Impact of rotavirus and hepatitis A virus by worldwide climatic changes during the period between 2000 and 2013

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Abstract:
Enteric viruses are present in the environment as a result of the discharge of poorly or untreated wastewater. The spread of enteric viruses in the environment depend to human activities like stools of infected individuals ejected in the external environment can be transmitted by water sources and back to susceptible individuals for other cycles of illness. Among the enteric viruses Rotaviruses (RV) and Hepatitis A viruses (HAV) is the most detected in wastewater causing gastroenteritis and acute hepatitis. Therefore, it is of interest to climate change, mainly temperature and carbon Dioxide (CO2) variations, on Rotavirus and Hepatitis A as a model of enteric viruses present in the aquatic environment using computational modelling tools. The results of genetic ratio showed a negative correlation between the epidemiological data and the mutation rate. However, the correlation was positive between the temperature, CO2 increase, and the rate of mutation. The positive correlation is explained by the adaptation of the viruses to the climatic changes, the RNA polymerase of the RV induces errors to adapt to the environmental conditions. The simultaneous increase in number of infections and temperature in 2010 has been demonstrated in previous studies deducing that viral pathogenicity increase with temperature increase.

Key words: Carbon dioxide, hepatitis A virus, mutation rate, rotavirus, temperature variations.

Background:
Rotaviruses (RV) are the most Common cause of diarrhea worldwide in children, rotavirus infections are associated to 200,000 deaths in children under 5 years of age in 2013 [1-2]. While hepatitis A virus (HAV) which is known as self-limiting disease, with high public health impact report about 1.300 new cases in 2014 [3-4]. Rotavirus belongs to Reoviridae, it is a double stranded RNA, genus is divided into at least 7 genetic groups or geno groups (A-G). Genogroup A is the most involved in gastroenteritis pathogenicity for both Human and animals [5-6]. Different host species, interspecies transmissions and intra genic recombination
are among the mechanisms responsible of genomic evolution of RV. Also, the accumulation of point mutations constantly in each RVs replication cycle leads to genetic draft [7-10]. And this is caused by the viral-encoded RNA-dependent RNA polymerase (RdRp) being error-prone [11].

Hepatitis A virus or HAV belong to Picornaviridae, spherical, about 30nm of diameter icosaedral capsid surrounding single stranded Monopartite, linear ssRNA(+) genome of 7.478 kb [12-14]. HAV has been initially classified in entero-virus genera in previously studies, although HAV has common characters with other genera of the picorna virus family, it is significantly different and, present unique properties in relation to its genetic structure and replication procedure, that it is classified in hepato-virus genus as a sole species [15]. HAV can infect Human and other primates, only one serotype and six different genetic groups, three isolated from Humans (I, II and III) and three from simian origin (IV, V, VI) have been described [16]. HAV mutation rate is significantly lower as compared to other members of the family Picornaviridae, and replication target and site of liberation of viral particles of HAV.

Rotaviruses (RV) and Hepatitis A virus (HAV) are transmitted mainly by fecal oral route. The contamination of the water represents the major cause of the spread of the virus in the environment. The surface runoff water is contaminated directly by discharge of none or undertreated wastewater or Human and animals swage in rivers or sea. While the underground water is contaminated through the soil by adsorption-desorption phenomenon [17-19]. Evolution and resistance of Rotaviruses (RV) and Hepatitis A virus (HAV) to different inactivation treatments are not depending only on error-prone nature of RV and HAV; also variations of climatic conditions have a major influence on genomic variation of viruses as a form of adaptation. It has been shown that variation of environment temperature have no effect on the prevalence of Rotaviruses; the infections linked to Rotaviruses were the same for all seasons, in winter as well as in summer, and also no correlation has been noticed for the other climatic factors such as rainfall, humidity or wind spread [20]. It is of interest to study the ratio between variation of rate of CO2 and Temperature, as climatic factors influencing on resistance of viruses in environment, and mutation rate on Rotaviruses (RV)and Hepatitis A virus (HAV) in different world areas for the period between 2000 and 2017.

### Table 1: Epidemiological data of Rotaviruses infections in 10 geographical areas, for period between 2000 and 2013

| Year | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | Moy |
|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| Total | 38,984 | 48,069 | 48,652 | 42,450 | 39,686 | 36,195 | 33,923 | 31,687 | 26,266 | 28,073 | 24,682 | 24,763 | 23,984 | 21,846 | 34,750 |

### Table 2: Epidemiology of Hepatitis A virus (HAV) in United Kingdom (UK) and United States of America (USA), variation of global temperature, CO2; and mutation rate between 2004 and 2013

| Year | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 |
|------|------|------|------|------|------|------|------|------|------|------|
| UK   | 753  | 632  | 617  | 605  | 623  | 623  | 403  | 492  | 545  | 477  |
| USA  | 448  | 397  | 297  | 258  | 197  | 167  | 139  | 152  | 179  | 129  |
| T (°C) | 0.57 | 0.65 | 0.64 | 0.64 | 0.63 | 0.7  | 0.7  | 0.62 | 0.7  |
| CO2 (ppm) | 374.88 | 380.62 | 385.22 | 384.05 | 386.56 | 388.33 | 390.14 | 395.31 | 394.19 | 396.74 |
| Ratio Mutation (10^-9) | 0.04 | 0.04 | 0.04 | 0.01 | 0.01 | 0.14 | 0.14 | 0.14 | 0.14 | 0.14 |

### Table 3: Hepatitis A virus sequences collected from database NCBI (National Center for Biotechnology Information) GenBank and used for determination of mutation rate by Mega Software

| Sequence Code | Year | Nomination |
|---------------|------|------------|
| KX052096.1    | 2012 | Hepatitis A virus isolate I881 complete genome |
| JQ652581.1    | 2012 | Hepatitis A virus strain HAS-15 complete genome |
| AB970326.1    | 2012 | Hepatitis A virus gene for polyprotein complete cds isolate: |
| AB970326.1    | 2012 | Hepatitis A virus gene for polyprotein complete cds isolate: |
| KJ699696.1    | 2012 | Hepatitis A virus strain DH01 complete genome |
| KJ871758.1    | 2012 | Tupaiahepatovirus A isolate TNI1 complete genome |
| NC028681.1    | 2012 | Tupaiahepatovirus A isolate TNI1 complete genome |
Methodology:
For this study, data of infections by HAV and RV were collected from CDC Centers for Diseases Control and Prevention websites for 10 regions in the world, Latin America, Central Asia, Eastern Asia, Southeast Asia, Southern Asia, Western Asia, Oceania, Northern Africa and Sub-Saharan Africa during the period between 2000 and 2013 for Rotavirus (Table 1) and between 2004 and 2013 for Hepatitis A virus (Table 2). However, data is limited to countries where infections by HAV and RV are notified. Most data were from United Kingdom (UK) and United States of America (USA) mainly for HAV for the other areas; knowledge web literature was using. For climatic change, rate of global temperature and carbon dioxide, in this study we used data given by NASA Global Climate Change. Global surface temperature relative to 2000-2013 average temperatures (https://climate.nasa.gov/vital-signs/global-temperature/) and global distribution and variation of the concentration of carbon dioxide in parts per million (ppm) (https://climate.nasa.gov/vital-signs/carbon-dioxide/). Data for mutation rate has been collected from previous studies for Rotavirus of a period from 2005 to 2013 [21-24]. While mutation rate of Hepatitis A virus has been studied from database NCBI (National Center for Biotechnology Information) GenBank, 49 sequences of Hepatitis A virus collected was analyzed by MEGA software and mutation rate has been determined (Table 3). The results of mutation rate for both HAV and RV are shown in Table 4.
Results and Discussion:
Results of data analysis have showed negative correlation between number of infections and change of temperature variations and CO₂ rate. The positive correlation have been shown between temperature variations and mutation rate for both viruses Hepatitis A and Rotavirus (Figures 1-2), also a positive correlation is shown between CO₂ and mutation rate in all studied geographical areas (Figures 3 - 4). For Rotavirus the curves of CO₂ and mutation rate are stackable, the mutation rate increase with increase of CO₂ (Figure 3). Variation of temperature and evolution of mutation rate are proportional for both studied viruses. For temperature variation a pick is shown in 2010 in all geographical areas. This study built a comprehensive database of RV and HAV, occurred between 2000 and 2013 in 10 geographical areas for RV and in UK and USA for HAV. Information about global temperature variation and carbon dioxide given by NASA has been also used. Analysis of these data shows a correlation between temperature variations, CO₂ and mutation ratio of both viruses' RV and HAV (Figure 5). The analysis of the epidemiological profiles at the level of the developing and sub-Saharan countries and the climatic parameters (essentially CO₂) shows an inverse relationship between the two parameters, whether at the level of the developed or sub-Saharan countries. Of the period between 2008 and 2012 a dive was observed in both populations but more intensive in the population of the developing countries and which cohere with a temperature increase of the earth's temperature. In order to better exploit this idea, we have to compare to the genomic level, whose mutation rate or the mutation ratio has almost the same speed and slope of the imitated amount of CO₂ and then the deviation of CO₂. According to our results, both viruses have the same slope, that mean that the mutation rate is the same for both RV and HAV viruses. Mutation production is not related to the characteristics of the virus itself, but it is a form of adaptation either to internalization or to resisting climate changes. Rotaviruses and HAVs are viruses that are present in the environment [release of Human waste into the external environment], the mutation rate increases for the entire genome of the virus including proteins adapting to environmental conditions [25]. It can be concluded that there is a strong correlation between climate change, including CO₂ and temperature changes and mutation rate, which is mainly due to errors induced by RNA polymerase. The correlation between the three studied parameters (infection rate, temperature and ratio mutation) is well observed especially for the period between 2009 and 2011 with a peak in 2010, or a significant temperature values was recorded worldwide (developed and undeveloped countries), this massive increase in temperature (caused by CO₂ increase) induced an increase in mutation ratio (Figure 6) and consequently increased pathogenicity for both RV and HAV viruses. Infections (epidemiological data given in Figures 1 and 2) related to RV and HAV still show significant values despite medical and pharmaceutical efforts to develop vaccines to limit the occurrence of infections. Moreover, the climatic changes of temperature and CO₂ are the major causes of appeared infections.
confirm that impact of climatic change on the pathogenicity is linked to the polymerase error [26]. However, the results have also shown a strong correlation between climate changes and increased viral pathogenicity and as a result, epidemics may emerge not only compared to Rotavirus and Hepatitis A virus but also to other RNA viruses. Therefore the effects of climate change must be taken particular account in development and monitoring programs. This study concerns two most interesting viruses for environmental virologists and explains the important numbers of pandemic and endemic events observed in Human and animal populations.

This is also confirmed by the relation established between the mutation rate and the deviation of CO₂ at the level of the terrestrial envelope, with a linear regression of 93% whereas via a polynomial correlation can reach more than 97% as correlation with a logistic equation of the order of n = 4. The same results were observed for the HAV. All this allows us to conclude that there is a strong relationship between climate change and viral pathogenicity (Figure 6). In the same context, our results confirm previous studies that have demonstrated that the climate change likely affect the biology of the viruses’ directly, because it is demonstrated that the higher temperature increase pathogen proliferation, we can explain that by the variation of mutations rate observed in our study that
Conclusions:
Rotavirus causes the majority of viral gastroenteritis worldwide, while the Hepatitis A virus is implicated in acute viral Hepatitis. Rotavirus and Hepatitis A virus replicate in the enterocyte and hepatocyte respectively, and both are excreted by the faecal material and are subsequently released into the environment through the untreated wastewater. Viruses in their living environment are under the influence of several climatic factors. Temperature variations and CO2 rate are among the factors acting t on the living beings in the environment. The interaction between the two climactic factors studied and the behaviour of the Rotavirus and Hepatitis A genes had a positive correlation, whereas the increase of CO2 terrestrial and / or temperature induces an increase in mutation ratio of the viral RNA, these mutations are a form of adaptation to climate changes, in particular the variations in temperature and CO2 that the world experienced in the last few years as a result of pollution and the greenhouse effect. Viral infections pose a challenge despite the efforts made for the development of vaccines. This is due in fact to the genetic and molecular properties of RV and to maintain their survival.

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Table 4: Temperature variations (°C), rate of CO2 (ppm) and mutation rate of HAV and RV between 2000 and 2013

| CO2 (ppm) | 2000  | 2001  | 2002  | 2003  | 2004  | 2005  | 2006  | 2007  | 2008  | 2009  | 2010  | 2011  | 2012  | 2013  |
|----------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| HAV      | 0.42  | 0.34  | 0.4   | 0.6   | 0.57  | 0.65  | 0.61  | 0.54  | 0.63  | 0.7   | 0.57  | 0.62  | 0.7   |       |
| RV       | 0.04  | 0.04  | 0.04  | 0.04  | 0.04  | 0.04  | 0.03  | 0.03  | 0.04  | 0.04  | 0.05  | 0.06  | 0.07  |       |
| Ratio mutation (10^-5) |       |       |       |       |       |       |       |       |       |       |       |       |       |       |

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