevant dimensions and the airflow parameters of the ensemble used. However, the *relative* transmissibility values might be obtained without this, provided that we simply incorporate those geometric coefficients to γ_0 as an unknown constant, and then make some further simplifying assumptions.

For the first phase, if we average the viral load received by all the healthy animals, we may, following the above, write the general infection probability as

$$P_1 = 1 - e^{-\gamma(T,H)\beta_{ref}\Delta t} \tag{2}$$

where γ is the relative transmissibility, which absolute values reflect also the geometric features of the particular ensemble. The reference nasal wash titers β_{ref} are collected in Table 1; we take the mean value[1] on day 2, when it is usually nearest the maximum. We also set Δt to 2 days for 20 ° C and to 4 days for 5 ° C as this is the approximate duration of the high titer period.

The probability of being infected during the second phase depends on the number of individuals infected during the first phase (n_1). As the relative positions of virus sources and targets are now different than in the previous phase, we must introduce an additional factor α in the exponent of Eq. (2). Again we assume that all the animals receive the same, average number of viral particles, but we also set all β_{ref} to a fixed, average value $\beta_0 = 10^7$. Hence the probability of infection

$$P_2 = 1 - e^{-\gamma\alpha\beta_0 t_0 n_1/2}. \tag{3}$$

The factor $n_1/2$ follows from the fact that a non-pre-infected individual has on average 3/2 non-pre-infected neighbors, of which the ratio $n_1/3$ has been infected in phase 1.

[1] For convenience, we use the geometric mean here, i.e., we take the arithmetic mean on a logarithmic scale.

Table 2
The obtained relative values of transmissibility ($\times 10^8$) that minimize the deviation function described in the main text. For 5 ° C and 35% humidity, all animals were infected during the first phase of experiments, leading to zero deviation element for any gamma not less than 6.9. However, as the infections seem to distribute nearly equally between days 1 and 4, it is reasonable to pick the least value that gives no deviation. For 20 ° C and 80% humidity, no infections occurred, so we may only set a top limit. For 5 ° C and 20% humidity, experiments were not performed.

T	H				
	20%	35%	50%	65%	80%
20 °C	1.0	2.0	1.1	3.4	<0.85
5 °C	–	6.9	3.6	1.8	2.0

Table 3
The deviation values for experiments performed under particular conditions. The total deviation is 0.74; most of it is generated by the (20 °C, 35%) case.

T	H				
	20%	35%	50%	65%	80%
20 °C	×	0.61	0.00	×	–
5 °C	–	×	×	0.02	0.11

3.2. Determination of parameter values

As the goal is to find the appropriate values of $\gamma(T,H)$ (for each set of T and H conditions used in the experiments), we need to quantify the differences between the real and the expected experimental results.

Let us consider the experimental cases for particular T and H. Let n_1 denote the total number of hosts that were infected during the first phase, and n_2, during the second. Given γ and α, we may calculate, for each of those cases, the probability of infection for both phases, P_1 and P_2, from Eqs. (2) and (3). Now let us compare n_1, n_2 with the respective expected values, x_1, x_2, derived from those probabilities. If they differ by less than 0.5, i.e., the number of infections occurred is the natural number closest to the expected value, there is no deviation. In the opposite case, the deviation element is $(|n_i - x_i| - 0.5)^2$. The total deviation for a particular set of parameters $\{\gamma(T,H), \alpha\}$ is the sum of all elementary deviations for each condition set.

Now we may simply search for the parameters that minimize the deviation value. We do it by checking all the combinations with $\gamma(T,H) \in G$ and $\alpha \in A$, where G consists of values from 10^{-9} to 5×10^{-7} with two decimal digit precision, and A, from 0 to 2 with step 0.02. If for certain conditions there exists a range of gamma values that give zero contribution to the deviation, we pick the middle value from this range.

4. Results and discussion

Following the procedure described in Section 3.2, we have obtained $\alpha = 0.78$ and $\gamma(T,H)$ as shown in Table 2. The deviation values for particular cases are shown in Table 3. These results seem to be much more accurate and precise than those obtained from our previous model (Żuk et al., 2009).

The most important shortcoming of the earlier work was the fact that our pseudo-simulations could not cover scenarios similar to the two that were observed for 20 ° C and 35% humidity. Both of them consisted of three infections in phase 1 and one infection in phase 2, at a very late time. Since the infection rate should generally be, from the statistical point of view, a decreasing function of time, using such a scenario for representing a statistically typical situation just must lead to an error. This problem has been solved in the present model as (1) we are no longer interested

in the infection occurrences with a daily resolution, (2) we calculate the probability of infection in phase 2 using the real, not the expected, number of infections in phase 1. Hence, the method is more robust with respect to the smallness of the data set, since it reduces the influence of statistical fluctuations and prevents their inter-phase summation. However, the (20 °C, 35%) case, which alone is responsible for most of the deviation, is still a little troublesome for yet another reason. The values of virus titer in the pre-infected animals are abnormally high, which makes the phase-related infection ratio 3:1 non-proportional to any reasonable expectations, particularly for experiment C. The transmissibility value obtained for these conditions may be somewhat underestimated regarding the experimental infection rate. A similar problem, but to a lesser extent, occurs for the (5 °C, 80%) case, which generates nearly all the remaining deviation, but there we encounter an extremely high variance of titer levels in the same experiment, rather than a strange mean value, which may make the equal-exposition approximation too poor.

Another major problem that could not have been managed within the previous model was the high value of transmissibility for 50% humidity at 20 °C, which we explained again by the fluctuations due to the insufficient number of infections (only 1 per trial). This is no longer an obstacle here, as our present method does not rely on any data other than the infection rates. For 20 ° C the transmissibility has a minimum at around 50% humidity, which fits the experimental data rather well. The shape of $\gamma(H)$ for 5 ° C looks also quite reasonable.

The general character of γ as a function of T, H leads to conclusions analogous to those obtained by Shaman and Kohn (2009), who examined the statistical significance of linear dependency

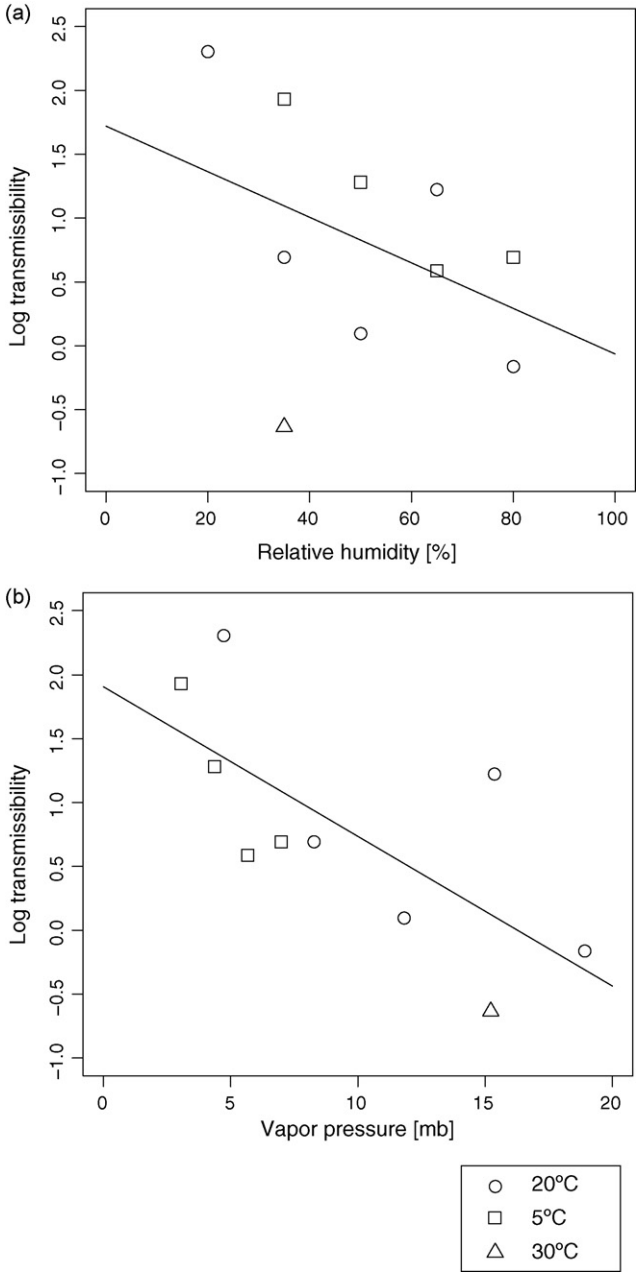

Fig. 1. Linear regression of the natural logarithm of transmissibility with respect to (a) relative humidity, and (b) partial pressure of water vapor. The p-value is 0.250 and 0.0218, respectively. We took γ (20 °C, 80%) = 0.85 and γ (30 °C, 35%) = 0.53, which are the largest values still not giving any deviation.

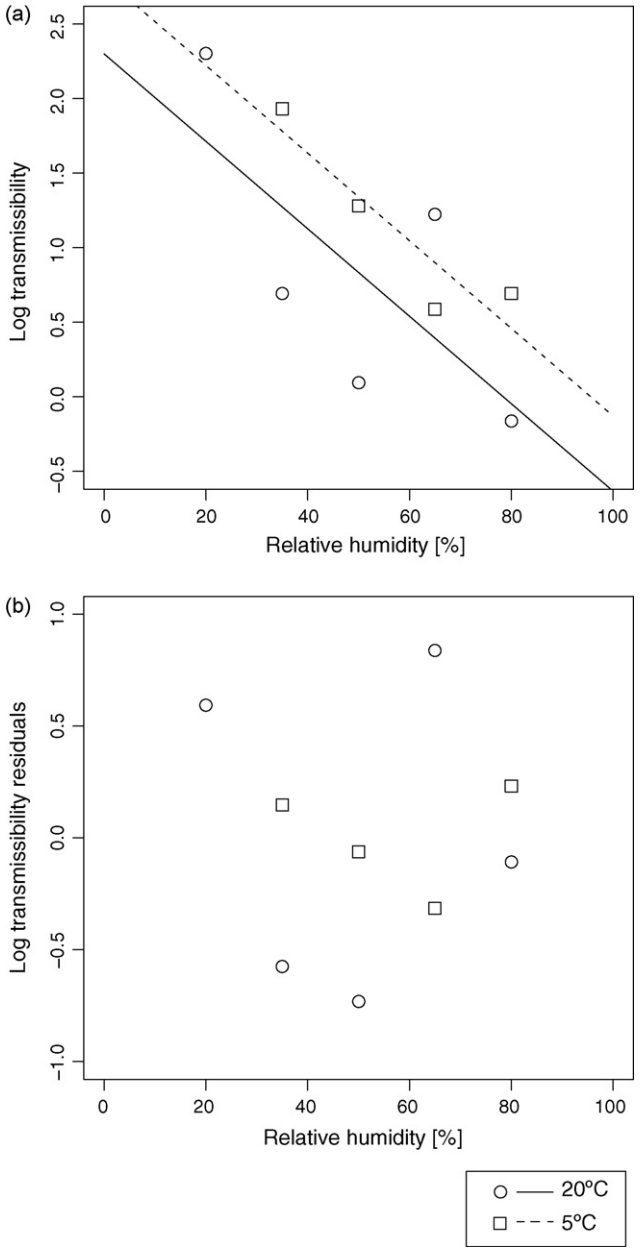

Fig. 2. Linear regression of the transmissibility as a function of H (note the logarithmic scale), separately for 20 ° C and 5 °C. The fitted lines (a) have the (negative) slopes of 0.02933 and 0.02939, and the intercept, 2.30 and 2.81, respectively.

between the total infection rate on one hand, and temperature, relative humidity, and absolute vapor pressure on the other, using the same experimental data. Only the latter turned out to be present without any doubt. The same procedure applied to $\ln \gamma$ gives the t-statistic p-values 0.250 for the relative humidity, and 0.0218 for the absolute vapor pressure[2] (Fig. 1).

On the other hand, although inference from 4 estimated points is not without risk, it seems interesting that the linear regression of $\gamma(H)$, performed separately for 20 ° C and 5 °C, gives two lines with nearly the same slope (Fig. 2a).

Also the deviations from these trends (Fig. 2b) display a certain regularity; one might try to describe them as oscillations (with respect to H) amplitude and phase of which rises with the temperature. This would lead to factorization of $\gamma(T, H)$ into the trend $a(T)e^{-bH}$ and the residual oscillations $e^{r(T,H)}$. The trend would reflect the phenomena involved in aerosol transportation as it is the *relative* humidity that determines the equilibrium concentration, and thus size, of the droplets. The other factor would be responsible for the virus stability, and involve also the *absolute* humidity (note the translation of phase with temperature changes).

The model presented here is therefore much better optimized for dealing with small data sets than our previous simulations (Żuk et al., 2009). The results it provides are disturbed to much lesser degree by the input sparseness—the situation rather common in many studies involving infectivity data, esp. for pathogens of high biohazard risk, and we believe might be of value for other situations. Of course, it would be interesting and highly beneficial to calibrate the model with larger data sets, should such data be available. Nevertheless, we believe the results presented here are sufficiently accurate to be incorporating in a large-scale modeling effort, which would be the next stage of the current project.

[2] These values may seem much poorer than the original 0.059 and 0.00027. Note, however, that the number of points is two times less as we have one point per condition set, and not per trial.

Acknowledgements

The authors were partially supported by the EU project SSPE-CT-2006-44405, and also partially supported from the 352/6.PR-UE/2007/7 grant.

References

Atkinson, M.P., Wein, L.M., 2008. Quantifying the routes of transmission for pandemic influenza. Bull. Math. Biol. 70, 820–867.
Brankston, G., Gitterman, L., Hirji, Z., Lemieux, C., Gardam, M., 2007. Transmission of influenza A in human beings. Lancet Infect. Dis. 7 (4), 257–265.
Lai, A.C.K., Cheng, Y.C., 2007. Study of expiratory droplet dispersion and transport using a new Eulerian modeling approach. Atmos. Environ. 41, 7473–7484.
Lipsitch, M., Viboud, C., 2009. Influenza seasonality: lifting the fog. PNAS 106 (10), 3645–3646.
Lofgren, E., Fefferman, N., Naumov, Y.N., Gorski, J., Naumova, E.N., 2007. Influenza seasonality: underlying causes and modeling theories. J. Virol. 81 (11), 5429–5436.
Lowen, A.C., Mubareka, S., Steel, J., Palese, P., 2007. Influenza virus transmission is dependent on relative humidity and temperature. PLoS Pathog. 3 (10), e151, 1470–1476.
Lowen, A.C., Steel, J., Mubareka, S., Palese, P., 2008. High temperature (30 °C) blocks aerosol but not contact transmission of influenza virus. J. Virol. 82 (11), 5650–5652.
Mäkinen, T.M., Juvonen, R., Jokelainen, J., Harju, T.H., Peitso, A., Bloigu, A., Silvennoinen-Kassinen, S., Leinonen, M., Hassi, J., 2009. Cold temperature and low humidity are associated with increased occurrence of respiratory tract infections. Respir. Med. 103, 456–462.
Shaman, J., Kohn, M., 2009. Absolute humidity modulates influenza survival, transmission, and seasonality. PNAS 106 (9), 3243–3248.
Tellier, R., 2006. Review of aerosol transmission of influenza A virus. Emerg. Infect. Dis. 12 (11), 1657–1662.
Viboud, C., Alonso, W.J., Simonsen, L., 2006. Influenza in tropical regions. PLoS Med. 3 (4), e89, 0468–0471.
Wang, B., Zhang, A., Sun, J.L., Liu, H., Hu, J., Xu, L.X., 2005. Study of SARS transmission via liquid droplets in air. J. Biomech. Eng. 127 (1), 32–38.
Weber, T.P., Stilianakis, N.I., 2008. Inactivation of influenza A viruses in the environment and modes of transmission: a critical review. J. Infect. 57 (5), 361–373.
Żuk, T., Rakowski, F., Radomski, J.P., 2009. A model of influenza virus spread as a function of temperature and humidity. Comp. Biol. Chem. 33, 176–180.