Mexico, D.F. a 21 Octubre de 2015.

Dr. Luis Norena Franco
Director de la Division de Ciencias Basicas e Ingenieria
Consejo Divisional de Ciencias Basicas e Ingenieria
P resente.

Reporte de periodo Sabatico de Dra. ELIA BENITEZ MARQUEZ
Del 18 de Agosto 2014 al 17 de Octubre de 2015

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Using differential calculus for testing risk models; se prevee su envio a peer review journal a mas tardar Diciembre 2015. Abstract anexo

Notas de cursos en proceso

Se cuenta con un primer borrador de las notas para el curso de Electrostatica y Magnetostatica, sin embargo se ha reconsiderado el trabajo para su publicacion como libro en vez de "Notas"; este cambio requiere de trabajo significativo adicional. El libro esta aun en progreso.

Atentamente [redacted]

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2014

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STATISTICAL STUDY OF THE INFECTION BY SOME ENTERIC PATHOGENS

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RESUMEN

Los microorganismos patógenos entéricos como la *Salmonella non typhi, Shigella, Cryptosporidium, E.coli-0157, Norovirus y Campylobacater j.* y otros no estudiados aquí, causan aproximadamente 48 millones de infecciones anuales en los USA y cerca de 2 millones de muertes en el mundo. Aquí se continúa con el estudio de modelos matemáticos de la evolución de dichos organismos en el ambiente, así como la importancia en el riesgo de infección, que tienen la toxicidad, el tamaño, respuesta a dosis, decaimiento y concentración ingerida. Los estudios epidemiológicos guían a políticas de profilaxis y de remediación. Análisis de las correlaciones sugieren que *Salmonella y Norovirus* tienen parámetros que desestiman su respuesta a la dosis, mientras que *Shigella y Campylobacter* tienen bajos números del parámetro de decaimiento, todo esto relativo a la buena predicción de hospitalización, comparados con los otros patógenos. Solo seis patógenos es un numero bajo de elementos como para tener conclusiones solidas en este estado. Esta es una investigación aun no terminada.

Palabras clave: infección entérica, modelos de riesgo de infección, epidemiología matemática.

ABSTRACT

The enteric pathogens such as *Salmonella n t, Shigella spp, Cryptosporidium, E.coli-0157, Norovirus y Campylobacater j.* cause about 2 millions of deaths per year globally, mainly among children in the 3rd world. This is a continuation study of the models of probability, fate and transport in the environment of such organisms, the equations help to calculate the probability to infection based upon different parameters for every pathogen. After analyzing correlates it was suggested that Salmonella and Norovirus have response parameters that underestimate their toxicity in comparison to the other pathogens' parameters as good in predicting hospitalization probability, while Shigella and Campylobacter may have lower decay parameter values relative to the remaining pathogens. The six pathogens are still few number as to call for conclusions, this is still an ongoing effort.

Keywords: enteric infection, risk of infection models, mathematical epidemiology

INTRODUCTION

The enteric infections have a profound impact on the children development and population performance, causing globally between 1.6 and 2.1 million deaths annually, mainly in children in the third world (Petri et al, 2008). The American Center of Disease Control and prevention CDC, estimated that in the USA, almost 48 million illnesses, 125,000 hospitalizations and more than 3000 deaths annually occur because foodborne diseases being the top pathogens causing these illnesses: *Salmonella, Campylobacter, Clostridium perfringens, Norovirus, and E. coli O157.* This is continuation of an effort to better understand the main factors causing enteric infections by being guide for statistical and mathematical analyses, focusing in the effect of toxicity, decay and response parameters, also in concentration. The mathematical models studied here are the classical exponential and Beta Poisson response models and we try to test how well those equations estimate the actual hospitalization cases occurred and published by the CDC in 2012. The estimates given by the models studied here may help to policy makers and regulatory agencies to address resources in the best direction helping to decrease the burden meant by enteric infections.

This work is mathematical and statistical study of the epidemiological equations that model the probability of infection by six pathogens which cause most of the illnesses and hospitalization cases due to enteric infections in the world. The main idea is to apply the basic functional analysis together with bivariate correlations between hospitalization cases and diverse parameters introduced in the equations. Since the equations studied are monotonically increasing or decreasing, the association between probability should follow the number of cases hospitalized. This is continuation study of the models for probability, now with better and polished data from the literature. Here it is thought that If the equations estimate clearly more probability of infection by some pathogen for example Salmonella than by E. Coli O157, then the number of hospitalized people by Salmonella should be higher than by E.coli O157 and so forth for all the pathogens, the rank of the number of cases (hospitalized or infected or death) should correlate to the rank of risk of infection and should correlate to the risk parameters (as independent variables) as well. The probability of infection is a linear function of the ingested concentration (number of pathogens), at the same time it is an exponentially growing function of response (a measure of toxicity) but the probability is an exponentially decreasing function of the decay parameter (pathogen population decreases in time).

METHODOLOGY

The Spearman's correlation coefficients calculations chosen, does not assume a normal distribution of the variables: hospitalized cases, concentration of pathogens (ingested), dose response total parameter and alpha, beta parameters, decay parameter, radius of the organism. SPSS 16.0.0 (2007) statistical analyses software was used for correlates and scatter plots. Hospitalized cases were copied from CDC website for hospitalized cases and from distributed literature (Pepper et al 2010, Teng 2012, Teunis 1996, Viau 2011, Wong 2010).

RESULTS AND DISCUSSION

The Table 1 shows the Spearman's correlation coefficients, the significance of the correlations and N number of data for each pair. The table shows only good association between ingested concentration and decay parameter, and associations between hospitalized and concentration, hospitalized and exponential decay parameter.

The correlation for alpha and beta parameters is a perfect "1" correlation, the correlation between response and alpha and beta is the same negative, which is puzzling, should be positive with alpha.

The theoretical curves shown in Figure 1, are for the functional relationships given the equations (models), however the correlation coefficients and the actual distributions of the dose response and decay parameters, are not distributed precisely as these theoretical formulas, as shown in the scatter plots. It is expected dispersion around the formal equations, however the scatter plots below, suggest bigger variation than the expected.

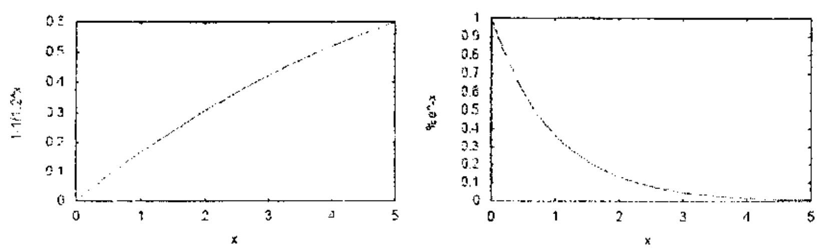

Figure 1. Dose-Response theoretical behavior for Beta poisson versus alpha (left), and the Exponential versus decay parameter (right).

Exponential decay is in agreement with negative correlation with hospitalized cases in table 1, however the significance is poor, as well as between hospitalized cases and dose response parameter, these two coefficients may signal a need of study of the models, however it is important to notice that Norovirus and Salmonella have a very small, relatively, response parameter, as the scatter plot for the dose-response parameters shows in Figure 2.

Table 1. Spearman's Non parametric correlation coefficients for Hospitalized cases, concentration, alpha, betha, and decay of pathogens in the environment

Correlations

		hospital	conc	alpha	beta	response	decay
hospital	Coefficient	1.000	.464	-.400	-.400	.143	-.486
	Sig	.	.354	.600	.600	.787	.329
	N	6	6	4	4	6	6
concent	Coefficient	.464	1.000	-.316	-.316	.116	-.928**
	Sig	.354		.684	.684	.827	.008
	N	6	6	4	4	6	6
alpha	Coefficient	-.400	-.316	1.000	1.000**	-.600	.400
	Sig.	.600	.684	.	.	.400	.600
	N	4	4	4	4	4	4
beta	Coefficient	-.400	-.316	1.000**	1.000	-.600	.400
	Sig	.600	.684	.	.	.400	.600
	N	4	4	4	4	4	4
response	Coefficient	.143	.116	-.600	-.600	1.000	-.200
	Sig.	.787	.827	.400	.400	.	.704
	N	6	6	4	4	6	6
decay	Coefficient	-.486	-.928**	.400	.400	-.200	1.000
	Sig.	.329	.008	.600	.600	.704	.
	N	6	6	4	4	6	6

**. Correlation is significant at the 0.01 level (2-tailed).

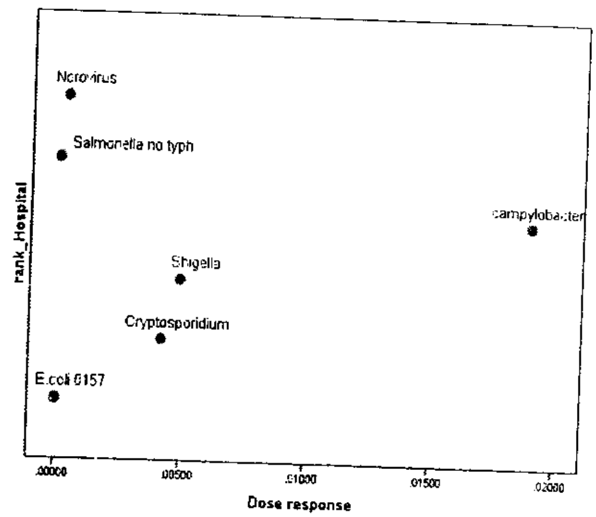

Figure 2. The scatter plot of hospital (ordinate) versus response (abscissa), shows the two up-left dots representing Salmonella and Norovirus values, which have smaller Dose-response value

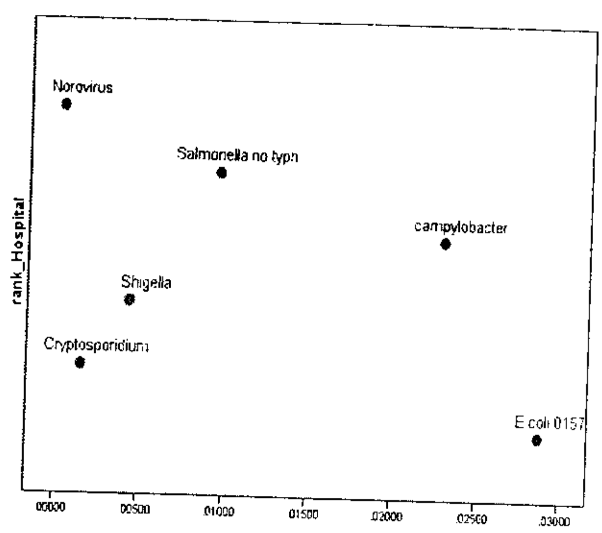

Figure 3. Scatter plot hospital vs. decay, should be decreasing function (theory). Here not shown such theoretical behavior, in agreement with not significant association (table 1). The two down left dots correspond to Cryptosporidium and Shigella.

CONCLUSIONS

The correlations and the scatter plots signal *Salmonella* and *Norovirus* as having too small dose-response values relative to the other pathogens, as for correctly predicting hospitalization cases, while *Cryptosporidium and Shigella* have lower decay values than the expected, however these decay values are directly related with the concentration which in turn is proportional to the risk, that is found in here. The literature shows different values for each parameter, the constant improvement in techniques and the natural mutation in the species make difficult to have one good parameter which gives good estimates of probability of infection, here were used parameters calculated mainly in the developed world.

The main idea of having guidance in the study of the infections by the correlates, looking in the probability estimates may be useful, still small amount of pathogens observed here and many possible choices for every parameter as to call for conclusions, this is an ongoing effort that seems interesting to follow on, by increasing the number of pathogens and parameters. Up to early 2014, the information available was still incomplete.

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TESTING PARAMETERS USED IN RISK QUANTIFICATION OF ENTERIC INFECTIONS

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RESUMEN

Las infecciones entéricas implican una inmensa carga incluyendo incapacidad, desarrollo deficiente y muerte del huésped. La Organización Mundial de la Salud (OMS) en 2013 estimo 760,000 muertes en niños menores de 5 años principalmente en el 3er mundo. La evaluación de riesgo de infección permite predicciones que informan a la política ambiental, investigación y aplicación de recursos para prevenir y atacar infecciones. Aquí se trata de evaluar o probar el grado de dependencia de parámetros en las funciones de evaluación de riesgo de infección, mediante la asociación estadística. Los parámetros y variables observados fueron: la concentración en biosólidos, decaimiento en el ambiente, respuesta a dosis, expresión, y dimensión o tamaño del patógeno. Se encontraron correlaciones estadísticamente significativas entre casos de hospitalizaciones y concentración de gérmenes en biosólidos Clase B y en excreciones. Estos hallazgos sirven de prueba de validación tanto de las ecuaciones como de los parámetros de los modelos de cálculo de riesgo de infección. No se encontraron asociaciones contradictorias.

Palabras clave: infecciones entéricas, diarrea niños, parámetros patogénicos, prueba estadística.

ABSTRACT

The global burden meant by enteric infections includes incapacities, children poor development and death of the host; indeed in the year 2013 the World Health Organization (WHO) estimated 760,000 deaths per year in children fewer than 5 years old, mainly in developing countries. The risk quantification of infections informs environmental policy, and research to prevention and control of diseases. This work intends to introduce a simple and robust test for the pathogenic parameters dependence in the risk quantification models, by analyzing the associations between risk of infection and: biosolids concentration, decay, dose-response, shedding, and diameter or length of the pathogen. The strong associations found here between hospitalized cases and concentration of germs, in biosolids Class B and concentration in shed masses, between decay rate and dose response parameters, decay rate and biosolids concentration, are all as expected and serve as validation test of models and parameters of risk of enteric infection calculations. There were not found contradictory associations.

Key words: children diarrhea, enteric infections, pathogenic parameters, statistical fit test.

INTRODUCTION

The burden of enteric infections mean about 2.2 million deaths globally and 760,000 diarrhea-deaths in children less than 5 years old. The WHO, found rotavirus as the highest cause of diarrhea in children in 2009 (WHO, 2009), for which the use of a rotavirus vaccine will prevent severe diarrhea and dehydration among children, helping to reduce the number of deaths, however the incidence of enteric infections keeps almost as large as before (Petri *et al.*, 2008, WHO, 2013). The common sources of infection are: contaminated food or water, and passing of shed germs (human, livestock). This work examined associations among hospitalized cases due to enteric infections and some parameters and variables included in the models of risk of infection. Developing countries are more strongly affected by infections of all kinds, in these countries about 1.1 billion people have no safe drinking water and ,2.6 billion lack of appropriate disposal of excretions (pit latrines) (Petri *et al.*, 2008, Viau *et al.*, 2011,WHO 2013)

In this work, we try to learn from the associations between cases actually hospitalized by enteric infection by each pathogen revised, and convenient variables. The pathogens observed here were: *E.coli* 0157, *Shigella, Campylobacter, Salmonella no typhi*, and Norovirus; the parameters and variables: decay rate, dose response, initial concentration in Class B biosolids, concentration in excretion of livestock animals, and size of the germs.

METHODS

The calculation of bivariate correlation coefficients between hospitalized cases, and selected parameter or variable, is supposed to evaluate their associations and therefore their goodness in calculating risk of infection, if the dependences between risk and parameter are modeled by monotonically changing models. When an independent variable grows in a monotonically growing function, the dependent variable will necessarily grow, therefore if let's say the parameter "k" grows it is expected that the risk of infection will grow as well.

The risk calculations are based upon known functions, here considered the exponential dose-response function which is a monotonically growing function of both: ingested dose variable, and of dose-response parameter "k", this function is increasing in proportion to concentrations of pathogens (biosolids and shedding). In other hand the risk is decreasing with the decay rate in the environment. The dependence of risk with size is more indirect. The dependence with size is not calculated by one equation and is not monotonically changing since size plays a role in the germ transport and fate in the environment as well as in the hosts, here we only will look for the statistical associations of size with final risk calculation, to learn from there.

Summarizing the dependence expected, perhaps coincidental to associations with risk of infection are:

1 Response parameter: monotonically growing relationship with risk implies "+" coefficient sign.
2 Decay rate in environment: monotonically decreasing relationship: "-" sign.
3 Concentration of pathogen in biosolids: growing, "+"
4 Concentration in shedding mass: growing, "+"

5 Radius, diameter or length of pathogen: not a single behavior, both: "+" or "-"

The variables correlated were: hospitalized cases (counts) by infection per each pathogen, maximum shedding in log units (amount of pathogens per gram e.g. Plaque forming units PFU/g), time lasting shedding (months) multiplied by mean shedding pathogens (PFU*months/g), concentration in biosolids Class B (colony forming units CFU/g, Plaque forming units PFU/g, oocyst/g, etc.), decay in the environment, germs radius (cm) and response parameter "k". The pathogens studied were: *E.coli* 0157, *Cryptosporidium p, Shigella, Campylobacter, Salmonella no typhi,* and Norovirus.

The Centers of Disease Control and Prevention (CDC, 2013) published the annual incidence, hospitalization, and death of cases of infection per pathogen. The response and decay rate were searched in the literature as well as shedding rates, times and concentrations both in human and livestock and wild animal, however we could not find enough data for human shedding of enteric pathogens by the end of this project, therefore included shedding rates from cattle and livestock animals.

The statistical analyses and graphs were made with SPSS, 2007, v 16.0.

RESULTS AND DISCUSSION

The correlation significant at the 0.01 and 0.05 level (2-tailed) were found between: hospitalizations (cases) and concentration in biosolids (Pearson's $R=1$, $p<0.001$ $N=6$), cases and shedding (maximum counts shed in log units) $R=0.90$, $p<.05$, $N=5$, concentration in biosolids with decay ($R= - 0.928$, $p<1$, $N=6$) and with response parameter ($R=1$, $p<0$, $N=6$), and between biosolids concentration and response ($R=1$, $p<0.001$, $N=6$) see Table 1, listing Spearman's non parametric correlation coefficients.

The Pearson's correlation is significant for hospital and biosolids concentration ($R= 1$, $p<.0001$, $n=6$), but not significant for hospital and shedding. Inversely the correlation between hospital and shedding is significant in Spearman's coefficient calculation. The reminded significant correlations were significant in both algorithms Pearson's and Spearman's. Since Spearman's are not parametric correlations, are not assumed Gaussian distribution of populations. Here present only the Spearman's because these do not assume Gaussian distribution of populations.

The size of the germs is negatively and significantly correlated to shedding mass (maximum shedding mass: Pearson's $R=-1$, $n=2$) and negatively but weakly associated to cases, and decay, but there are only three data points, therefore there is no power to conclude.

Table 1. Spearman's correlation coefficients indicating that maximum shedding rates are strongly associated with hospitalized cases.

Spearman's Correlations

		hospital	shed x time	Max shedd	Conc Biosol	Decay Mean	radius	response Mean
hospital	Coeff	1.000	.600	.900*	.464	-.486	-.866	.464
	Sig.	.	.208	.037	.354	.329	.333	.354
	N	6	6	5	6	6	3	6
shedxTim	Coeff	.600	1.000	.800	-.058	.143	-.866	-.058
	Sig.	.208	.	.104	.913	0.79	.333	.913
	N	6	6	5	6	6	3	6
Maxshedlog zNh	Coeff	.900*	.800	1.000	.359	-.400	-1.00	.359
	Sig.	.037	.104	.	.553	.505	.	.553
	N	5	5	5	5	5	2	5
Conc_sep	Coeff	.464	-.058	.359	1.000	-.928**	.000	1.000**
	Sig.	.354	.913	.553	.	.008	1.000	.
	N	6	6	5	6	6	3	6
decaymeanJT	Coeff	-.486	.143	-.400	-.927**	1.000	-.866	-.928**
	Sig.	.329	.787	.505	.008	.	.333	.008
	N	6	6	5	6	6	3	6
radius	Coeff	-.866	-.866	-1.000**	.000	-.866	1.000	.000
	Sig.	.333	.333	.	1.000	.333	.	1.000
	N	3	3	2	3	3	3	3
respMean	Coeff	.464	-.058	.359	1.000**	-.9276**	.000	1.000
	Sig.	.354	.913	.553	.	.008	1.000	.
	N	6	6	5	6	6	3	6

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

CONCLUSIONS

The strong associations between hospitalized cases and concentration of germs, in biosolids Class B and concentration in shed masses, are as expected, supporting the functional proportionality between risk of infection and concentration (ingested). The shedding data used is for livestock animals, which miss the human-host self-infection factor, as well as transmission to household companions. A guess based upon the significance of the correlations with shedding, is the importance of shedding mass, as transcendent as the importance of the dose concentration itself, in the self re-infection and transmission to others nearby.

The high significance in the negative associations between decay and response parameters existed in both, Pearson's and Spearman's algorithms, as theoretically expected.

Therefore the stronger conclusion from these associations might be that the functional relationship of decay rate, dose response, and dose concentration, in the mathematical models for risk calculations are validated here. The validation serves for the parameters used as well as for the equations constituting the models of risk of enteric infection.

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EPIDEMIOLOGICAL STUDY OF ENTERIC INFECTIONS IN CHILDREN BY COMPARING DIFFERENT COUNTRIES

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RESUMEN

Correlaciones entre muertes por diarrea en niños y parámetros tanto socioeconómicos como ambientales, son estudiados aquí para 10 países, mostrando asociaciones entre casos y población, lluvia y producto interno bruto (PIB). Las variables correlacionadas incluyen: casos de muerte, población (total y densidad), área (tierra y agua), temperatura promedio, lluvia, productividad, desigualdad de ingreso (índice Gini), indicador de alta tecnología (tecnología de desarrollo de armas nucleares). Cuando se divide en 2 grupos la base de datos: países desarrollados y en desarrollo, algunas asociaciones crecen para los países en desarrollo (R más grandes, p-values <0.05). Las correlaciones encontradas aquí apoyan que el exceso de lluvias y los asentamientos atestados contribuyen a la transmisión de las infecciones; dando a entender que la densidad de población impone un límite práctico en el control de las infecciones entéricas en los países en desarrollo.

Palabras clave: diarrea, niños, países en desarrollo, infecciones entéricas.

ABSTRACT

Correlates among diarrhea-deaths in children, and social and environmental parameters, are studied here for 10 countries, showing significant associations among cases and population, rainfall, and gross domestic product (GDP). The variables correlated include: cases, population (total and density), area (land and water), average temperature, rainfall, productivity (GDP), income inequality (Gini index), and hi-technology indicator (by nuclear weapons technology). When the dataset is split in two sets: developed and developing countries, some of the associations for developing countries grow up (larger R, p-values < 0.05). Correlations found here support that excessive rainfall and crowded settlements contribute to the transmission of infections; hinting that population density imposes a practical boundary in controlling enteric infections in developing countries.

Key words: diarrhea, children, developing countries, enteric infections.

INTRODUCTION

The World Health Organization WHO, estimated that 35% of deaths in children are associated with malnutrition (WHO UNICEF 2013), being pneumonia and diarrhea the two leading killers. The enteric infections overt diarrhea and are estimated to cause 760,000 deaths in children of developing countries where about 1.1 billion people have no safe drinking water and 2.6 billion lack of pit latrines (Petri et al, 2008, Viau et al, 2011). Advances in fighting diarrhea, include the use of glucose electrolyte ORT, vaccination when possible, and application of antibiotics and antiviral drugs, these have greatly diminished the amount of deaths, from 4.6 million per year in 1980's, to 0.76 million in 2013; however the morbidity of enteric infections has not decreased, adding up to 1.7 billion cases worldwide, potentially impairing the hosts for life, and shortening their life expectancy (Petri et al. 2008, WHO 2013b).

The transmission and spreading of enteric infections are strongly associated to hygiene when preparing and eating food, and to keeping separate the human and domestic animal excretions. Here we observe variables as indirect indicators of inadequate domestic hygiene, such as population density as indicator of crowded towns, and probably not clean, GDP as measurement of wealth/productivity per capita, indirectly indicating existence of sewage, latrines or WC in houses, and adequate disposal of biologic trash, Gini as indicator of income inequity or poverty, number of nuclear weapons as indirectly signaling hi-technology and infrastructure available in the country. Temperature, rainfall and water area (km of total area), may be good indicators of pathogens survival and spreading by being carried in streams to surface or to groundwater, and far away locations. However all these are indirect indicators, careful interpretation is needed to better understand spreading of infections.

This study looks for the possibility of find interesting "external" factors to the spreading and transmission of enteric infections, here are neither considered host's nor germ's parameters.

METHODS

This is a statistical analyzes of correlates among number of diarrhea-deaths in children (or cases), and social and environmental parameters: population (total and per square kilometer), productivity (GDP per capita), wealth inequity % (Gini index), rain precipitation per year (mm/year), annual average temperature (Celsius), and total water area (km2) in different countries. The inclusion of nuclear weapons here, serves because the technology to develop the nuclear weapons and the infrastructure needed in that, tell that the country have those human, software and hardware resources. By the end of this manuscript, May 2015, the data collected was analyzed and reported, however notice this is a continued effort.

DATA BASE: Petri et al. (2008) reported that China and Pakistan had about 120,000 deaths caused by diarrhea in children under 5 yo. in the year 2000, India had more than 450,000 deaths, Mexico had 12,500 deaths, Myanmar 35,000 deaths. The USA Center of Disease Control and Prevention CDC, reported 400 deaths due to diarrhea for 1992, dropping to about 50 by 2012 (CDC 1992, CDC 2012), The population, population density, GNP and Gini indexes, rain fall, temperatures averages, and nuclear capabilities were acquired from Wikipedia.org* by searching for: "Climate of *country*" and "*Country*". Notice that for Myanmar (previously Burma) was not found the Gini index, and the rainfall amounts were neither found for Colombia nor Cameroon with the precision required by the end of this report. (*Note that Wikipedia collects information from accredited international databases such as: International Monetary Fund, Britannica Encyclopedia, CIA, United Nations, etc.)

Statistical analyses and graphs by SPSS 16.0 (2007).

RESULTS AND DISCUSSION

The number of death cases is significantly associated with the population, total (R=.742, p-value=.014, N=10) and density (R=.801, p=value=.005), and with rain fall per year (R=0.77, p-value=.024, N=8). The cases per million inhabitants per square kilometer, are significantly correlated with GDP, Gini indexes, and rain (R=-.636, p-value=.048, N=10; R=- 0.635, p-val=.066 N=9; R=.669, p-val=.07) and cases per population density are associated with GDP, rain (R=-.62, p-v=.057, N=10, and R=.794, p-v=.019, N=8), some associations shown in Figures 1 and 2. If the dataset is split in developed and developing countries, cases per million habitants is strongly associated with GDP index (R= -0.922, p-value=.001, N=8) as graphically shown by Scatter plot in figure 2. Some complicated variables may help to understand infections, but need for more analyses on them should be done, for example GDP*Gini vs. cases/pop (R= - .811, p-value < 0.027, N=7). The factorization of GDP by Gini index magnified, as expected, the correlations, highlighting that income inequality is associated with infective diseases.

The larger countries in respect to inhabitants are China (1.3 billion people) and India (1.2), but China extends in almost three times the area of India, resulting in 0.38 times the India's population density, explaining partially, why are fewer cases in China and more than expected in the UK.

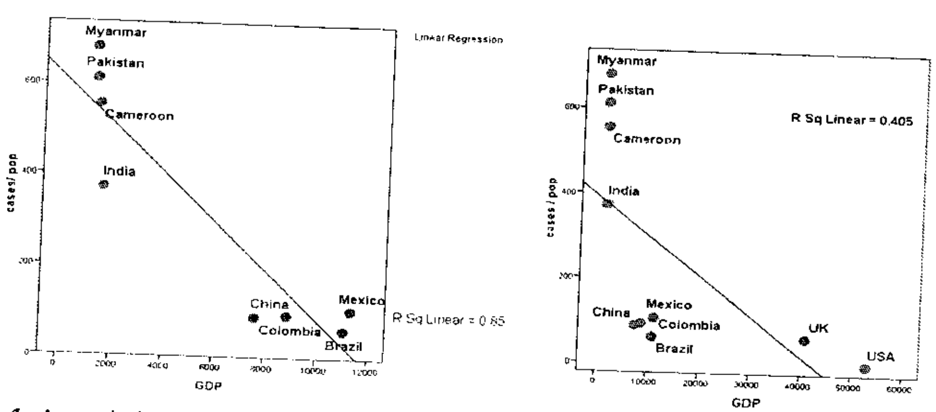

Figure 1. Association between child death cases per million of population, and GDP. Left Scatter plot for 3rd world countries (R= - 0.922 p-value=0.001, N=8), right plot includes USA and UK which decreases the correlation and its significance (R= - 0.636, p-value=0.048, N=10)

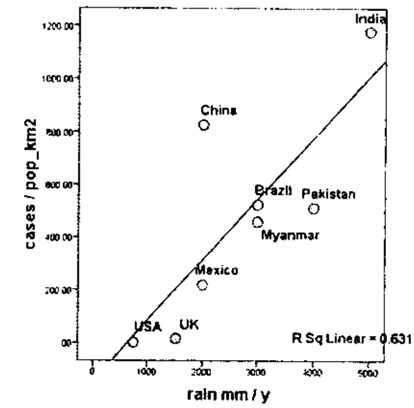

*Figure 2. Association between child death cases per population density and total rain fall per year in millimeters (averages),*R=.794, p-value=0.019, N=8. *The Southern Asia Monsoon affects to India, Pakistan and Myanmar (of the studied here). (rain data only for 8 countries).*

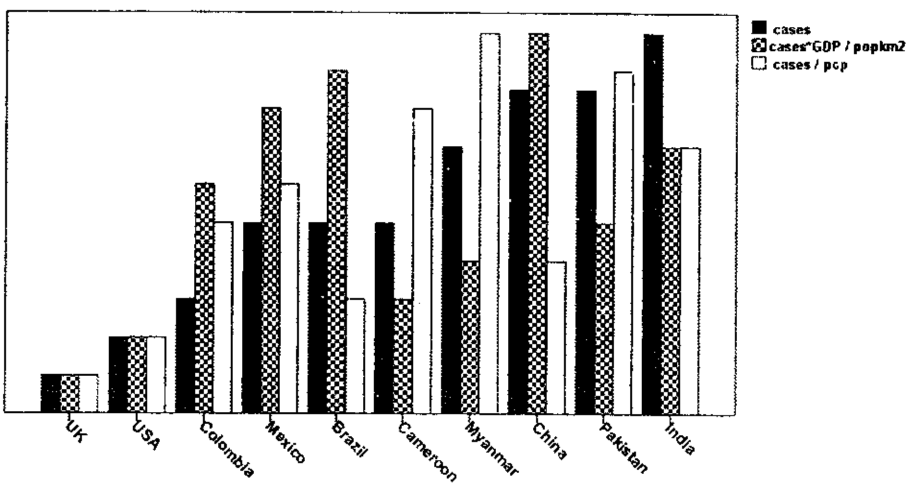

Figure 3 Comparison of ranks: cases of death in children (black), deaths per population (clear), and deaths per population density times GDP (chess pattern), which also can be interpreted as some kind of cost in $US dollar of diarrhea-deaths in children. India change place comparing cases vs. cases GDP/popkm2 (cases*GDP/pop/km2), and cases vs. cases/population.*

To consider the productivity in the analysis, we test if GDP (productivity) is linked to deaths of children by enteric infections. When the number of child deaths are divided by population-density, and multiplied by GDP, the pattern changes. Figure 1 shows some differences between 1st and 3rd worlds. The Figure 2 shows rainfall associations (detailed rain data were found only for 8 countries by the end of this report), and Figure 3 add the wealth of every country as GDP. The three BRIC countries studied here (Brazil, India and China) show, as a group, the smallest average value of deaths in the 3rd world studied, however these individual countries of BRIC, have very high absolute number of cases. (By the time this report was produced, could not find enough precise data for Russia). Considering population and GDP, India ranks as more advanced country than it ranks for cases, moving from the country with more cases, to ahead of Mexico, Brazil, and China; and in other hand Mexico falls among the worst cases*GDP/pop/km2, despite of wealth, see Figure 3. Therefore the wealth appears not such an important factor, in Mexico, for helping to prevent child death by diarrhea.

CONCLUSIONS

The most important associations among the social and environmental variables studied here, with cases of deaths in children caused by enteric pathogens, suggest that population density and rain are factors helping infections to constantly spread throughout the population, despite of GDP, Gini or Hi-Tech (nuclear) capabilities. Most of the enteric pathogens have smaller decay times in water than in dry environments; notice that India, Pakistan and Myanmar are subjected to the extreme South-Asia Monsoon phenomenon, and then they are the most affected by humidity in summer when the highest temperatures run by the countries.

The product of death cases times GDP divided by population (or population density too), may give a useful variable for studying developing countries, as shown in Figure 3. For example the fact that in Mexico die between 5,000 and 20,000 children per year (WHO 2013), when Mexican GDP per capita is high among developing countries, tells that wealth, or medium technological product (GDP), is not an important factor, in Mexico, to controlling children deaths due to diarrhea.

Correlations found here support that excessive rainfall and crowded settlements contribute to the transmission of infections; hinting that population density imposes a practical boundary in controlling enteric infections in developing countries.

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ASSOCIATIONS BETWEEN ENTERIC INFECTIONS IN CHILDREN AND GEO-ECONOMICAL FACTORS

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Manuscript Type:	Original Contributions
Key Words:	boundaries disease control, children diarrhea, enteric infections, population density, infections 'BRIC' countries

ASSOCIATIONS BETWEEN ENTERIC INFECTIONS IN CHILDREN AND GEO-ECONOMICAL FACTORS

ABSTRACT (184 words)

The WHO estimated in 2013 that diarrhea causes annually 760,000 deaths in children, mostly in the 3rd world. This study looks for the associations of environmental factors (socio-economical and climate) by observing few convenient variables. Pearson's correlates among cases (diarrhea-deaths in children), show significant associations with: population, population density, and rainfall. Three out of the four 'BRIC' countries were included here (Brazil, India, China), trying to understand possible association of cases with: economic growth, population growth, inequality of wealth distribution; found correlations with GDP and Gini index, hints that BRIC group is doing better than other developing countries in controlling diarrhea deaths. Of the 10 countries considered, India has the largest number of cases, but considering the population and GDP, UK has the largest number (GDP times cases/population), Mexico the 2nd largest, suggesting that population density imposes a practical boundary in controlling enteric infections (close to 255/km2). For the 3rd world may be effective and robust solution in fighting diarrhea, to work in spreading large clusters of population toward ampler settlements, which include pit latrines and drinking water, looking for decreasing the population density.

Key words : boundaries disease control, children diarrhea, enteric infections, population density, infections 'BRIC' countries.

(Text words: 1157)

The enteric infections frequently cause diarrhea and are estimated to cause 2.2 million deaths globally and 760,000 in children mostly of developing countries where about 1.1 billion people have no safe drinking water and 2.6 billion lack of appropriate disposal of excretions (pit latrines) (2, 3). The morbidity of enteric infections has not decreased, adding up to 1.7 billion cases worldwide, potentially impairing the hosts for life, and shortening their life expectancy (2, 4) although deaths are fewer cases. Children deaths associated with malnutrition were 35% as the World Health Organization WHO, estimated in 2013 (1), being pneumonia and diarrhea the two leading killers. Advances in fighting diarrhea, include the use of glucose electrolyte ORT, vaccination when possible, and application of antibiotics and antiviral drugs, these have greatly diminished the amount of deaths, from 4.6 million per year in 1980's, to 2.2 million in 2013. Archer and Kvenberg (5) estimated that the 68.7 to 275 million cases of diarrhea in the USA mean a burden of billions of dollars per year.

This study looks for the associations of external factors (social and climate) by observing few convenient variables (that possibly affect the spreading and transmission of enteric infections); here are neither considered the host's nor germ's parameters (immune response, dose-response parameters, pathogen decay, etc.).

METHODS

This study analyzes the statistical correlates among number of diarrhea-deaths per year, in children < 5 years old, or "cases", and social and environmental parameters. Of the 10 countries we examined: population (total and per square kilometer), productivity (GDP), wealth inequality Gini index (%); also averages for 8 countries of: precipitation of rain per year (mm), annual average temperature (Celsius), surface area, and water area (km2). Combination of variables and countries were correlated as well, and scrutiny of changes in significance (Pearson's and Spearman's) among sets lead to the correlates discussed in the Results section. Statistical analyses and graphs were made with SPSS 2007, v 16.0.

The countries were chosen to include 1 st world, and 3 rd world countries, from America (US, Mexico, Colombia, Brazil), Europe (UK), Africa (Cameroon) and Asia (China, India, Pakistan and Myanmar). The possible association of cases with economy, productivity, and wealth inequality, suggested choosing the "BRIC" countries (missing Russia because details of child deaths could not be found, by the end of the project).

Database and Units. Petri et al. (2) reported thousand deaths per year caused by diarrhea in children < 5 years old in the year 2000 (Table 1). The USA Center of Disease Control and Prevention reported 400 deaths due to diarrhea for 1992, which decreased to about 50 by 2012 (6, 7). The total population, population density (1/km2), GDP ($US dollars per capita), Gini indexes (%), rain fall (m), temperatures annual averages of mean temperatures (Cesius degrees), and amount of nuclear weapons data (counts), were acquired from Wikipedia.org. Table 1 reports averages rounded up but all calculations were using the precise numbers reported.

RESULTS AND DISCUSSION

The number of death cases is significantly associated with the population, total (R=0.742, P =0.014, N=10) and density (R=0.806, P =0.005), and with rain fall per year (R=0.775, P =.024, N=8) see Table 2. The cases per million inhabitants are significantly correlated with GDP, Gini indexes, and rain (R=-0.636, P=0.048, N=10; R=-0.635, P=0.066 N=9; R=0.669, P=0.07) and cases per population density are associated with GDP and rain (R=-0.62, P=0.057, N=10, and R=0.794, P =0.019, N=8). When the dataset is split in developed and developing countries, cases per million habitants is strongly associated with GDP index (R= -0.922, P =0.001, N=8); this suggests that developed countries (discriminated by GDP), belong to a different population in respect to factors such as population, rainfall, temperature.

Most of the species of enteric pathogens live longer in water than in dry environments, and the rain and floods transport germs from infected people (and other animals) to another animals and into water (surface and groundwater) (8), therefore it is expected that the number of cases in developing countries will be more strongly associated with rainfall, which is supported here by finding Pearsons' R=0.775, P=0.024, N=8 (Spearmans' R=0.835, P=.01). In other hand, notice that India, Pakistan and Myanmar are subjected to the extreme South-Asia Monsoon phenomenon, then they are the most affected by humidity in the summer (with high temperatures). Considering that India has 4 and 4.8 times the areas of Pakistan and Myanmar respectively, the fighting to enteric infections in India may cost much more resources.

The larger countries in respect to number of inhabitants are China (1.3 billion people) and India (1.2 billions), but China extends in almost three times the area of India, resulting in 0.38 times the India's population density, explaining partially, why are fewer cases in China and more than expected in the UK. The total population is associated with cases less clearly (smaller P values) than population density. Figure 1 shows distributions of countries in ranks: i) ranks of deaths reported (2 Petri et al. 2008), ii) ranks of the deaths per population, and iii) ranks of deaths times the GDP per population. India passes from having the highest rank of cases (deaths/year) to having less (modified: cases*GDP/pop) than Mexico or the UK, when the later has the highest number of modified variable caseGdp/pop, suggesting the importance of population (total and density) for the incidence of enteric infections that result in death of children less than 5 years old.

For the 3rd world may be more effective and robust solution in diarrhea fighting, working to spread large clusters of population (toward settlements including drainage or pit latrines, and drinking water), looking for decreasing the population density, rather than expending in development of hi-biotech and food-technology remedies (such as vaccines, food complements, additives, etc.)

CONCLUSIONS

The most important associations among the variables studied here, with cases per year of deaths in children caused by enteric pathogens, suggest that population total and density, constitute a factor helping infections, probably because of the faster and constant spreading throughout the population (cases vs. pop/km2: R=0.806, P=0.005, N=10), independently of GDP, Gini, climate, or Hi-Tech capability (nuclear weapons development). For example the GDP in Mexico ($11,300 usd) seems not relevant to prevent child death by diarrhea (up to 20,000/year); in other hand the number of cases in the UK is high (4000/year) relative to its GDP ($40,880 usd) probably due to its high population density (256/km2). The three BRIC countries studied here show the 2 nd smaller value of modified-variable cases*GDP/pop, as if these countries are expending less (GDP $usd per capita) in fighting diarrhea deaths (Figure 1), despite of India having the highest number of deaths/year.

In other words if in the year 2013 an advanced country like UK, has 4,000 child diarrhea-deaths per year, then maybe extremely difficult to reduce that amount of deaths when the population density is higher than 255/km2. It is suggested that population density puts a practical boundary to the control of enteric infections, and probably to another infections as well.

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Table 1. Average Values of Data Bases Used Here. From Petri et al. (2008), US CDC (2012 and Wikipedia.org (2015).

Country	deaths year thousand	pop million	Pop per km2	Mkm2 area tot	GDP $usd	Gini %	water area%	temp year C	Rain year m	nuclear weapon
USA	0.05	320.2	34	9.15	53042	45	7.0	11.55	0.7	4,800
UK	4.0	64.1	256	0.24	40880	40	134	17.30	1.5	225
Brazil	12.5	202.8	24	8.52	11067	51	0.65	20.00	3.0	
Cameroon	12.5	22.5	40	0.48	1426	45	0.57			
Colombia	4.0	42.9	41	1.14	8858	59	8.8			
China	120.0	1357.4	145	9.60	7634	47	0.28	0.00	2.0	250
India	450.0	1210.2	382	3.29	1626	37	9.60	16.50	5.0	110
Mexico	12.5	118.4	57	1.97	11321	52	2.50	20.00	2.0	
Myanmar	35.0	51.4	76	0.68	1269		3.06	12.00	3.0	
Pakistan	120.0	196.2	234	0.80	1307	31	3.10	23.50	4.0	120

Table 2. Pearson Correlation Coefficients of Deaths by Diarrhea in Child per Year, and Variables Correlated.

		cases/y	Cases /Mpop	deths*GDP/pop	pop p Mill	pop/km2	GDP	gdpgini	rain mm_y	Nuclear rank
deaths/year	Coeff	1	.249	-.048	.742*	.806**	-.367	-.435	.775*	-.696
	Sig.		.488	.928	.014	.005	.297	.242	.024	.192
	N	10	10	6	10	10	10	9	8	5
casespM/pop	Coeff	.249	1	.357	-.146	.207	-.636*	-.659	.669	-.723
	Sig.	.488		.487	.687	.566	.048	.053	.070	.167
	N	10	10	6	10	10	10	9	8	5
deths*GDP/pop	Coeff	-.048	.357	1	-.227	.031	-.765	-.728	.327	-.842
	Sig.	.928	.487		.666	.953	.076	.163	.528	.158
	N	6	6	6	6	6	6	5	6	4
pop p Mill	Coeff	.742*	-.146	-.227	1	.526	-.165	-.240	.299	-.222
	Sig.	.014	.687	.666		.118	.649	.534	.472	.720
	N	10	10	6	10	10	10	9	8	5
pop/km2	Coeff	.806**	.207	.031	.526	1	-.106	-.221	.607	-.951*
	Sig.	.005	.566	.953	.118		.771	.568	.110	.013
	N	10	10	6	10	10	10	9	8	5
GDP	Coeff	-.367	-.636*	-.765	-.165	-.106	1	.995**	-.787*	.775
	Sig.	.297	.048	.076	.649	.771		.000	.020	.124
	N	10	10	6	10	10	10	9	8	5
gdpgini	Coeff	-.435	-.659	-.728	-.240	-.221	.995**	1	-.817*	.816
	Sig.	.242	.053	.163	.534	.568	.000		.025	.092
	N	9	9	5	9	9	9	9	7	5
rain mm_y	Coeff	.775*	.669	.327	.299	.607	-.787*	-.817*	1	-.874
	Sig.	.024	.070	.528	.472	.110	.020	.025		.053
	N	8	8	6	8	8	8	7	8	5
nuclear_rank	Coeff	-.696	-.723	-.842	-.222	-.951*	.775	.816	-.874	1
	Sig.	.192	.167	.158	.720	.013	.124	.092	.053	
	N	5	5	4	5	5	5	5	5	5

*. Correlation is significant at the 0.05 level (2-tailed).