On the connection between supersaturation in the upper airways and «humid-rainy» and «cold-dry» seasonal patterns of influenza

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Abstract

We have originally shown for the first time the two different climatic patterns of seasonality of influenza and common colds have an only one common "link". It is the effect of supersaturation and condensational growth in the upper airways which occurs under specific environmental conditions when flu seasons take place in the tropical/subtropical and temperate regions.

We have found that under climatic conditions which are peculiar to the seasonal patterns of influenza and common colds ("humid-rainy" and "cold-dry") the effect of supersaturation and condensational growth may be additional factor/reason leading to the next:

- dramatic rise of deposition rate of infectious agents from inhaled air in the upper airways;
- additional acidification of epithelial lining fluid in the local areas of the respiratory tract, and, as a result, may lead to destructive impacts on host cells and weakening of the defense mechanisms of the airways;
- additional affecting on the critical local cooling and reducing (as a consequence) the antiviral immune response of the airway epithelial cells.

Thus, the effect of supersaturation and condensational growth in the upper airways can act as a common trigger for influenza, common colds and other respiratory infection in both mid-latitudes and in the tropics/subtropics.

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Introduction

For over a hundred years scientists have come up with multiple hypotheses on why influenza outbreaks are so strongly tied to the calendar. So far there is no clear understanding and explanation for the whole pattern of the seasonality of respiratory infections. Two distinct types of climatic conditions associated with influenza and common colds were observed globally by many explorers: "cold-dry" (for temperate climate) and "humid-rainy" (for tropical countries). The main difference consists in the specific effect of humidity and temperature on the pronounced seasonality of influenza and common colds (Viboud et al., 2006; Lipsitch and Viboud, 2009; Moura et al., 2009; Tamerius et al., 2011; Shaman et al., 2011; Tamerius et al., 2013; Deyle et al., 2016). The main factors/reasons affecting the influenza seasons in the world are listed in the **table1**.

Table 1 Factors/reasons affecting the influenza seasons in the world (Ishmatov, 2016c)

	Cold-Dry	Humid-Rainy
1	Relatively Humidity(RH) < 60%; T = -15C.. +15C; (Relatively Absolute Humidity<7g/kg)	Relatively Humidity(RH)>70%; T = +17C..+25C (Absolute Humidity>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 et al., 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: airborne** (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	**Oppression of immune response due to respiratory cells cooling** (Tyrrell and Parsons, 1960; Eccles, 2002; Mourtzoukou and Falagas, 2007; Makinen et al., 2009; Foxman et al., 2015)	**not clear**

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Thus, low temperatures and low humidity are key climate predictors of influenza seasonality in the countries with temperate climate (influenza outbreaks occur at the temperatures of T<+15°C and at low humidity RH<60%); and rainy seasons is key climate predictor of influenza seasonality in tropical and subtropical regions (influenza outbreaks driven by the high humidity (RH>80%) and occur during the rainy season or transmit year-round without a well-defined season (Tamerius et al., 2013)).

It is pointed that humidity affects the virus survival: survival of influenza and respiratory viruses increases as humidity decreases, such that the airborne virus remains viable longer at lower humidity (see reviews in (Shaman and Kohn, 2009; Shaman et al., 2011; Ikaheimo et al., 2016; Deyle et al., 2016)). Even a hypothesis of U-shaped relationship between humidity and virus viability has been suggested (with altered virus survival and transmission in different climatic conditions): low humidity for cold and temperate climates (survival and airborne transmission is high) and high humidity for tropical and subtropical regions (pathogens survival is high but the transmission route rises a questions(Tamerius et al., 2013)) (Lowen and Steel, 2014; Gustin et al., 2015; Yang et al., 2012; Deyle et al., 2016). However, contradictions in the literature on the relationship between humidity and virus survival (especially for high humidity and for tropical and subtropical regions) remains unexplained and controversial as other studies reported (Shaman and Kohn, 2009; McDevitt et al., 2010), see also the literature review in(Yang and Marr, 2012; Yang, Elankumaran and Marr, 2012).

Here I do not list all of the existing theories and hypotheses of seasonality of respiratory infections and influenza, but the one thing we can say – there is no a reliable theory of the seasonality of influenza in tropical/subtropical countries nor a unified theory for all regions and for wide climatic conditions (temperate zone, tropics, subtropics). It is the **age-old epidemiologic mystery of influenza seasonality** in the different climatic conditions: '*Why the disease is the same one but the etiology and epidemiology for different climatic conditions are different*?'

1 Connecting link for the two climatic patterns of influenza seasonality

Based on detailed analysis (Ishmatov, 2016c; 2016a; 2016b) I have found that exactly the effects of supersaturation and condensational growth in the upper airways, that have place when breathing cold/cool air, may be the common/connecting link for the two climatic patterns of influenza seasonality in temperate, tropical and subtropical regions.

supersaturation and condensational growth in the airways occurs when flu seasons in the temperate climate (*note: «cold-dry» seasonal pattern – when a temperature of the air below 15˚C and RH<60% (Lipsitch and Viboud, 2009; Tamerius et al., 2011; Shaman et al., 2011; Tamerius et al., 2013)*);

supersaturation and condensational growth in the airways occurs when flu seasons in the tropical and subtropical climate *(note: «humid-rainy» seasonal pattern – when rainy seasons and RH rise up 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).*

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The known data (based on systematic literature review in (Ishmatov, 2016c)) on the supersaturation and condensational growth in the upper respiratory tract under different conditions of inhaled air are listed in the table1.

Table 1 Supersaturation and condensational growth in the airways under different environmental conditions (Ishmatov, 2016c)

Inhaled air		**Maximum of RH(%) in the airways**	**Growth factor of inhaled particles**	**Ref.**
T,˚C	**RH**			
47˚C	100%	>=101%	**up to 17.5** (for hydroscopic particles of 0.2 μm)	(Ferron et al., 1988)
20˚C	60%	<100%	**no effect of supersaturation and condensational growth**	(Ferron et al., 1984; Longest et al., 2011; Jinxiang et al., 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)

2 Why are supersaturation and condensational growth in the airways so important?

The **connection/correlation** between supersaturation and condensational growth in the upper airways and «humid-rainy» and «cold-dry» seasonal patterns of influenza and common cold may be found from the table2. And this observation/finding is very important.

Precisely the effect of supersaturation and condensational growth is(may be) the only common link between the two seasonal patterns of influenza. The effect depends simultaneously (at the same time) on both temperature and humidity of inhaled air. ***Thus, temperature and humidity are the parameters of one simple function*** (it is effect of supersaturation and condensational growth) and now we can use this function to analyze the correlation between climatic parameters and seasonal patterns of influenza. That is, no

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longer need to consider the separately influence of humidity or temperature on correlation with «humid-rainy» and «cold-dry» seasonal patterns of influenza. Moreover, even the differentiation of absolute and relative humidity as environmental drivers of influenza seasons (Deyle et al., 2016) no longer need to consider.

From this point of view the controversial hypothesis of U-shaped relationship between humidity and virus viability (Shaman and Kohn, 2009; McDevitt et al., 2010) can be revised as a hypothesis of U-shaped relationship between humidity and supersaturation (and condensational growth) in the upper airways.

2.1 Supersaturation and condensational growth as additional factor of transmission of respiratory viruses

As we have originally shown in (Ishmatov, 2016c) the risk of respiratory infections during cold seasons (in temperate climates) and rainy seasons (in tropics) has the additional factor for dramatic rise. It is the factor of high deposition rate of infectious agents from inhaled air into the respiratory tract due to the supersaturation and condensational growth in the upper airways. The deposition of infectious bioaerosols in the airways is clearly and strongly connected with climatic factors: the deposition rate may dramatically rise from **3%..20%** (for normal conditions) up to **96%** when flu seasons take place in the tropical and temperate regions.

Thus, the supersaturation and condensational growth may be additional major factor/reason for transmission and deposition of infectious agents in the upper airways.

It is important to understand that as mentioned by professor Ferron in 1988 (Ferron et al., 1988): "*Supersaturation occurs only in small areas in airways cross sections in the trachea and upper bronchi. Not all of the particles will see this supersaturation*."

2.2 Supersaturation and condensational growth as additional factor of critical cooling and reduction of antiviral immune response of airway epithelial cells

There is an opinion that airway epithelial cells are critically cooled by inhaled cold/cool air and it lead to the cold stress of the cells, the reduction of antiviral response of the cells, the inhibition of mucociliary clearance and phagocytic activity (Tyrrell and Parsons, 1960; Eccles, 2002; 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 antiviral immune response of airway epithelial cells of mice: the ability of rhinovirus strains replicate more robustly in the cells at cooler temperature (33°C) than at core body temperature (37°C). The similar data were published in 2016 by Foxman et al. (Tyrrell and Parsons, 1960; Eccles, 2002; Mourtzoukou and Falagas, 2007; Makinen et al., 2009; Foxman et al., 2016) where was clearly shown the role of cooling of human bronchial epithelial cells in the host cell antiviral restriction mechanisms: restriction mechanism operating more effectively at 37°C than at 33°C. Thus, the cooling of airway epithelial cells may be associated with influenza and common cold.

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It is commonly believed that heat and mass transfer in the airways occurs by convection (is the dominant form of heat and mass transfer in the upper airways) and conduction (is the dominant form of heat and mass transfer in the lower airways) (see reviews in (Hunt, 2006; Fischer and Widdicombe, 2006; Clary-Meinesz et al., 1998)). But one additional affecting factor is never taken into account: it is the factor of supersaturation in the human airways when breathing under specific environmental conditions.

The existing literature (Ferron et al., 1984; Zhang et al., 2006; Longest and Hindle, 2011) (see also review in (Ishmatov, 2016)) states that the processes of supersaturation and condensation growth take place in the nasal cavity and further into the upper airway. As was mentioned in (Ferron et al., 1988) precisely this effect may to explain the enhanced transport of heat and water vapor in the human upper respiratory tract.

Why the supersaturation and condensational growth can greatly impact the heat and mass transfer in the upper airways?

Supersaturation (supersaturated vapor) is boundary conditions of phase transition from a vapor to a liquid phase. A water vapor in the upper airways may spontaneously begin to condense in the presence of nucleation centers; in other words, the vapor begins to change to tiny water droplets (liquefaction of vapor).

Due to the above the liquid droplets may lead to intense exposure of the epithelial cells to the cold in local areas of the upper airways. The topicality of this consideration is caused by the fact that the heat transfer through the liquid droplets may be significantly more effective than convection and conduction in gases (which as was previously believed is the dominant form of heat and mass transfer in the airways). In other words, such droplets can act as an effective additional transport for "cold" in the respiratory tract and lead to the intensive cooling of the airway epithelial cells in contact with such droplets, which creates conditions for the oppression of the immune response of cells to viruses and infections.

Thus, the effects of supersaturation and condensational growth may be an additional major factor affecting on critical local cooling and reducing (as a consequence) the antiviral immune response of airway epithelial cells under specific environmental conditions when flu seasons take place in the tropical and temperate regions.

2.3 Supersaturation and condensational growth as additional major factor affecting the airway surface pH reduction

We hypothesize the next

Supersaturation and condensational growth lead to liquefaction of water vapor in the upper airways (see above). The specific conditions in the airways lead to formation of liquid droplets with high concentration of carbon dioxide (CO2) and as a consequence it leads to high acidity of droplets (low pH). Thus, the deposition of these droplets on the airway surface may lead to additional acidification of epithelial lining fluid in the local areas of the airways.

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2.3.1 On the airway pH

Airway pH (logarithm of inverse concentration of H+) is central to the physiologic function and cellular biology of the airway. Even a very mild airway acid (pH reduction) insult triggers cough, bronchospasm, and neurogenic inflammation mediated by vagal c fibers and other pathways (Hunt, 2006). The pH reduction (in healthy airways pH~6.6 (Fischer and Widdicombe, 2006) is a main feature of inflammatory respiratory diseases and plays a role in bronchoconstriction, impaired ciliary function (and ciliary beat frequency in the upper respiratory tract (Clary-Meinesz et al., 1998)), increased airway mucus viscosity (Holma and Hegg, 1989), and in turn can enhance inflammation and airway dysfunction (Ricciardolo et al., 2004; Hoffmeyer et al., 2015).

2.3.2 On the pH of droplets and weakening of airway defense mechanisms

Breath (exhales air) is strongly enriched with carbon dioxide (CO2) relative to ambient air. CO2 is a volatile gas that is a precursor to carbonic acid. In aqueous environments, CO2 is hydrated to carbonic acid, which subsequently dissociates to H+ and HCO3-. Therefore, CO2 leads to a substantial acidification (pH reduction) of the formed droplets in such specific conditions (Davis and Hunt, 2012). Hoffmeyer et al (Hoffmeyer et al., 2015) have found that in conditions of exhaled air the pH of exhaled breath condensate is pH 5.5 -6.5 (pH[neat]) and pCO2 (pCO2[neat]) were experimentally determined immediately (within 1 min) in an aliquot of the EBC sample (55 µL)).

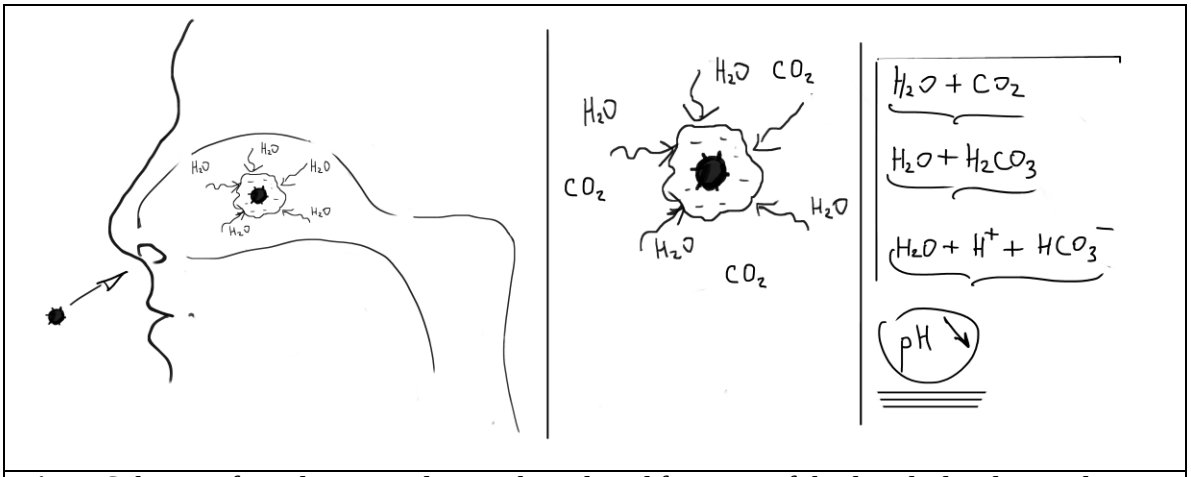

Fig.1. Scheme of condensational growth and acidification of the liquid droplets under conditions of presence of carbon dioxide in the upper airways

Thus, the effects of supersaturation and condensational growth in the upper airways may lead to the formation of liquid droplets and their pH is likely to be acidic. Localization of the effects in the upper airways (see above and review in (Ishmatov, 2016c)) may lead to additional acidification of epithelial lining fluid in the local areas of the airways. As a result, ***the supersaturation and condensational growth in the upper airways may lead to additional destructive impacts and may play a role of trigger in an additional weakening of the defense mechanisms of the airways: enhance inflammation, airway dysfunction, bronchoconstriction, impaired ciliary function, increased airway mucus viscosity***.

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Remark

It should be noted the fact that we could not find the information on direct measurements of the acidity of droplets which were formed in the respiratory tract due condensational growth. The estimate of pH of formed droplets in the airways is a simplification. The real pH may be far more complicated due to interactions between different solutes, influence of the chemical components of the surrounding air and air inside the tract and etc. With regard to the above, such measurements are necessary to conduct. And it is important to take into account the additional chemical impact of the presence of various chemical compounds both in the surrounding air and in the air inside the respiratory tract. All of these require further scientific study.

Future directions

I believe the next directions for research are very important to carry out in near future:

1 *Empirical dynamic modeling to elucidate role of the effect of supersaturation and condensational growth in the upper airways (as a simple function of humidity and temperature) in explaining and forecasting the seasonality and dynamics of influenza and respiratory infections at the local, regional, and global scales.*

2 *Replication efficiency, pathogenicity, and transmissibility of influenza viruses under short-term exposition to acidic and cold stress in the upper airways (due to the effects of supersaturation and condensational growth).*

**Short-term exposure: the exposure to acidic stress in the epithelial lining fluid in the local areas of the airways will exist as long as there is the effect of condensational growth while breathing cold air (under normal environmental conditions the effects do not exist –see above).*

3 *The effect of supersaturation and condensational growth as a risk factor for COPD and asthma and other respiratory diseases.*

* As was mentioned above the airway pH is central to the physiologic function and cellular biology of the airway. Even a very mild airway pH reduction insult triggers cough, bronchospasm, and neurogenic inflammation (Hunt, 2006; Fischer and Widdicombe, 2006). The pH reduction is a main feature of inflammatory respiratory diseases and plays a role in bronchoconstriction, impaired ciliary function (Clary-Meinesz et al., 1998), increased airway mucus viscosity (Holma and Hegg, 1989), and in turn can enhance inflammation and airway dysfunction (Ricciardolo et al., 2004; Hoffmeyer et al., 2015). The some useful data on the incidence of asthma induced by cold air may be found in the studies provided by Millqvist et al (Millqvist et al., 1995b; 1995a).

Conclusion

During seasonal patterns of influenza both in the tropical/subtropical and temperate regions the one common reason/factor for infecting and spreading the respiratory infections exists. It is the effect of supersaturation and condensational growth in the upper airways.

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1 This effect is additional major factor/reason for dramatic rise of deposition rate of infectious agents in the upper airways: the deposition rate of infectious aerosols in the upper airways may rise up to 96% when flu seasons take place in the tropical/subtropical and temperate regions.

2 This effect may be an additional major factor affecting on critical local cooling and reducing (as a consequence) the antiviral immune response of the airway epithelial cells under specific environmental conditions when flu seasons take place in the tropical/subtropical and temperate regions.

3 This effect may be an additional major factor affecting on acidification of epithelial lining fluid in the local areas of the airways and, as a result, may lead to additional destructive impacts on host cells and may play a role of trigger in an additional weakening of the defense mechanisms of the airways: enhance inflammation, airway dysfunction, bronchoconstriction, impaired ciliary function, increased airway mucus viscosity.

The effect depends simultaneously on both temperature and humidity of inhaled air and combines these environmental/climatic parameters into one single function. And it is a new very important function for analyzing the correlation between climatic parameters and seasonal patterns of influenza and other respiratory infections in the world. These findings are of great interest in forecasting and analyzing the respiratory infections dynamics at the local, regional, and global scales.

Thus, we have originally shown for the first time that the effect of supersaturation and condensational growth in the upper airways correlates with «humid-rainy» and «cold-dry» seasonal patterns of influenza, and perhaps the effect is the only one common link between the two seasonal patterns.

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.

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