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

Objective:

The main aspects of influenza transmission via fine and ultrafine bioaerosols were considered. Here, we aimed to estimate the impact of the different environment conditions on the processes of heat and mass transfer in the upper respiratory tract and its role in the deposition rate of the infectious bioaerosols in the lungs.

Background:

The latest researches show the infected people generate the fine and ultrafine infectious bioaerosols with submicron particles/droplets (size below 1 µm). The airborne transmission of these particles/droplets is effective. It is considered the deposition of submicron particles in the respiratory tract (RT) has very low probability. But most studies examined the deposition of the particles in the lungs under normal environmental conditions and did not paid attention to the different environmental factors.

Methods:

We review the problems of epidemiology of respiratory infections and aspects of airborne transmission/spread of infectious agents. We contrast these approaches with known data from next area: inhalation toxicology, respiratory drug delivery and physics of heat and mass transfer in the airways.

Results:

On the basis of these analyses, we propose the next main concepts:

1 Breathing cool air leads to the supersaturation of air in RT;

2 the air supersaturation leads to the intensive condensational growth(CG) of inhaled viruses or bacteria in RT;

3 CG leads to the intensive and dramatically growth of deposition rate of viruses or bacteria in RT.

We have shown:

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

b) Breathing cool/cold air of T<+15˚C and RH of [30..60]% leads to the supersaturation in the airways and it can dramatically increase the deposition rate of inhaled bioaresols in the lungs (up to 97%).

c) With an increase in RH of inhaled air the supersaturation in RT occurs even at warm temperature of

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inhaled air (for inhaled air of T<20°C and RH>70% ; T<25°C and RH>90%). It also indicates the high deposition rate of bioaerosols in the lungs.

Conclusion:

Under specific environmental conditions (when flu seasons) the processes of supersaturation in the RT can be observed. These results indicate the high probability of virus deposition on epithelium of RT and correspond to influenza and seasonal respiratory infections in temperate and tropical climates.

We believe the effect of supersaturation in the lungs can be the key to understanding of ‘the age-old epidemiologic mystery of influenza seasonality in the different climatic conditions’.

(by Alex Ishmatov; 2016)

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, flu, airborne transmission, respiratory infections, seasonality, airway, epidemiology, public health

Highlights

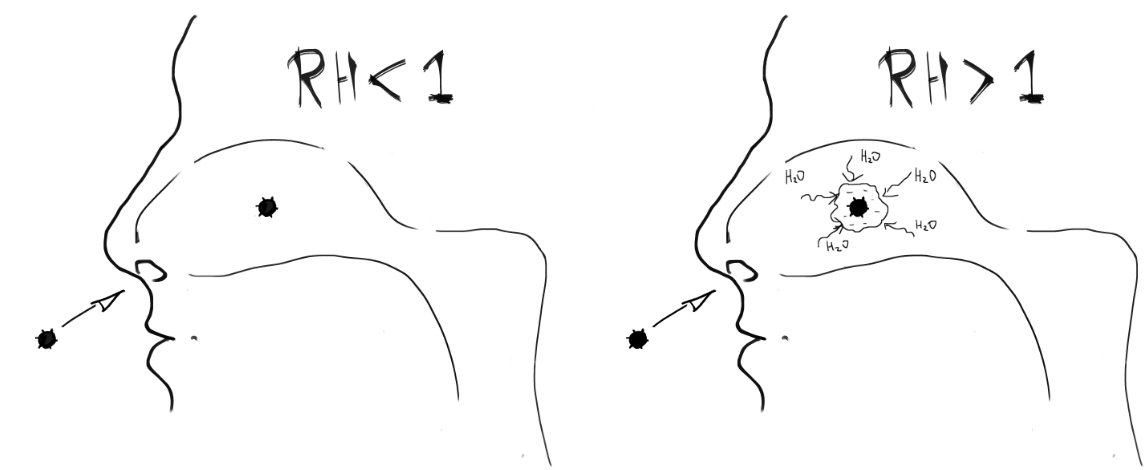
In this study the main aspects of influenza transmission via fine and ultrafine bioaerosols were considered and investigated.

The main concept of the manuscript:

step 1: breathing cool/cold 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 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

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In this study the main aspects of influenza transmission via fine and ultrafine bioaerosols were considered. Here, we aimed to estimate the impact of the different environment conditions on the processes of heat and mass transfer in the upper respiratory tract and its role in the deposition rate of the infectious bioaerosols in the lungs.

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c) With an increase in RH of inhaled air the supersaturation in RT occurs even at warm temperature of inhaled air (for inhaled air of T<20°C and RH>70% ; T<25°C and RH>90%). It also indicates the high deposition rate of bioaerosols in the lungs.

Conclusion:

Under specific environmental conditions (when flu seasons) the processes of supersaturation in the RT can be observed. These results indicate the high probability of virus deposition on epithelium of RT and correspond to influenza and seasonal respiratory infections in temperate and tropical climates.

We believe the effect of supersaturation in the lungs can be the key to understanding of '*the age-old epidemiologic mystery of influenza seasonality in the different climatic conditions*'.

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1 Introduction // How Influenza viruses spread

Marc Lipsitch and Cécile Viboud (2009) (Lipsitch and Viboud, 2009)*:"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.*

1.1 Airborne transmission as one of main route for spreading of influenza

There are the next main routes of transmission of influenza and common cold infections: by direct contact (person-to-person), by contact with contaminated objects and airborne(Hall, 2007; Shaman and Kohn, 2009; Milton et al., 2013). The relative importance of these transmission modes remains a subject of much debate (see review in (Shaman and Kohn, 2009)).

In the recent studies Cowling et al and Benjamin Killingley et al (Cowling et al., 2013; 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. Airborne route is the dominant mode of transmission for many of the diseases in the world that can lead to global pandemics.

1.2 Humans as a source of fine and ultrafine bioaerosols

The infectious bioaerosol may be generated by individuals via coughing, sneezing, speaking and breathing. Coughing and sneezing generate coarse bioaerosols (large-particles aerosols) containing droplets varying in size: geometric mean diameter below of 13.5 µm; for speaking it is 16 µm (Chao et al., 2009). It should be pointed that data on droplets size is various in studies (see review in (Chao, Wan, Morawska and Johnson, 2009) and other studies described in this section below). Such droplets may deposit in upper airways (the probability to reach the lower airways is too small for such droplets), but such droplets settle rapidly in the environmental air and are transmitted only over short time and distance(Hall, 2007).

Infected people also generate fine and ultrafine infectious bioaerosols (size of the exhaled particles below 1µm) by normal breathing and tidal breathing (Edwards et al., 2004; Fabian et al., 2008; Chen et al., 2009; Tellier, 2009; Johnson and Morawska, 2009; Milton et al., 2013; Cowling et al., 2013; Lindsley et al., 2016). Such bioaerosols practically do not settle in the environmental air and can be transmitted over long distance(Hall, 2007).

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 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.

Lindsley et al. (Lindsley 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".

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

Remark:

1. *About limitations on bioaerosol measurements. It is important to note that there are many studies on measurement of respiratory aerosols producing by individuals (see search terms "respiratory droplet" and "respiratory aerosol"). But the measurement techniques in majority of these studies focused on microsized aerosols and have limitations on measurement of nanosized aerosols. These limitations may be critical and information on nanosized particles in exhaled air may be lost in many cases/studies.*

   The most techniques have the collection efficiencies <30% (see review in (Yu et al., 2016)). It is dramatically small and due to this we can't to talk with certainty in present time about the full picture of spreading of infections via ultrafine bioaerosols.

   For example: It is pointed the collection efficiency for particles with diameters between 0.02 and 0.7µm less than 20% (Spanne et al., 1999); 30-100 nm – less than 20 % (Wei et al., 2010); and in (Hogan et al., 2005)was discovered that for particles in range of 30-100 nm the collection efficiency was <10%.

   We believe that in near future the new insights on important of ultrafine bioaerosols in spreading on infectious will be appear due to the new precise measurements.

2. *About the infectious doses and exposure. As mentioned by Cowling et al (Cowling et al., 2013): "Individuals infected with influenza viruses generate infectious doses at a low rate, so that larger outbreaks would only result from prolonged exposures in optimal conditions … it is likely that the greatest risk of aerosol transmission is in close proximity to infected persons (Tellier, 2009)".*

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

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

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

For fine airborne particles of 0.3 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 (Hinds, 1999; Longest et al., 2011; Oberdorster et al., 2005; Jinxiang et al., 2015).

However, the aspects of deposition of submicron and ultrafine particles in the lungs raise a question. Particularly, Morawska et al. (Morawska et al., 1999) pointed that of the order of 50% particles (tobacco smoke) in the lower submicrometer range deposit in the lungs.

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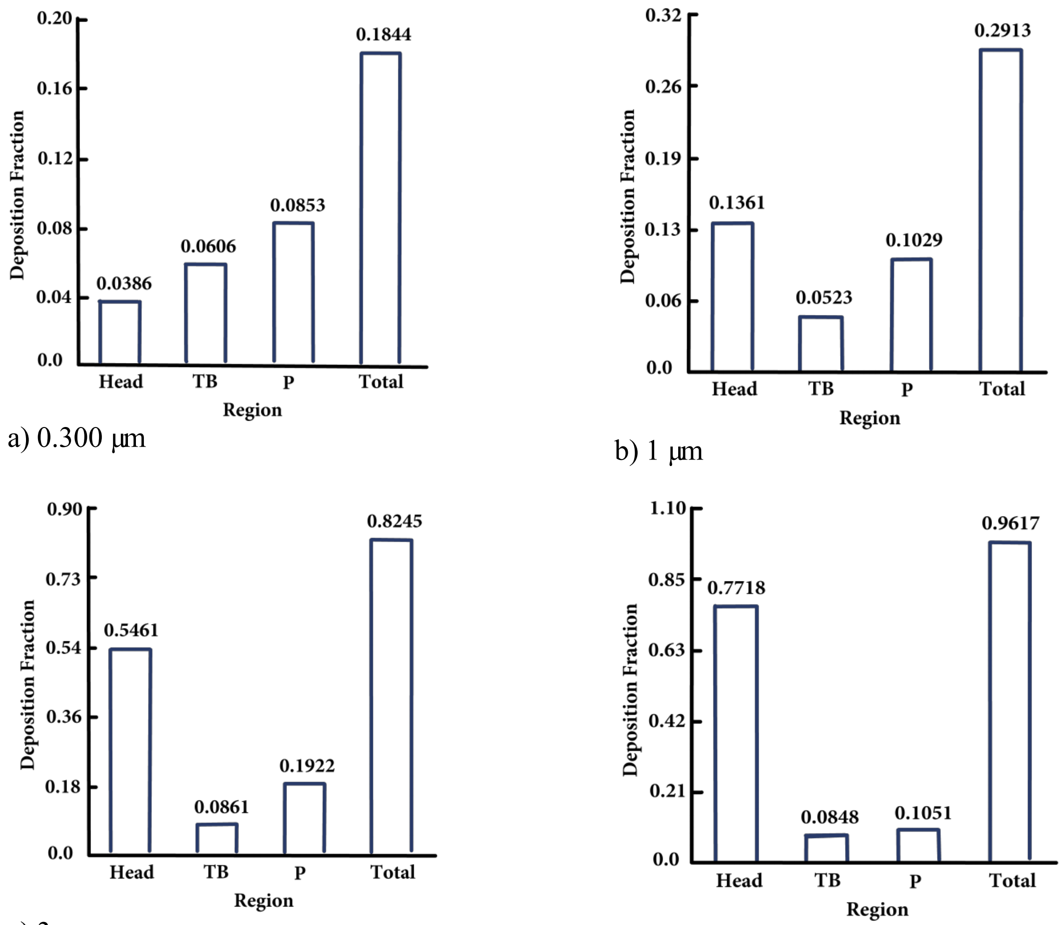
1.4 Upper airways are target area of influenza viruses: Is it additional problem for target virus delivery via ultrafine and fine bioaerosols?

Due to the fact that the most human influenza viruses predominantly infect the upper airways (we do not consider in this part of the study the avian influenza and pneumonia) (van Riel et al., 2007; 2010; Ettensohn et al., 2016). We suggested that the first step of virus infections is the deposition of influenza viruses on the epithelial cells of upper airways (see remark below #about virus attach).

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. Under normal conditions the deposition rate about 4% (for 0.3 µm) - it is dramatically much smaller than deposition rate for the lungs, that is also confirmed by (Hinds, 1999; Oberdorster et al., 2005; Tellier, 2009; Hoppentocht et al., 2014; Jinxiang et al., 2015).



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).
Breathing parameters. Tidal volume:624ml. Breathing frequency: 12l/min. Geometric standard deviation of 1. Concentration: 1 mg/m3. Other parameters were the default values.

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Thus, under normal environmental conditions the probability of virus and bacteria deposition on epithelial cells of upper respiratory tract is very small. Further in the study the special attention is paid to the aspects of "target" delivery/deposition of fine and ultrafine bioaerosols in the upper airways under different environmental conditions (it is the most important aspect of the study and it is "the base" for a new hypothesis of influenza seasonality). See also remark "about the infectious doses and exposure" (above).

Remark

1 About cells cooling

There is an opinion that it is caused by the upper airway during respiration are critically cooled by inhaled cold/cool air and it lead to the reduction of antiviral response, the inhibition of mucociliary clearance and cold stress of the cells (Tyrrell and Parsons, 1960; Salah et al., 1988; Eccles, 2002b; Mourtzoukou and Falagas, 2007; Makinen et al., 2009; Foxman et al., 2015; 2016).

Foxman et al. (Iwasaki lab) (Foxman et al., 2015) clearly shown the mechanism of reducing the immune response of cells of the respiratory tract of mice during cooling of cells. The ability of various strains of rhinoviruses replicate more better in the respiratory epithelial cells at 33 °C than at the normal lung temperature of 37 ° C (the cooling process of respiratory epithelial cells is associated with influenza and common cold). Some similar data can also be found in (Tyrrell and Parsons, 1960; Eccles, 2002; Mourtzoukou and Falagas, 2007; Makinen et al., 2009; Foxman et al., 2016). In 2016 Foxman et al. published new results on rhinovirus infection in human bronchial epithelial cells and H1-HeLa cells and clearly shown the role of cells cooling in the host cell antiviral restriction mechanisms (restriction mechanism operating more effectively at 37°C than at 33°C).

2 (about virus attach)

Human influenza viruses attached more strongly to human trachea and bronchi (van Riel et al., 2007; 2010; Ettensohn et al., 2016). Most strains of rhinovirus and the common cold virus, replicate better in the nasal cavity (Foxman et al., 2015; 2016). And pattern of viral attachment of avian influenza is rare in the trachea and increased progressively toward the bronchioles(van Riel et al., 2007).

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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 present study (the main hypothesis):

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

- supersaturation in the airways leads to the intensive condensational growth of inhaled fine and ultrafine bioaerosol (and viruses and bacteria) in the respiratory tract;

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

<u>Summary (discussions on this matter see below):</u>

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 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 and freely/easily/effectively deposit on epithelial cells of the respiratory tract.

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 (some information see in (Martonen et al., 1982; Ferron et al., 1984; Zhang et al., 2006; Martonen et al., 1985; Li and Hopke, 1993; Robinson and Yu, 1998; Longest and Hindle, 2011; Vu et al., 2015; Winkler-Heil et al., 2014; Grasmeijer et al., 2016)).

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) (Martonen et al., 1982; 1985; Li and Hopke, 1993; Robinson and Yu, 1998; Longest and Hindle, 2011; Vu et al., 2015; Winkler-Heil et al., 2014; Grasmeijer et al., 2016; Vu et al., 2016).

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.

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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.

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 (Zhang et al., 2006; Longest et al., 2011; Jinxiang et al., 2015).

2.3 When the supersaturation occurs 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 in the respiratory tract (RH in the lungs always <100%) (Ferron et al., 1984; Longest et al., 2011; Jinxiang et al., 2015; Golshahi et al., 2013; Winkler-Heil et al., 2014). And under these conditions the particle growth by condensation is insignificant and probability of deposition of fine and ultrafine particles (and 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 when breathing air (see next sections). The supersaturation is possible in the nasal turbinate region and upper airways, it has been shown in (Ferron et al., 1984; Longest et al., 2011; Jinxiang et al., 2015; Golshahi et al., 2013; Winkler-Heil et al., 2014).

2.3.1 Breathing hot and warm saturated air

Longest et al have shown in a series of studies (Longest and Hindle, 2011; Longest et al., 2011; Kim et al., 2013; Jinxiang et al., 2015) that supersaturation (RH>100%) occurs in the human airways when breathing hot/warm saturated air of temperature above of 40°C; they did improve a drug delivery efficiency of the submicron and ultrafine particles to the upper airways under these conditions. Longest and Xi (Worth Longest and Xi, 2008) considered the mechanism of deposition of cigarette smoke in upper airways, when initially 200 nm and 400 nm particles to increase in size due condensational growth in the airways to above 3-8 μm near the trachea inlet. The same results obtained by Xi in (Jinxiang, Xiuhua and Jong, 2015) for submicron particles when inhaling saturated air of 47°C.

2.3.2 Breathing cold/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/cool air.

The effect of supersaturation in the respiratory tract when breathing cold/cool air was pointed by (Ferron, Haider and Kreyling, 1984; 1985; Zhang et al., 2006b; Longest, Tian and Hindle, 2011).

Ferron et al (Ferron, Haider and Kreyling, 1984) have determined the local supersaturation in the lungs under conditions of inhaled cold/cool 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/cool air (less than 10˚C) and nearly saturated air of 20˚C, RH=100%.

Longest et al (Longest, Tian and Hindle, 2011) have pointed that supersaturation can occur in the lungs like the supersaturation 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, Kleinstreuer and Kim, 2006b) based on the numerical calculations 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 (based on a systematic literature review) 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**			
47˚C	100%	>=101%	**up to 17.5** (for hydroscopic particles of 0.2 μm)	(Jinxiang et al., 2015)
20˚C	60%	<100%	**no effect**	(Ferron et al., 1984; Longest et al., 2011; Jinxiang, Xiuhua and Jong, 2015; Golshahi et al., 2013; Winkler-Heil et al., 2014)
21.8˚C	97.5%	101%	**2.5** (for hydroscopic particle of 0.9 μm)	(Longest, Tian and Hindle, 2011)
20˚C	100%	102	**4** (for dry NaCl particle with an aerodynamic diameter of 0.3 μm)	(Ferron, Haider and Kreyling, 1984)
10˚C	80%	104%	**---**	(Zhang et al., 2006)
10˚C	50%	105%	**5** (for dry NaCl particle with an aerodynamic diameter of 0.3 μm)	(Ferron, Haider and Kreyling, 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, Haider and Kreyling, 1984)

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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 18˚C (Lipsitch and Viboud, 2009; Tamerius et al., 2011; Shaman et al., 2011; Tamerius et al., 2013)*);

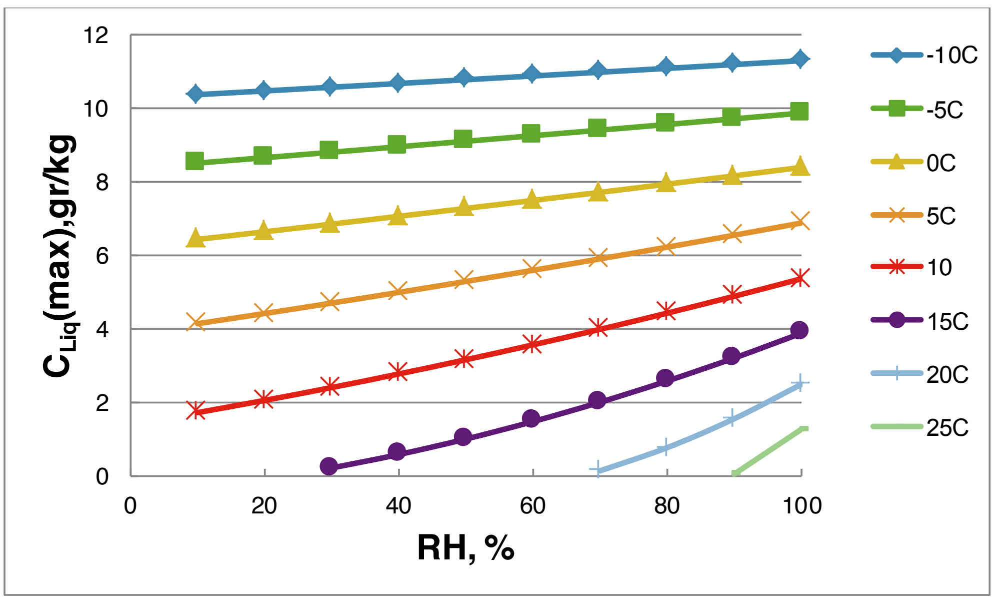
- supersaturation in the airways occurs when flu seasons in the tropical climate *(note: influenza seasons when rainy seasons; when the RH of environmental air rise to saturated conditions and air temperature falls below 25˚C (Viboud et al., 2006; Lipsitch and Viboud, 2009; Moura et al., 2009; Tamerius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

Remark:

It is the first observation of such sort – I have not found any such observation in any studies and researches (see search strategy and table 2 in the end of the manuscript).

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 the psychrometric chart may be used (Mollier's chart. It is widely-used as the tool for determining of isobaric psychrometric processes of moist air (Barenbrug, 1974; Siemens Switzerland Ltd HVP, 2016; Shaviv, 2015)). The results of preliminary estimation are presented in fig3.



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 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, %.

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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 also 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/cool 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/cool inhaled air (for information: volume of inhaled air is 500cm3; 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 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 (McFadden et al., 1982; Jinxiang et al., 2015; Grasmeijer et al., 2016)).

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 in the upper respiratory tract.

3.2 Supersaturation and target deposition of fine bioaerosols in the lungs

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

Fig 3d (reprinted from (Jinxiang, Xiuhua and Jong, 2015)) shows the intensive deposition of the fine particles in the upper airways due to condensational growth under supersaturated conditions. Fig 3c shows that even slightly oversaturated conditions (see data on supersaturation in fig2) may 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 bioaerosols when supersaturation occurs in the lungs when breathing cold/cool air (breathing cold/cool air leads to the supersaturation like breathing hot air – see above fig2 and table1).

It is important to note that similar calculations for inhalation of cold/cool air were not conducted (we did not found any data). The some information can be found in (Ferron et al., 1984; 1985; Zhang et al., 2006; Longest et al., 2011).

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

As mentioned above the supersaturation in the airways when breathing cold/cool or hot/warm saturated air leads to the intensive condensational growth of the inhaled particles. Here the results of the estimation for inhalation hot/warm saturated air (Worth Longest and Xi, 2008; Jinxiang et al., 2015) 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*).

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

Xi et al (Worth Longest and Xi, 2008; Jinxiang et al., 2015) 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 under supersaturated conditions to rise up by ***400%***; 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* ***97%*** *as for particles of 7-8 µm – see above fig1*).

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// PLEASE FINDE THE FIG IN

1 *(Jinxiang, Xiuhua and Jong, 2015) Heat Transfer and Fluid Flow in Biological Processes / editors: Sid Becker and Andrey Kuznetsov /chapter 5: Characterizing Respiratory Airflow and Aerosol Condensational Growth in Children and Adults Using an Imaging-CFD Approach, by Jinxiang Xi, Xiuhua A.Si and Jong, , W.K., P.125-155*
Page 141/ fig 5.9
http://www.sciencedirect.com/science/article/pii/B9780124080775000055

2 THE SAME FIG AND ESTIMATIONS FOR CHILDREN CAN BE FOUND IN OPEN ACCCESS
Jong Won Kim, Jinxiang Xi, Xiuhua A. Si Hygroscopic Growth of fine Aerosols in the Nasal Airway of a 5-year-old Child // in Risk Assessment and Management // Publisher: Academy Publish // Publish date: 2012-11-03 // ISBN: 978-0-9835850-0-8 // Editor: Prof. Zhang // P 312-325.
page 317 / fig 4
page 318 / fig 6
http://www.academypublish.org/papers/pdf/454.pdf

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3 See also the same fig in

Kim, J. W., Xi, J. and Si, X. A. (2013), Dynamic growth and deposition of hygroscopic aerosols in the nasal airway of a 5-year-old child. Int. J. Numer. Meth. Biomed. Engng., 29: 17–39. doi:10.1002/cnm.2490

Fig 8 and Fig 10

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Fig 3. Particle condensation growth and surface deposition in the adult nasal airway under four psychrometric 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)*

Reprinted from: (Jinxiang, Xiuhua and Jong, 2015) Heat Transfer and Fluid Flow in Biological Processes / editors: Sid Becker and Andrey Kuznetsov /chapter 5: Characterizing Respiratory Airflow and Aerosol Condensational Growth in Children and Adults Using an Imaging-CFD Approach, by Jinxiang Xi, Xiuhua A.Si and Jong, , W.K., P.125-155, Copyright (17 june 2016: License Number: 3891311134700 for Alex Ishmatov), with permission from Elsevier.

3.3 Supersaturation in the airways and two patterns of influenza seasonality

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 common colds were observed globally by many explorers: "cold-dry" type (for temperate climate) and "humid-rainy" type (for tropical countries) (Viboud et al., 2006; Lipsitch and Viboud, 2009; Moura et al., 2009; Tamerius et al., 2011; Shaman et al., 2011; Tamerius et al., 2013). The main difference consists in the problem of influence of the humidity of the air on the seasonality of influenza in different climatic condition.

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 (The Eurowinter Group, 1997; Lofgren et al., 2007; Mourtzoukou and Falagas, 2007; Lipsitch and Viboud, 2009; Tellier, 2009; Shaman et al., 2011; Tamerius et al., 2013; Foxman et al., 2015)). See also the panel 'Search strategy' and table2 (in the end of the manuscript). 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 pattern)

In accordance with (Gregg et al., 1978; The Eurowinter Group, 1997; Lofgren et al., 2007; Falagas et al., 2008; Bishop et al., 2009; Makinen et al., 2009; Shaman et al., 2010; 2011; Elert, 2013; Centers for Disease Control and Prevention., 2015): 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}) may reach of [0·2..12·1]g/kg. Under these conditions the growth of inhaled particles (viruses or bacteria) by condensation in the respiratory tract may be 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/cool air and may be 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 respiratory viruses in the air by airborne route (Lowen et al., 2007; Halloran, Wexler and Ristenpart, 2012); and low temperatures are favorable for the emergence of the effects 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.

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Note:

I have to make remarks here.

1. Respiratory cells cooling

Additional processes of cooling of respiratory cells when breathing cold/cool air should be taken into account. As mentioned above (section 1.4), the cooling (from 37°C to 33°C) of the respiratory cells leads to the critical reduction of the immune response of epithelial respiratory cells.

Also the inhibition of mucociliary clearance by the inhalation of cold-dry air (Salah et al., 1988) should be taken into account. It is evident that the time during which there is an influence of the 'bad conditions' on the respiratory tract can play an important role (see also remark regarding the infectious doses and exposure in the beginning of the manuscript). The more attention will be given to the cooling process in the next parts of the study (see "Afterword" and "Potential partnership" sections in the end of the manuscript). Some aspect were discussed in (Ishmatov, 2016).

2. Remark on body cooling and immune function

For countries with temperate and cold climates there is opinion (cite from (Ikaheimo et al., 2016)) that cooling of the body surface and even acute chilling of the feet could elicit a reflex of vasoconstriction in the nose and upper airways, inhibit the respiratory defense and convert an asymptomatic subclinical viral infection into a symptomatic clinical infection (Eccles, 2002; Johnson and Eccles, 2005).

But as mentioned in (Ikaheimo et al., 2016) there is no clear association between immune function and cold exposure of body. Douglas et al (Douglas Jr and Lindgren, 1968) demonstrate that there was no evidence altered host resistance to cold virus as a result of whole-body cold exposure.

***3 (!!!) Remark** on virus survival and aerosol transmission (question on humidity)*

Relative humidity is major factor in airborne transmission of pathogens. The more low humidity the more effective the airborne transmission (low humidity lead to the fast evaporation of droplet. Droplets decreases in sizes and may be transmitted over long distance) (Lowen et al., 2007; Halloran et al., 2012).In some studies was pointed that relative humidity affects the virus survival (see review in (Shaman and Kohn, 2009; Shaman et al., 2011; Ikaheimo et al., 2016)).

It is pointed that influenza virus survival increases as RH decreases, such that the airborne virus remains viable longer at lower relative humidity (Shaman and Kohn, 2009).Even a bimodal pattern has been suggested with altered virus survival and transmission in different climatic conditions: very low humidity for cold and temperate climates (survival is high) and high humidity for tropics (pathogens survival is high too) (Tamerius et al., 2013).

Although in (Ikaheimo et al., 2016) an association between humidity and human rhinovirus infections were not observed.

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

In the tropics and subtropics, flu season driven by the high humidity or the heavy monsoon rains (Tamerius, Shaman, Alonso, Alonso, Bloom-Feshbach, Uejio, Comrie and Viboud, 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'.

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Data form table1 and fig2 (see above) shown that probability of supersaturation under conditions of 'humid-rainy' pattern of seasonality of influenza 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 may be 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 fine and ultrafine particles (and viruses or bacteria) by condensation in the respiratory tract can occur, and the probability of deposition of virus or bacteria on the epithelium of the respiratory tract is high.

Remark on virus spreading in tropics

However, outbreaks of influenza were not observed in regions comparable in strength to the cold ones (in 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 (Note: this aspect raises questions in most studies) (Lowen et al., 2007; Halloran et al., 2012). In my opinion, the mechanism of the virus transmission in tropics occurs or by the fine and ultrafine bioaerosols when close contacts occurs (distance at 'arm's length'; see also remark regarding the infectious doses and exposure in the beginning of the manuscript; 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 environmental conditions (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 fine and ultrafine bioaerosols (virus or bacteria) on the epithelium of the respiratory tract is low. This conclusion is also confirmed by (Ferron et al., 1984; Longest et al., 2011; Jinxiang et al., 2015; Golshahi et al., 2013; 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. I think as due from above the probability of infection is correlated with probability of deposition of viruses on epithelial of respiratory tract. The experimental study on airborne transmission of influenza viruses between guinea pigs (Lowen et al., 2006; 2007)may be used for more information – in that study the experimental data on probability of infections of animals presented by Lowen et al.

Conclusion

Main points of the part I:

1 Breathing cold/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 fine and ultrafine bioaerosols (and viruses or bacteria) in the respiratory tract.

3 Intensive condensational growth leads to the dramatically growth/rise of the deposition rate of the fine and ultrafine bioaerosols (and viruses or bacteria) in the upper airways (up to 4x for upper airways) and full deposition of fine bioaerosol in the lungs can reach 97%.

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

Thus we have originally shown the delivery and deposition of fine and ultrafine bioaerosols (and viruses or bacteria) in the respiratory tract connected with environmental conditions: in flu seasons the deposition rate of these bioaerosols in the human airways can dramatically rise from 3%..20% (for normal conditions) up to 97% (when flu seasons).

Thus the present study has originally shown for the first time the next important observation. 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 cold/cool air. It may have great value for understanding of 'the age-old epidemiologic mystery of influenza seasonality' in the different climatic conditions.

Some aspect were discussed in (Ishmatov, 2016; Ishmatov, 2016b).

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

Future directions

<u>The next parts of the study will be posted in near feature:</u>

part II: Concept of open door in the airways and critical reduction of the antiviral immune defense of epithelial respiratory cells;

part III: Concept of open door and critical changes in physical and chemical environment inside the lungs;

part IV: Concept of open door and infections of the lower airways (Pneumonia);

part V: Aspect of the climatic factors in the statistical study of cases of influenza in the countries with 'borderline' climate (And some aspects of epidemiology in "European migrant crisis").

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

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I believe the supersaturation in the airways is very important for environmental health risks (as high risk of deposition of fine and ultrafine aerosols in the lungs), asthma, COPD and other respiratory diseases.

I believe the effects of supersaturation in the lungs can dramatically change the current views on air pollution by ultrafine aerosols and their deposition in the lung under various weather conditions.

Moreover, 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 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 and respiratory 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 (mist formation occur by condensational growth when cool air enters throw the door in the hot and humid environmental air). Therefore, I called this effect the "The concept of open door". Metaphorically, this effect "opens the door" of the immune system to respiratory infections and influenza.

PS2

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

***Search strategy and selection criteria**

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

Table 2

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**) (Gregg et al., 1978; Bishop et al., 2009; Shaman et al., 2010; 2011; Elert, 2013; Centers for Disease Control and Prevention., 2015)	**local rainy season (without well-defined influenza seasons)** (Viboud et al., 2006; Lipsitch and Viboud, 2009; Moura et al., 2009; Tamerius et al., 2011; Shaman, Goldstein and Lipsitch, 2011; Tamerius et al., 2013)
3	**Decreased exposure of solar radiation vitamin D deficiency** (Dowell, 2001; Cannell et al., 2006; Ginde et al., 2009; Camargo et al., 2012)	**not associated**
4	**Inhibition of mucociliary clearance by the inhalation of cold-dry air** (Salah et al., 1988; Eccles, 2002)	**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: <u>airborne</u>** (Edwards et al., 2004; Fabian et al., 2008; Chen et al., 2009; Tellier, 2009; Milton et al., 2013; Cowling et al., 2013; Lindsley et al., 2016; Killingley et al., 2016)	**not clear**
7	**Respiratory cells cooling** (Tyrrell and Parsons, 1960; Eccles, 2002; Mourtzoukou and Falagas, 2007; Makinen et al., 2009; Foxman et al., 2015)	**not clear**
	'Effect of supersaturation and condensational growth in the airways' **<u>Effect Occurs</u>** (Common reason of Flu Seasons for two pattern of seasonality) T < +18˚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***); **<u>No Effect</u>** T>20˚C; RH<60% (normal conditions – no effect – no influenza)	

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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 and discussed my ideas; Anna Shandenkova for help in English.

Potential partnership

I open for suggestions (numerical calculation and models; in vivo and in vitro experiments; epidemiology; preventive of influenza and common colds).

Contact me directly if you have any questions.

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