Why respiratory viruses or bacteria have the highest probability to be deposited in the respiratory tract in flu seasons

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Keywords: influenza, respiratory infections, seasonality, airway, epidemiology, public health

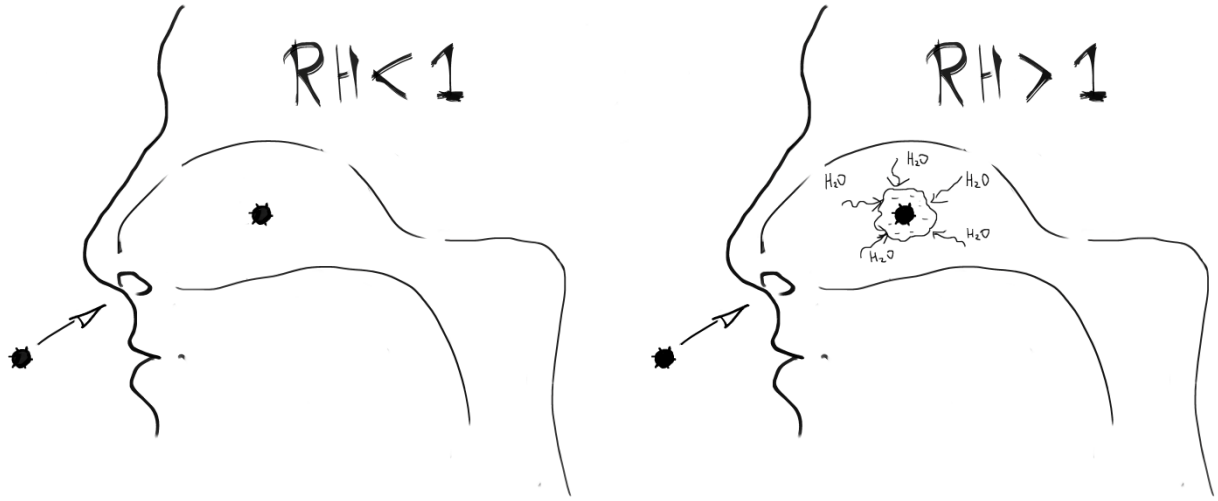
Highlights

The main concept of the manuscript:

step 1: breathing cool air (which correspond to environmental conditions during flu seasons) leads to the supersaturation in the respiratory tract;

step 2: the air supersaturation leads to the intensive dramatic condensational growth of inhaled viruses or bacteria in the respiratory tract;

step 3: condensational growth leads to the intensive deposition of viruses or bacteria in the respiratory tract.



Abstract

"Seasonal variation in the incidence of communicable diseases is among the oldest observations in population biology, dating back at least to ancient Greece, yet our understanding of the mechanisms underlying this phenomenon remains hazy at best." : **Marc Lipsitch and Cécile Viboud (2009)** (Lipsitch and Viboud, 2009).

The latest researches show the infected people when breathing generate the infectious aerosols with particles below 1 μm. The airborne transmission of these particles is effective but the deposition of submicron particles in the respiratory tract (RT) has very low probability.

Here I investigated the processes in RT when breathing cold air and its role in the delivery of viruses and bacteria of submicron and ultrafine sizes in RT.

The original hypothesis of the highest probability of delivery and deposition of viruses or bacteria from inhaled air in the respiratory tract during flu seasons in different climatic conditions was investigated.

On the basis of estimation I have originally shown: *Breathing cool air leads to the supersaturation of air in RT; the air supersaturation leads to the intensive condensational growth(CG) of inhaled viruses or bacteria in RT; CG leads to the intensive and dramatically growth of deposition rate of viruses or bacteria in RT.*

Under normal conditions of inhaled air (T>20˚C; RH=60%) there is no transition in oversaturated condition in RT (CG is insignificant and probability of virus deposition on epithelium of RT is low – no more than 20%).

But with an increase in RH of inhaled air the oversaturation in RT occurs even at warm temperature of inhaled air. For inhaled air of T=20°C, RH>70% - the local supersaturation in the airways occurs: the concentration of liquid water in the mixed air in RT (C_{Liq}) is C_{Liq}<2·4g/kg and for T=25°C; RH>90% - C_{Liq}<1·2g/kg.

The estimation also shown that for conditions of breathing cold air of T [-15..+15]˚C and Relatively Humidity (RH) of [30..60]% the supersaturation in the airways occurs: the concentration of liquid water in the mixed air in RT (C_{Liq}) is [0·2..12·1]g/kg. Under these conditions the growth of inhaled particles by condensation in RT is significant. It lead to the dramatically growth of deposition rate of the viruses and bacteria in RT (up to 97%).

These results correspond to influenza and seasonal respiratory infections in temperate and tropical climates and indicate the high probability of virus deposition on epithelium of RT.

It may be the key to '*the age-old epidemiologic mystery of influenza seasonality in the different climatic conditions*'.

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1.1 Airborne transmission is main route for spreading of influenza

There are three main routes of transmission of influenza: direct contact, by contact with contaminated objects and airborne. In the recent study Benjamin Killingley et al (Killingley et al., 2016) question the relative importance of the direct contact transmission of influenza and transmissions via contaminated surfaces and shown that airborne transmission of influenza viruses via fine droplets and particles (below 5 μm) can play a major role in spread of influenza.

1.2 Fine bioaerosol and airborne transmission of influenza

The infectious bioaerosol may be generated by individuals via coughing, sneezing, speaking and breathing.

Coughing and sneezing generate a coarse bioaerosol containing droplets varying in size: geometric mean diameter below of 13.5 μm; for speaking it is 16 μm (Chao et al., 2009). Such droplets deposit in upper airways, the probability to reach the lower airways is too small for such droplets.

Infected people also produce the fine infectious bioaerosol (size of the exhaled particles below 1μm) by normal breathing and tidal breathing (Chen et al., 2009; Cowling et al., 2013; Edwards et al., 2004; Fabian et al., 2008; Lindsley et al., 2016; Milton et al., 2013; Tellier, 2009).

Fabian et al. (Fabian et al., 2008) shown that "exhaled influenza virus RNA generation rates ranged from <3.2 to 20 influenza virus RNA particles per minute" and over 87% of exhaled particles under 1 μm in diameter, during tidal breathing. Papineni and Rosenthal (Papineni and Rosenthal, 1997) (reference from (Cowling et al., 2013)) and Fabian et al (Fabian et al., 2011) found that concentrations of particles in exhale breath vary from 0.1 to >7200 particles per liter, with the majority <0.3 μm in diameter.

Killingley et al. (Killingley et al., 2016) pointed: "Because individuals breathe much more often than they cough, these results suggest that breathing may generate more airborne infectious material than coughing over time".

Both coarse bioaerosol generated via coughing, sneezing and speaking, and fine and ultrafine bioaerosols producing via breathing could be important in airborne influenza transmission.

In this study the main aspects of influenza transmission via fine and ultrafine bioaerosols were considered.

1.3 Problem of delivery and deposition of fine airborne particles with virus in human airways

The airborne transmission of fine particles in the environmental air is effective (Cowling et al., 2013; Halloran et al., 2012; Oberdorster et al., 2005), but the deposition of these particles in the respiratory tract has the very low probability (very low deposition efficiencies)(Hinds, 1999; Hoppentocht et al., 2014; Jinxiang et al., 2015; Oberdorster et al., 2005; Tellier, 2009).

For fine airborne particles ranging from 0.1 μm to 1 μm, the deposition rate in the lungs is very low (no more than 20% for total deposition in the lungs, most particles are simply exhaled); within the range of 2-7 μm the deposition rate increases dramatically (fig1) (Hinds, 1999; Jinxiang et al., 2015; Longest et al., 2011; Oberdorster et al., 2005).

The deposition rate of fine and ultrafine particles depends on the substance of the particles and conditions of the inhaled air and breathing pattern (Ferron et al., 1984; 1985; 1988; Longest et al., 2011; Oberdorster et al., 2005; Winkler-Heil et al., 2014).

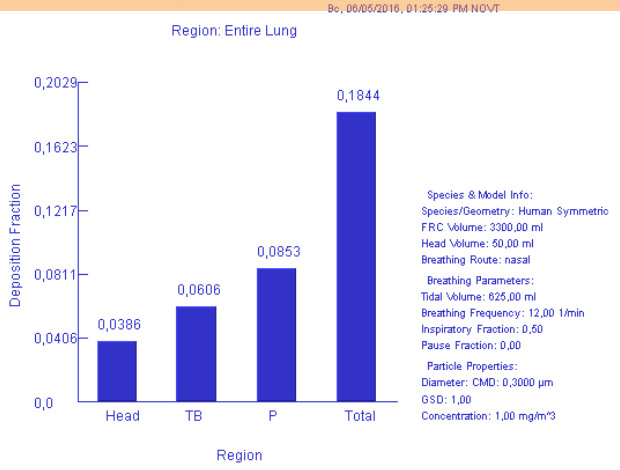
For preliminary estimation of deposition rate of fine bioaerosol in the respiratory tract it is also possible carry out independent calculations using a freely available software tools such as the Multiple-Path Particle Dosimetry Model (MPPD) (by Applied Research Associates, 2016). Results of estimation for particles' size of 0.300 μm, 1 μm, 3 μm and 5 μm are presented in fig1.

1.4 Nose and upper airways is target area of influenza viruses: Is it additional problem for target virus delivery via ultrafine and fine bioaerosols?

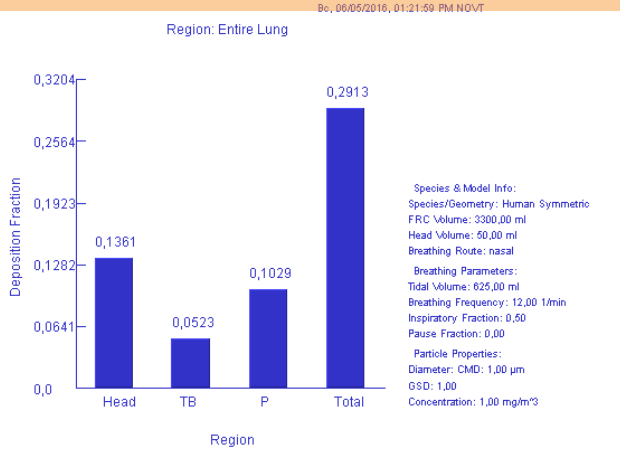
Answer for the question: Yes.

Due to the fact that the influenza is upper respiratory tract infection, the target area for influenza viruses is the upper airways and nasal cavity (as a first step of flu infection). There is an opinion that it is caused by the upper airway during respiration are critically cooled by inhaled cold air (Eccles, 2002; Foxman et al., 2015; Makinen et al., 2009; Mourtzoukou and Falagas, 2007; Tyrrell and Parsons, 1960), more information on this matter see in the part II of the study (will be posted in the near months).

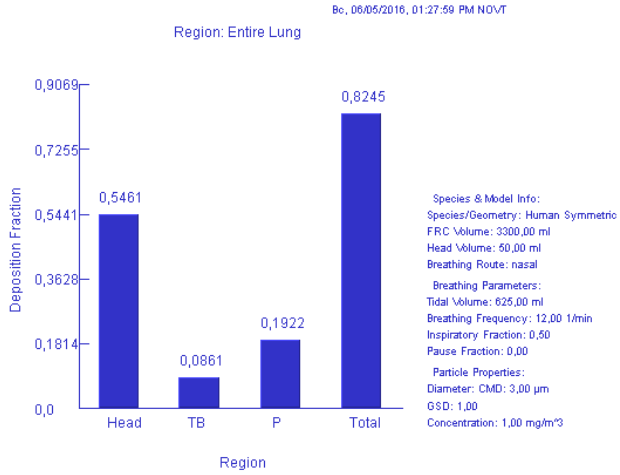
The data in fig1 shows the deposition rate of the fine bioaerosol (particles size below 1 μm) in the upper airways has the critically low values (deposition rate about 4% (for 0.3 μm) - it is dramatically much smaller than deposition rate for the lungs), that also confirmed by (Hinds, 1999; Hoppentocht et al., 2014; Jinxiang et al., 2015; Oberdorster et al., 2005; Tellier, 2009).



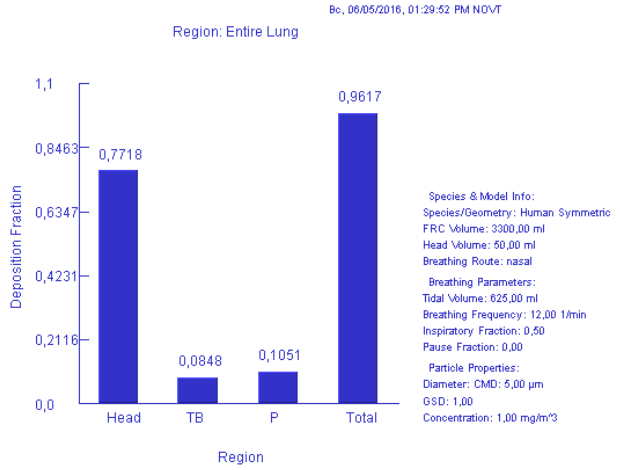
a) 0.300 µm



b) 1 µm



c) 3 µm



d) 5 µm

Fig. 1. Deposition rate of airborne particles in the respiratory tract for nasal breathing (calculated by Multiple-Path Particle Dosimetry Model (MPPD) (by Applied Research Associates, 2016)):
TB – Tracheabronchial tree;
P – Pulmonary region (respiratory bronchioles to terminal alveolar sacs).

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2 Why condensational growth is important (background)

2.1 Summary of the main concept of the study

The main concept of the part I (the main hypothesis):

- the breathing cool air leads to the supersaturation in the respiratory tract;

- the supersaturation in the airways leads to the intensive condensational growth of inhaled viruses or bacteria in the respiratory tract;

- the condensational growth leads to the intensive deposition of respiratory viruses or bacteria in the respiratory tract.

Summary (all discussions on this matter see below):

The mechanism of depositing of viruses or bacteria in the respiratory tract due to the intensive condensation growth when breathing cool air has a great value for understanding of 'the age-old epidemiologic mystery of influenza seasonality';

- this effect significantly increases the risk of the influenza and respiratory infections (more viruses deposit on the respiratory cells, the more probability of the infection and the severity of the disease);

- this effect is the strongest when breathing cool air – when seasons of respiratory infections and influenza are observed.

2.2 Hygroscopic and condensational growth in the lungs

When airborne particles enter the respiratory tract the condensational and hygroscopic growth may occur (particles and droplets become massive).

The hygroscopic and condensational growth are one of the main mechanisms that determine the effectiveness of deposition of fine and ultrafine particles in the upper airways. The hygroscopic and condensational growth are determined by humidity of the air in the respiratory tract. The more oversaturated air, the more intensive growth of the inhaled particles in the respiratory tract (Ferron et al., 1984; Grasmeijer et al., 2016; Li and Hopke, 1993; Longest and Hindle, 2011; Martonen et al., 1982; 1985; Robinson and Yu, 1998; Vu et al., 2015; Winkler-Heil et al., 2014; Zhang et al., 2006a).

2.2.1 Effects of Hygroscopic Growth

Hygroscopic growth factor for airborne hygroscopic particles is determined by relative humidity (RH) below 100%. The hygroscopic growth of fine particles in the respiratory tract (RH =99.5%) is expected to be a small size change (factor = 1.4 – 1.7 with maximum of 4 for rare case) (Grasmeijer et al., 2016; Li and Hopke, 1993; Longest and Hindle, 2011; Martonen et al., 1982; 1985; Robinson and Yu, 1998; Vu et al., 2015; Winkler-Heil et al., 2014).

2.2.2 Effects of Condensational Growth

Condensational growth factor for airborne particles is determined by relative humidity (RH) in the airways >100% (oversaturated and supersaturated conditions). The growth of the fine and ultrafine particles by condensation is not particularly limited. The effects of oversaturation and supersaturation of the air in the respiratory tract are used for controlled respiratory drug delivery of

ultrafine drug particles to a target area of the upper respiratory tract (Jinxiang et al., 2015; Longest et al., 2011; Zhang et al., 2006a).

For significant growth of the droplets and particles in multiple sizes (growth factor up to 20 (Ferron et al., 1984; Jinxiang et al., 2015)) it is necessary that the air in the respiratory tract to be oversaturated.

2.3 When the supersaturation may occur in the human airways

It is known that when the breathing air under normal conditions (T=20..25 ˚C; RH=60%) there is no transition in oversaturated condition (RH<100%) in the respiratory tract (Ferron et al., 1984; Golshahi et al., 2013; Jinxiang et al., 2015; Longest et al., 2011; Winkler-Heil et al., 2014). And under these conditions the particle growth by condensation is insignificant and probability of deposition of virus or bacteria on the epithelium of the respiratory tract is low.

But there are specific conditions of environmental air when the effect of supersaturation occurs in the airways (see below) when breathing air. The supersaturation is possible in the nasal turbinate region and upper airways, it has been shown in (Ferron et al., 1984; Golshahi et al., 2013; Jinxiang et al., 2015; Longest et al., 2011; Winkler-Heil et al., 2014).

2.3.1 Breathing hot and warm saturated air

Longest et al have shown in a series of studies (Jinxiang et al., 2015; Kim et al., 2013; Longest et al., 2011; Longest and Hindle, 2011; Worth Longest and Xi, 2008) that supersaturated conditions (RH>100%) are possible in the human airways when breathing warm saturated air; they did improve a drug delivery efficiency of the submicron and ultrafine particles to the upper airways under these conditions.

For the inhalation, initially 0.2 and 0.4 μm particles were observed the increasing in size to above 7-8μm entering the trachea (for the inhalation of saturated air of 47°C) (Jinxiang et al., 2015; Worth Longest and Xi, 2008).

2.3.2 Breathing cold and cool air

It is important to note that it has been paid little attention to the effect of supersaturation in the airways (very few studies). And there are practically no studies on supersaturation in the airways when inhaled cold and cool air.

The effect of supersaturation in the respiratory tract when breathing cold air pointed by (Ferron et al., 1984; 1985; Longest et al., 2011; Zhang et al., 2006b).

Ferron et al (Ferron et al., 1984) have determined the local supersaturation in the lungs under conditions of inhaled cold air; the supersaturation starts in the nose and lasts until the entrance of the trachea. Based on the numerical calculation they found that supersaturation of the air in the airways occurs during the inhalation of cold air (less than 10˚C) and nearly saturated air of 20˚C, RH=100%.

Longest et al (Longest et al., 2011) have pointed that supersaturation can occur when cool humid airstream passing through a channel with warm wet walls. This effect is similar to the principle behind water-based condensation particle counters (Hering and Stolzenburg, 2005).

Zhang et al (Zhang et al., 2006b) based on the calculation pointed that starting with an inhaled air temperature of 283K (10˚C) and RH=80%, the RH in the airways reach supersaturation condition (RH about 104% in the pharynx/larynx region).

The known data on the supersaturation in the lungs under different conditions of inhaled air is shown in the table1.

Table 1 - Supersaturation in the airways for different conditions of inhaled air

Inhaled air		Maximum of RH(%) in the airways	Growth factor (change of particle size)	Ref
T,˚C	RH			
20˚C	60%	<100%	no effect	(Ferron et al., 1984; Golshahi et al., 2013; Jinxiang et al., 2015; Longest et al., 2011; Winkler-Heil et al., 2014)
21.8˚C	97.5%	101%	**2.5** (for hydroscopic particle of 0.9 μm)	(Longest et al., 2011)
10˚C	80%	104%		(Zhang et al., 2006b)
20˚C	100%	102	**4** (for dry NaCl particle with an aerodynamic diameter of 0.3 μm)	(Ferron et al., 1984)
10˚C	50%	105%	**5** (for dry NaCl particle with an aerodynamic diameter of 0.3 μm)	(Ferron et al., 1984)
0˚C	50%	125%	**20** and **8** (for dry NaCl particle with an aerodynamic diameter of 0.1 μm and 0.3 μm)	(Ferron et al., 1984)
47˚C	100%	>=101%	**up to 17.5** (for hydroscopic particle of 0.2 μm)	(Jinxiang et al., 2015)

3 Results and discussions ()

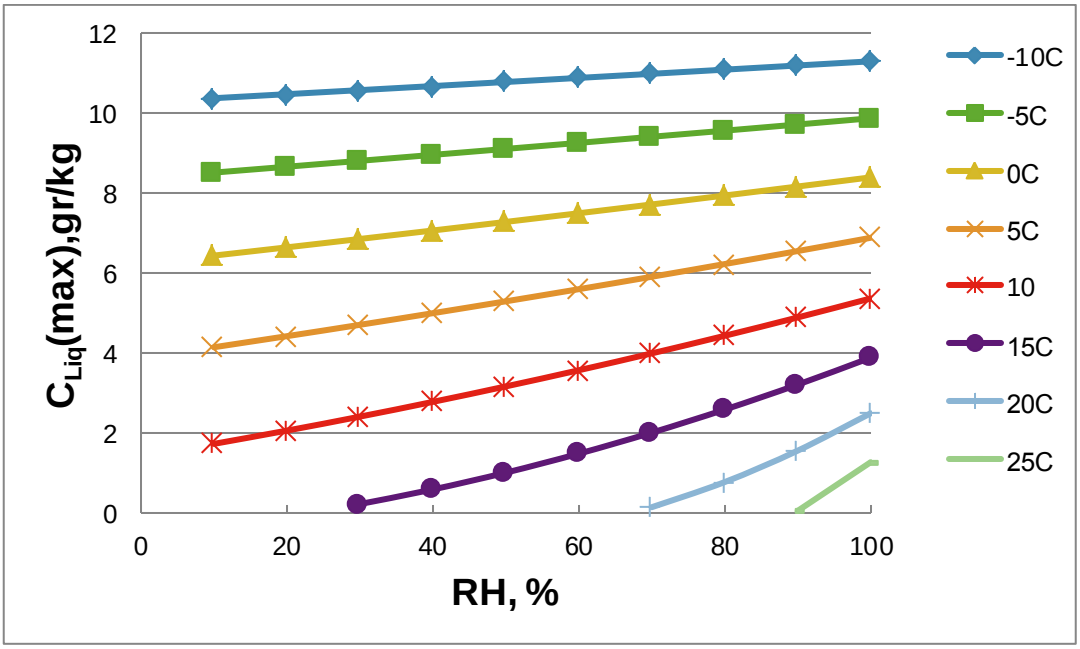
The data in the table1 shows an important connection/correlation of the effect of supersaturation in the airways and environmental conditions and flu seasons:

- supersaturation in the airways occurs when flu seasons in the temperate climate (*note: influenza season when a temperature of the air below* 15˚C(Lipsitch and Viboud, 2009; Shaman et al., 2011; Tamerius et al., 2011; 2013));

- supersaturation in the airways occurs when flu seasons in the tropical climate *(note: influenza seasons when rainy seasons; when the RH of environmental air rise to saturated conditions and air temperature falls below* 25˚C (Lipsitch and Viboud, 2009; Moura et al., 2009; Shaman et al., 2011; Tamerius et al., 2011; 2013; Viboud et al., 2006)).

3.1 local supersaturation in the airways (preliminary estimation)

To make an additional preliminary estimation of the probability of the local supersaturation when mixed the warm air (whose parameters correspond to those inside the lungs*) and inhaled ambient air, I used the Psychrometric chart (Mollier's chart. It is widely-used as the tool for determining of isobaric psychrometric processes of moist air. See information in (Barenbrug, 1974; Shaviv, 2015; Siemens Switzerland Ltd HVP, 2016)). The data on estimation presented in fig2.



estimation data for hot and warm air saturated airs (RH=100%, T>40˚C):
40˚C – boundary conditions– air in the airways is slightly oversaturated;
47˚C – air in the airways is supersaturated; C_{Liq}*(max)=1.7g/kg.*

Fig.2. Concentration of liquid water in the mixed air in the oversaturated state (mixture of the inhaled air at different humidity and temperatures (T=-10˚C;-5˚C; 0˚C; 5˚C; 10˚C; 15˚C; 20˚C; 25˚C) with the air which parameters correspondent to the air inside of the airways (initial conditions: RH=99.47; T=37˚C)).
C_{Liq}(max) – is maximal local concentration of liquid water in the mixed air (gr of water / kg of air); RH – Relative humidity of the inhaled air, %.

Results of the mathematical modeling and complicated numerical calculations on supersaturation for real conditions of respiratory tract when breathing air can be found in table1; these results correspondence to the results of the preliminary estimation in fig2. The some additional data may be found in fig3 (see below).

3.1.1 A few words about heat and mass transfer in the airways

Most researchers pay attention only to the processes of heating and humidification of the inhaled cold air and don't take under consideration another important process which takes place in the respiratory tract when breathing cold air. It is the process of local cooling of warm and humid air in the respiratory tract by cold inhaled air (for information: volume of inhaled air is 200-800cm3; volume of warm air in upper airways before inhalation is 150-180cm3; the functional residual capacity of the lungs is 3000cm3; T=37°C; RH=99.47% (Winkler-Heil et al., 2014)).

The process of local cooling of the internal air (the air in the respiratory tract) occurs when the inhaled cool air mixes with the warm and moist air in the respiratory tract. The process of local cooling of the internal air causes the local oversaturation in the airways. This process has a fleeting character and occurs in the boundary of the mixing airs.

The heat and mass transfer in the lungs occurs by convection (is the principal means of heat transfer in the upper airways) and conduction (in the lower airways) (see reviews in (Grasmeijer et al., 2016; Jinxiang et al., 2015; McFadden et al., 1982)). The more information see in the Part II (will be posted in near months).

3.2 Supersaturation and target deposition of fine bioaerosols in the lungs

The effects of supersaturation and condensational growth in the lungs dramatically increase the deposition rate of the fine and ultrafine airborne particles in the lungs (Ferron et al., 1984; Golshahi et al., 2013; Jinxiang et al., 2015; Longest et al., 2011; Winkler-Heil et al., 2014). To preliminary estimation of the deposition rate the fig3 and fig1 (see above the section 1.4) may be used.

Fig 3d (reprinted from (Jinxiang et al., 2015)) shows the intensive deposition of the fine particles in the upper airways under supersaturated conditions. Fig 3c shows that even slightly oversaturated conditions (see data on supersaturation in fig2) lead to the intensive deposition of fine aerosol in the upper airways.

The data in the fig3c and fig3d can be correlated with processes of deposition of fine bioaerosol when supersaturation occurs in the lungs when breathing cold air (breathing cold air lead to the supersaturation like breathing hot air – see fig2 and table1).

3.2.1 A few words about deposition rate of the fine bioaerosols in the airways

As mentioned above the supersaturation in the airways when breathing cold or hot and warm saturated air leads to the intensive condensational growth of the inhaled particles. The results of the estimation for inhalation hot and warm saturated air (Jinxiang et al., 2015; Worth Longest and Xi, 2008) can be used for preliminary estimation of the growth factor and deposition rate of the inhaled particles when breathing cold air (*remark: on the basis of the fact that breathing cold air lead to the supersaturation like breathing hot air – see the data in the table1, fig2 and fig3*).

Under conditions of supersaturation in the airways (RH>101% - for the inhalation of saturated air of 47°C), for the inhalation, initially 0.2 and 0.4 μm particles were observed the increasing in size to above 7-8μm entering the trachea(Jinxiang et al., 2015; Worth Longest and Xi, 2008).

Xi et al a(Jinxiang et al., 2015; Worth Longest and Xi, 2008) have shown that the deposition rate of the fine particles in ***the upper airways*** for this circumstance dramatically rise: up from 3% (normal conditions) to 10%-12% (supersaturated conditions), for adult and 5-years-old child upper airways.

Thus deposition rate of inhaled fine particles in the upper respiratory tract rise up to ***400%*** under supersaturated conditions in the airways; it is may be connected/correlated with breathing cold air when flu seasons in the world (***note:*** *the full deposition for initially 0.2μm particles in the lungs may rise up to* ***96%*** *as for particles of 7-8 μm – see above fig1*).

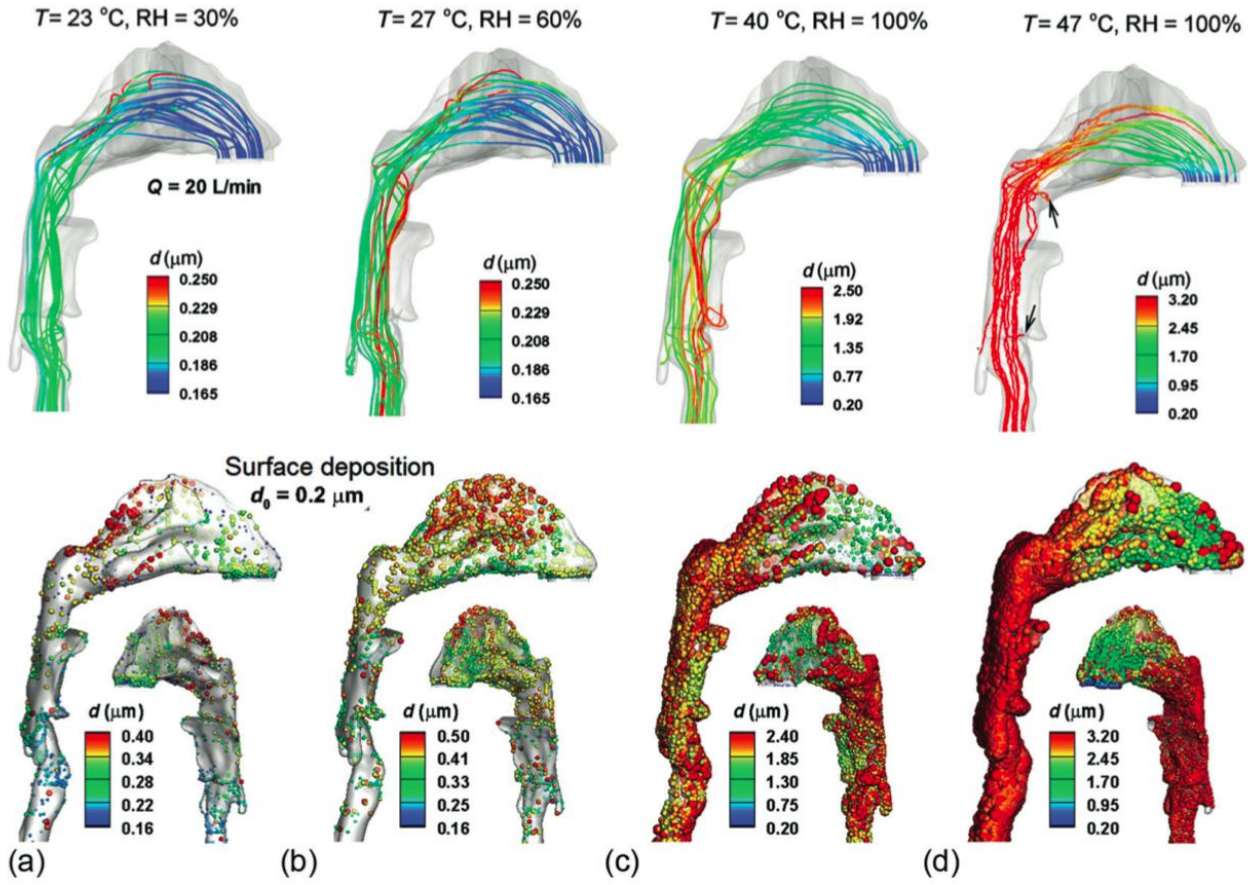


Fig 3. Particles growth by condensation and their deposition in the adult upper airway under different psychometric inhalation conditions (for initially 200 nm particles).
*(*fig3c,d can be correlated with processes when breathing cold air (breathing cold air lead to the supersaturation like breathing hot air – see fig2 and table1)*

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3.3 Supersaturation in the airways and two patterns of influenza seasonality

Remark:

One can read a long series of studies describing different kinds of hypotheses and theories explaining the seasonality of influenza and colds in different climatic conditions, but there is no a reliable theory of the incidence of influenza in tropical countries nor a unified theory for all regions (see reviews and additional references in (Foxman et al., 2015; Lipsitch and Viboud, 2009; Lofgren et al., 2007; Mourtzoukou and Falagas, 2007; Shaman et al., 2011; Tamerius et al., 2013; Tellier,

2009; The Eurowinter Group, 1997)). See also the panel 'Search strategy' and table2 (in the end of the manuscript).

Here I will not list all of the existing theories and hypotheses of seasonality of influenza and respiratory infections.

I note only the fact that two distinct types of climatic conditions associated with influenza and colds seasons were observed globally by many explorers: "cold-dry" type (for temperate climate) and "humid-rainy" type (for tropical countries) (Lipsitch and Viboud, 2009; Moura et al., 2009; Shaman et al., 2011; Tamerius et al., 2011; 2013; Viboud et al., 2006).

The main difference consists in the problem of influence of the humidity of the air on the seasonality of influenza in different climatic condition (Lipsitch and Viboud, 2009; Moura et al., 2009; Shaman et al., 2011; Tamerius et al., 2011; 2013; Viboud et al., 2006).

I found neither a reliable theory of the seasonality of the influenza and colds in tropical climate nor a unified theory for wide climatic conditions (the main question is:'Why the disease is the same one but the etiology and epidemiology for different climatic conditions are different?').

3.3.1 Flu seasons in temperate climate (cold-dry type)

In accordance with (Bishop et al., 2009; Centers for Disease Control and Prevention., 2015; Elert, 2013; Falagas et al., 2008; Gregg et al., 1978; Lofgren et al., 2007; Makinen et al., 2009; Shaman et al., 2010; 2011; The Eurowinter Group, 1997): the peak of incidence and the most severe influenza outbreaks occur at the temperatures of T<+15°C and at low humidity RH<60%.

The preliminary estimation (fig2) and the data in the table1 shown that for conditions of breathing cool air of T [-15..+15]˚C and Relatively Humidity (RH) of [30..60]% the concentration of liquid water in the mixed air (C_{Liq}) is [0·2..12·1]g/kg. Under these conditions the growth of inhaled viruses by condensation in the respiratory tract is significant (much greater than their original size).

These results indicate the high probability of deposition of influenza viruses or bacteria on the epithelium of the upper respiratory tract when breathing cold air and correspond to influenza and seasonal respiratory infections in temperate climate.

Thus, the low relative humidity (RH) of the environmental air is the determining parameter for the transmission of the virus in the air (Halloran et al., 2012; Lowen et al., 2007); and low temperatures are favorable for the emergence of the effect of supersaturation in the upper airways and dramatic growth/rise of the deposition rate of the respiratory viruses or bacteria in the upper airways due to the intensive condensational growth.

There is an imbalance if the temperature and humidity of the environmental air will deviate in any direction – either the effect of supersaturation in the airways is not so strongly expressed, or the conditions do not contribute to the spreading of the influenza viruses in the air and in this case the influenza outbreaks do not reach full strength. It is also evident that a major role is the time during which there is an influence of the 'bad conditions' on the respiratory tract.

3.3.2 Flu seasons in tropical climate (humid-rainy type)

In the tropics and subtropics, flu season driven by the high humidity or the heavy monsoon rains (Tamerius et al., 2013).

As mentioned before: there is no clear theory of influenza seasonality in tropical climate (pattern of 'humid-rainy type') – it is the one of the aspects of the' age old mystery of epidemiology of influenza'.

Data form table1 and fig2 (see above) shown that probability of supersaturation under conditions of 'humid-rainy' pattern is high and probability of virus deposition in the upper airways is high too:

- for inhaled air of T=20°C, RH>70% - C_{Liq}<2.4g/kg and for T=25°C; RH>90% - C_{Liq}<1.2g/kg.

These results correspond to the seasons of influenza and respiratory infections in the tropical and subtropical climates and indicate that under these conditions the growth of inhaled viruses or bacteria by condensation in the respiratory tract occurs, and the probability of deposition of virus or bacteria on the epithelium of the respiratory tract is high.

However, outbreaks of influenza were not observed in regions comparable in strength to the cold ones (temperate climate). This is explained by the fact that the climate in the tropical countries does not sufficiently contribute to airborne spreading of influenza viruses (this aspect raises questions in most studies) (Halloran et al., 2012; Lowen et al., 2007). In my opinion, the mechanism of the virus transmission in tropics is likely in indoors or by the fine bioaerosols when close contacts occurs (distance at 'arm's length'; more data will be posted in the next parts of the main study).

3.3.3 Normal environmental conditions – No supersaturation in the airways – No Flu

Under normal conditions of inhaled air (T>20˚C; RH=60%) there is no transition in oversaturated condition in the respiratory tract (in this circumstance the condensation growth is insignificant and probability of the deposition of virus or bacteria on the epithelium of the respiratory tract is low). This conclusion is also confirmed by (Ferron et al., 1984; Golshahi et al., 2013; Jinxiang et al., 2015; Longest et al., 2011; Winkler-Heil et al., 2014), where as a result of the numerical simulations and the experimental data it is shown that at such circumstances along the entire length of the respiratory tract there is no transition in oversaturated condition (RH<1).

Therefore, these parameters can be accepted with a high level of confidence as the boundary conditions.

♦ remark: under these conditions the risk of influenza exists, but the probability of the deposition of the influenza viruses in the airways is small and the risk of infection is small too (for more information see the experimental study on guinea pigs (Lowen et al., 2006; 2007)).

Conclusion

It has become obvious the mechanism of the delivery of the respiratory viruses and bacteria in the respiratory tract during flu seasons is similar to the mechanism of controlled respiratory delivery of fine and ultrafine drug particles, when supersaturation in the airways is used for effective deposition of ultrafine drug particles in the upper airways. And this mechanism is the strongest when breathing cool air – when seasons of respiratory infections and influenza are observed in the temperate and in the tropical and subtropical climates.

The part I of the present study have originally shown for the first time that two distinct patterns of seasonality of influenza and respiratory infections: "cold-dry" for temperate climate and "humid-rainy" for tropical climate, in fact, may be considered as unified pattern if take into account the processes of supersaturation and condensational growth in the lungs when breathing cool air. It may

have great value for understanding of 'the age-old epidemiologic mystery of influenza seasonality' in the different climatic conditions.

Some information on the factors of predictors of flu seasons see in table2:"Patterns of influenza for different climatic conditions and reasons for influenza seasonality" (in the end of the manuscript).

Main points of the part I:

1 Breathing cool air leads to the supersaturation of air in the respiratory tract.

2 Supersaturation in the airways leads to the intensive condensational growth of inhaled viruses or bacteria in the respiratory tract: **growth factor rises up to 20**.

3 Intensive condensational growth leads to the dramatically growth/rise of the deposition rate of the influenza viruses and bacteria in the upper airways (up to 4x for upper airways and full deposition of fine bioaerosol in the lungs can reach 96%).

4. Effect of the supersaturation in the lungs strongly connected/correlated with flu seasons for different climatic conditions (in temperate, tropical and subtropical climates).

Future directions

I believe the 'concept of open door' (supersaturation in the airways) is very important for: environmental health risks (as high risk of deposition of fine and ultrafine aerosols in the lungs) and asthma and COPD and other lung diseases.

Moreover, even differences in the structure of the respiratory tract of an adult, a child, physiological and pathological age-associated changes in the respiratory tract may have an impact on the gas-dynamic processes and as a consequence to influence on the processes of heat and mass transfer (and change the effects of condensational growth) in the lungs while breathing and have impact on the etiology and epidemiology of respiratory infections.

Afterword

During the preparation of the project: "Concentrated ultrafine aerosol forms of drugs: problems of portable personalized devices for pulmonary drug delivery" (grant RSCF №15-15-10008), I had a question burning in my mind: "Can respiratory viruses or bacteria to use the same mechanism of deposition in the respiratory tract as the mechanism of controlled respiratory drug delivery?"

And now I can answer on this question: YES! – the influenza viruses and bacteria use the mechanism of controlled respiratory delivery in flu seasons.

PS1

I spent an analogy of supersaturation and intensive condensational growth of fine infectious bioaerosol in the human airways with process of the mist formation in a wet steam room while opening a door (when cool or cold air from out of the room enters throw the door in the hot and humid environmental air). Therefore, I called this effect the "open door effect". Metaphorically, this effect "opens the door" of the immune system to respiratory infections and influenza.

425 **PS2**

426 All findings and conclusions in this part of the study are made on the basis of the well-known data.
427 But no one had ever come to such conclusions and no one look at the problem of seasonality of
428 respiratory infection in different climatic condition from this point of view.

429 The other parts of the study will be posted in near feature:

430 **part II**: Concept of open door in the airways and critical reduction of the antiviral immune
431 defense of epithelial respiratory cells (2016-17);

432 **part III**: Concept of open door and critical changes in physical and chemical environment
433 inside the lungs (2016-17);

434 **part IV**: Concept of open door and infections of the lower airways (Pneumonia) (summer-
435 winter 2016 – will be posted as hypothesis in nearest months);

436 **part V**: Aspect of the climatic factors in the statistical study of cases of influenza in the
437 countries with 'borderline' climate – or when vaccination should be given and additional
438 aspect for poor countries and aspects of epidemiology in "European migrant crisis"; = will
439 be posted as short letter in summer 2016.

440 **part VI**: "Does size matters? Are there limits for experiments with small animals for the
441 study of the epidemiology of influenza?" (2016-17).

442

***Search strategy and selection criteria**

I searched PubMed, Google and Google Scholar for studies published before Jun, 2016.

I used the search terms "Influenza" or "Flu" or "Respiratory Diseases" or "Respiratory Infections" or "common cold" in combination with "Supersaturation", or "oversaturation", or "condensational growth", or "Condensation", or "Aerosols", or "Theory", or "Models", or "Pattern", or "Hypothesis", or "Climatic Condition", or "Seasonality", or "Seasonal Factors", or "Weather", or "Environmental Factors", or "Humidity", or "Temperature", or "UV irradiation", or "Solar Radiation", or "Melatonin", or "Vitamin D", or "Mucociliary Clearance", or "Hyperthermia", or "Cells Temperature", or "Cells Cooling", or "Airway Epithelium", or "Airways Cooling", or "Immune Response", or "Antiviral Immune Response", or "Survival", or "Transmission", or "Spread", or "Coronavirus", or "Epidemiology", or "Virology", or "Management", or "Prevention", or "spread", or "bioaresol", or "virus deposition", or "pulmonary delivery".

I also searched websites of global and national public health agencies such as system for searching of new studies http://www.storkapp.me, the Influenzavir.com, WHO National Influenza Centre of Russia, the European Centre for Disease Prevention and Control, Public Health England, the US Centers for Disease Control and Prevention. I selected publications in English, in Russian. I also searched the reference lists of articles identified by my search strategy.

**In the study I excluded from consideration of the reasons of flu connected with the solar radiation, UV irradiation, the inhibition of mucociliary clearance, a vitamin deficiency, melatonin, vitamin D because they do not relate to the "humid-rainy" type (for countries with warm tropical climate.

443

444 **Table 2**
445 Patterns of influenza for different climatic conditions and reasons for influenza seasonality

	Cold-Dry	Humid-Rainy
1	RH < 60%; T = -15C.. +15C; (Absolute Himidity<7g/kg)	RH > 70%; T = 17..25C (Absolute Himidity>17g/kg)
2	**Cold seasons (highly synchronized with winter months)** (Bishop et al., 2009; Centers for Disease Control and Prevention., 2015; Elert, 2013; Gregg et al., 1978; Shaman et al., 2010; 2011)	**local rainy season (without well-defined influenza seasons)** (Lipsitch and Viboud, 2009; Moura et al., 2009; Shaman et al., 2011; Tamerius et al., 2011; 2013; Viboud et al., 2006)
3	**Decreased exposure of solar radiation vitamin D deficiency** (Camargo et al., 2012; Cannell et al., 2006; Dowell, 2001; Ginde et al., 2009)	**not associated**
4	**Inhibition of mucociliary clearance by the inhalation of cold-dry air** (Eccles, 2002; Salah et al., 1988)	**not associated**
5	**School cycles (crowding as a factor) = flu cycles** (see review in (Cauchemez et al., 2008))	**not clear**
6	**Main mechanism of transmission: airborne** (Chen et al., 2009; Cowling et al., 2013; Edwards et al., 2004; Fabian et al., 2008; Killingley et al., 2016; Lindsley et al., 2016; Milton et al., 2013; Tellier, 2009)	**not clear**
7	**Respiratory cells cooling** (Eccles, 2002; Foxman et al., 2015; Makinen et al., 2009; Mourtzoukou and Falagas, 2007; Tyrrell and Parsons, 1960)	**not clear**
'Effect of supersaturation and condensational growth in the airways' **Effect Occurs** (Common reason of Flu Seasons for two pattern of seasonality) T = -15 ..+15˚C, RH = 30% ..60% (***cold seasons in temporal climate***); T<20°C, RH>70% (***rainy seasons in tropics***); T<25°C; RH>90% (***rainy seasons in tropics***); T>40°C; RH>99% (when inhaled hot air is cooled in the airways – ***not associated with influenza***); **No Effect** T>20˚C; RH<60% (normal conditions – no effect – no influenza)		

Declaration of interests

I report no competing interests. The study was conducted without the involvement of any funding sources. The opinions expressed in this manuscript are those of the author and do not necessarily reflect the opinions of the institutions with which he is affiliated.

Acknowledgements

I thank Prof. Vladislav I. Maslowski as first man who support my ideas; Anna Shandenkova for help in English; Prof. *Y.V.* Kistinev and Prof. *I.V.* Ivonin for organization of the English translation of the first version of the manuscript in the Tomsk State University in 2015.

Potential partnership

I open for suggestions, and I will be happy to discuss and take part in any studies for developing the new concepts and ideas (numerical calculation and models; in vivo and in vitro experiments; epidemiology; preventive of influenza or common colds or other respiratory diseases).

Please contact me directly if you have any questions.

References

Barenbrug AWT. Psychrometry and psychrometric charts. Chamber of Mines of South Africa; 3rd edition (1974) 1974: 59.

Bishop JF, Murnane MP, Owen R. Australia's winter with the 2009 pandemic influenza A (H1N1) virus. N. Engl. J. Med 2009; 361: 2591-4.

Camargo CA, Ganmaa D, Frazier AL, Kirchberg FF, Stuart JJ, Kleinman K, et al. Randomized trial of vitamin D supplementation and risk of acute respiratory infection in Mongolia. Pediatrics 2012; 130: e561-7.

Cannell JJ, Vieth R, Umhau JC, Holick MF, Grant WB, Madronich S, et al. Epidemic influenza and vitamin D. Epidemiol. Infect 2006; 134: 1129-40.

Cauchemez S, Valleron AJ, Boelle PY, Flahault A, Ferguson NM. Estimating the impact of school closure on influenza transmission from Sentinel data. Nature 2008; 452: 750-4.

Centers for Disease Control and Prevention. . The Flu Season. <http://www.cdc.gov/flu/about/season/flu-season.htm> 2015

Chao CYH, Wan MP, Morawska L, Johnson GR. Characterization of expiration air jets and droplet size distributions immediately at the mouth opening. Journal of Aerosol Science 2009; 40: 122–133.

Chen SC, Chio CP, Jou LJ, Liao CM. Viral kinetics and exhaled droplet size affect indoor transmission dynamics of influenza infection. Indoor Air 2009; 19: 401-13.

Cowling BJ, Ip DK, Fang VJ, Suntarattiwong P, Olsen SJ, Levy J, et al. Aerosol transmission is an important mode of influenza A virus spread. Nat Commun 2013; 4: 1935.

Dowell SF. Seasonal variation in host susceptibility and cycles of certain infectious diseases. Emerging Infect. Dis 2001; 7: 369-74.

Eccles R. An explanation for the seasonality of acute upper respiratory tract viral infections. Acta Otolaryngol 2002; 122: 183-91.

Edwards DA, Man JC, Brand P, Katstra JP, Sommerer K, Stone HA, et al. Inhaling to mitigate exhaled bioaerosols. Proc. Natl. Acad. Sci. U.S.A 2004; 101: 17383-8.

Elert E. Why is There a Winter Flu Season?. Popular Science 2013: <http://www.popsci.com/science/article/2013-01/fyi-why-winter-flu-season> 2013.

Fabian P, Brain J, Houseman EA, Gern J, Milton DK. Origin of exhaled breath particles from healthy and human rhinovirus-infected subjects. J Aerosol Med Pulm Drug Deliv 2011; 24: 137-47.

Fabian P, McDevitt JJ, DeHaan WH, Fung RO, Cowling BJ, Chan KH, et al. Influenza virus in human exhaled breath: an observational study. PLoS ONE 2008; 3: e2691.

Falagas ME, Theocharis G, Spanos A, Vlara LA, Issaris EA, Panos G, et al. Effect of meteorological variables on the incidence of respiratory tract infections. Respir Med 2008; 102: 733-7.

Ferron GA, Haider B, Kreyling WG. Conditions for measuring supersaturation in the human lung using aerosols. Journal of Aerosol Science 1984; 15: 211-215.

Ferron GA, Haider B, Kreyling WG. A method for the approximation of the relative humidity in the upper human airways. Bull. Math. Biol 1985; 47: 565-89.

Ferron GA, Haider B, Kreyling WG. Inhalation of salt aerosol particles—I. Estimation of the temperature and relative humidity of the air in the human upper airways. Journal of aerosol science 1988; 19: 343-363.

Foxman EF, Storer JA, Fitzgerald ME, Wasik BR, Hou L, Zhao H, et al. Temperature-dependent innate defense against the common cold virus limits viral replication at warm temperature in mouse airway cells. Proc. Natl. Acad. Sci. U.S.A 2015; 112: 827-32.

Ginde AA, Mansbach JM, Camargo CA. Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey. Arch. Intern. Med 2009; 169: 384-90.

Golshahi L, Tian G, Azimi M, Son YJ, Walenga R, Longest PW, et al. The use of condensational growth methods for efficient drug delivery to the lungs during noninvasive ventilation high flow therapy. Pharm. Res 2013; 30: 2917-30.

Grasmeijer N, Frijlink HW, Hinrichs WLJ. An adaptable model for growth and/or shrinkage of droplets in the respiratory tract during inhalation of aqueous particles. Journal of Aerosol Science 2016; 93: 21-34.

Gregg MB, Hinman AR, Craven RB. The Russian flu. Its history and implications for this year's influenza season. JAMA 1978; 240: 2260-3.

Halloran SK, Wexler AS, Ristenpart WD. A comprehensive breath plume model for disease transmission via expiratory aerosols. PLoS ONE 2012; 7: e37088.

Hering SV, Stolzenburg MR. A method for particle size amplification by water condensation in a laminar, thermally diffusive flow. Aerosol Science and Technology 2005; 39: 428–436.

Hinds WC. Aerosol technology: properties, behavior, and measurement of airborne particles. 2nd ed. John Wiley & Sons Inc; 1999.

Hoppentocht M, Hagedoorn P, Frijlink HW, de Boer AH. Technological and practical challenges of dry powder inhalers and formulations. Advanced drug delivery reviews 2014

Jinxiang Xi, Xiuhua A.Si, Jong W.K. Characterizing Respiratory Airflow and Aerosol Condensational Growth in Children and Adults Using an Imaging-CFD Approach. In: Sid Becker and Andrey Kuznetsov , editor(s). Heat Transfer and Fluid Flow in Biological Processes. ISBN: 978-0-12-408077-5. Elsevier B.V; 2015. p. 125-155.

Killingley B, Greatorex J, Digard P, Wise H, Garcia F, Varsani H, et al. The environmental deposition of influenza virus from patients infected with influenza A(H1N1)pdm09: Implications for infection prevention and control. J Infect Public Health 2016; 9: 278-88.

Kim JW, Xi J, Si XA. Dynamic growth and deposition of hygroscopic aerosols in the nasal airway of a 5-year-old child. Int J Numer Method Biomed Eng 2013; 29: 17-39.

Li W, Hopke PK. Initial size distributions and hygroscopicity of indoor combustion aerosol particles. Aerosol Science and technology 1993; 19: 305-316.

Lindsley WG, Blachere FM, Beezhold DH, Thewlis RE, Noorbakhsh B, Othumpangat S, et al. Viable Influenza A Virus in Airborne Particles Expelled during Coughs vs. Exhalations. Influenza Other Respir Viruses 2016

Lipsitch M, Viboud C. Influenza seasonality: lifting the fog. Proc. Natl. Acad. Sci. U.S.A 2009; 106: 3645-6.

Lofgren E, Fefferman NH, Naumov YN, Gorski J, Naumova EN. Influenza seasonality: underlying causes and modeling theories. J. Virol 2007; 81: 5429-36.

Longest PW, Hindle M. Numerical Model to Characterize the Size Increase of Combination Drug and Hygroscopic Excipient Nanoparticle Aerosols. Aerosol Sci Technol 2011; 45: 884-899.

Longest PW, Tian G, Hindle M. Improving the lung delivery of nasally administered aerosols during noninvasive ventilation-an application of enhanced condensational growth (ECG). J Aerosol Med Pulm Drug Deliv 2011; 24: 103-18.

Lowen AC, Mubareka S, Steel J, Palese P. Influenza virus transmission is dependent on relative humidity and temperature. PLoS Pathog 2007; 3: 1470-6.

Lowen AC, Mubareka S, Tumpey TM, Garcia-Sastre A, Palese P. The guinea pig as a transmission model for human influenza viruses. Proc. Natl. Acad. Sci. U.S.A 2006; 103: 9988-92.

Makinen TM, Juvonen R, Jokelainen J, Harju TH, Peitso A, Bloigu A, et al. Cold temperature and low humidity are associated with increased occurrence of respiratory tract infections. Respir Med 2009; 103: 456-62.

Martonen TB, Barnett AE, Miller FJ. Ambient sulfate aerosol deposition in man: modeling the influence of hygroscopicity. Environ. Health Perspect 1985; 63: 11-24.

Martonen TB, Bell KA, Phalen RF, Wilson AF, Ho A. Growth rate measurements and deposition modelling of hygroscopic aerosols in human tracheobronchial models. Ann Occup Hyg 1982; 26: 93-108.

McFadden ER, Denison DM, Waller JF, Assoufi B, Peacock A, Sopwith T. Direct recordings of the temperatures in the tracheobronchial tree in normal man. J. Clin. Invest 1982; 69: 700-5.

Milton DK, Fabian MP, Cowling BJ, Grantham ML, McDevitt JJ. Influenza virus aerosols in human exhaled breath: particle size, culturability, and effect of surgical masks. PLoS Pathog 2013; 9: e1003205.

Moura FE, Perdigao AC, Siqueira MM. Seasonality of influenza in the tropics: a distinct pattern in northeastern Brazil. Am. J. Trop. Med. Hyg 2009; 81: 180-3.

Mourtzoukou EG, Falagas ME. Exposure to cold and respiratory tract infections [Review Article]. Int J Tuberc Lung Dis 2007; 11: 938-943.

Oberdorster G, Oberdorster E, Oberdorster J. Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. Environ. Health Perspect 2005; 113: 823-39.

Papineni RS, Rosenthal FS. The size distribution of droplets in the exhaled breath of healthy human subjects. J Aerosol Med 1997; 10: 105-16.

Robinson RJ, Yu CP. Theoretical analysis of hygroscopic growth rate of mainstream and sidestream cigarette smoke particles in the human respiratory tract. Aerosol Science and Technology 1998; 28: 21-32.

Salah B, Dinh Xuan AT, Fouilladieu JL, Lockhart A, Regnard J. Nasal mucociliary transport in healthy subjects is slower when breathing dry air. Eur. Respir. J 1988; 1: 852-5.

Shaman J, Goldstein E, Lipsitch M. Absolute humidity and pandemic versus epidemic influenza. Am. J. Epidemiol 2011; 173: 127-35.

Shaman J, Pitzer VE, Viboud C, Grenfell BT, Lipsitch M. Absolute humidity and the seasonal onset of influenza in the continental United States. PLoS Biol 2010; 8: e1000316.

Shaviv NJ. Condensation of your exhaled breath [Electronic resource]: URL: http://www.sciencebits.com/exhalecondense. 2015

Siemens Switzerland Ltd HVP . The training module B05HV_en "Psychrometric chart: Structure and application". 2016

Tamerius J, Nelson MI, Zhou SZ, Viboud C, Miller MA, Alonso WJ. Global influenza seasonality: reconciling patterns across temperate and tropical regions. Environ. Health Perspect 2011; 119: 439-45.

Tamerius JD, Shaman J, Alonso WJ, Alonso WJ, Bloom-Feshbach K, Uejio CK, et al. Environmental predictors of seasonal influenza epidemics across temperate and tropical climates. PLoS Pathog 2013; 9: e1003194.

Tellier R. Aerosol transmission of influenza A virus: a review of new studies. J R Soc Interface 2009; 6 Suppl 6: S783-90.

The Eurowinter Group . Cold exposure and winter mortality from ischaemic heart disease, cerebrovascular disease, respiratory disease, and all causes in warm and cold regions of Europe. The Eurowinter Group. Lancet 1997; 349: 1341-6.

Tyrrell DA, Parsons R. Some virus isolations from common colds. III. Cytopathic effects in tissue cultures. Lancet 1960; 1: 239-42.

Viboud C, Alonso WJ, Simonsen L. Influenza in tropical regions. PLoS medicine 2006; 3: e96.

Vu TV, Delgado-Saborit JM, Harrison RM. A review of hygroscopic growth factors of submicron aerosols from different sources and its implication for calculation of lung deposition efficiency of ambient aerosols. Air Quality, Atmosphere & Health 2015; 8: 429-440.

Winkler-Heil R, Ferron G, Hofmann W. Calculation of hygroscopic particle deposition in the human lung. Inhal Toxicol 2014; 26: 193-206.

Worth Longest P, Xi J. Condensational growth may contribute to the enhanced deposition of cigarette smoke particles in the upper respiratory tract. Aerosol Science and Technology 2008; 42: 579-602.

Zhang Z, Kleinstreuer C, Kim CS. Isotonic and hypertonic saline droplet deposition in a human upper airway model. J Aerosol Med 2006a; 19: 184-98.

Zhang Z, Kleinstreuer C, Kim CS. Isotonic and hypertonic saline droplet deposition in a human upper airway model. J Aerosol Med 2006b; 19: 184-98.

by Applied Research Associates Raleigh. ARA Multiple-path particle deposition (MPPD 2.1, beta version): A model for human and rat airway particle dosimetry. https://www.ara.com/node/561 2016.