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A Statistical Analysis of Trends in Mortality from Major Infectious Diseases of Global burden, 1990-2015

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ABSTRACT

Background: Infectious diseases are the world's foremost cause of death that presents one of the most significant health and safety challenges facing the global community. Studying about infectious diseases has become an important aspect because of its unexpected fluctuations in mortality rates and changing the demographic scenario of any nation.

Aim: This paper provides an outlook in the trends of mortality rates of major infectious diseases (ID's) at the global level.

Data and Methodology: The data collected from Institute for Health Matrix and Evaluation (IHME) and has been tested for the normality and homogeneity of residuals by Shapiro-Wilk test and standard Normal Homogeneity test respectively. Joinpoint Regression analysis was carried out to estimates of Annual Percent Change (APC) and trends of ID's

Results: The result shows a gradual decrement from 1990 to 2015 in the death rates from ID's. But in case of HIV with TB, HIV/AIDS and Malaria, death rates increased till 2004 and later it was decreased gradually along with the crude mortality rates. The joinpoint regression method also identifies different inflation points to the different ID's.

Discussion and Conclusion: The diseases like Lower respiratory infections shows highest death rate among other major ID's mortality followed by diarrheal diseases and drop off in recent years and least rates are seen in Intestinal Infectious Diseases. The implementation of health policies by WHO and advancement of technology in health science reduces the mortality rates of Infectious diseases.

Key Words: Joinpoint Regression, Infectious diseases, HIV, TB

INTRODUCTION

Infectious diseases (ID's) are the important contributing factor to the human mortality and morbidity in recent times. Today ID's still account for the large proportion of deaths and disability globally and in certain regions remain the important cause of ill health. The term 'Infectious diseases' is not refers to the homogenous set of illness rather to a broad group of widely varying conditions. The relative and absolute important of particular infection or group of infections varies drastically across regions.

ID's leading causes of death of children and adolescent, and one of the leading causes for the adults in the worldwide. ID's have spread across populations and regions throughout history and it is likely that newly emerging ID's will continue to be identified. In recent years, Ebola outbreaks in West Africa have killed the 11315 people of six countries and rapidly became the deadliest occurrence of disease. The first case of Ebola was reported in March 2014 but since it's discovered in 1976 (WHO, 2015).

The ID's has been now geographically spreading much faster than at any time in history because of high mobility, interdependent and interconnected society. This result that ID's have become causes of serious public health issues and their threat has been increasing, (WHO, 2007). Some ID's have emerging and re-emerging with different biological structure and more viral than previous in new location because of environmental and climate change, human behavior, new technologies, microbial adoptions and host impaired immunity (MacLehose L et al., 2002).

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In high- income countries, deaths from infectious diseases are overwhelmingly due to respiratory infections and HIV/ AIDS. In sub-Saharan Africa, respiratory infections, diarrheal diseases, HIV/AIDS, TB and Malaria account for roughly similar proportions of total infectious disease deaths (Murray and Lopez, 1997). An analysis of Global Burden of Disease Study (GBDS) data concludes that the poorest 20% of the world's population experiences a far higher burden of infectious disease compared to the remaining 80% of the world's population (Gwatkin et al., 1999).

In south Asia, infectious diseases are major cause of children deaths and disability. Among the estimated 3.7 million deaths of children in the year 2000 there were two third of deaths of children due to infections such as Pneumonia, Diarrheal and Measles (Black RE et al., 2003). Of the overall burden of deaths related to infectious diseases in the South Asia around 63% are in children aged under 5 years (Lopez AD, 1993).

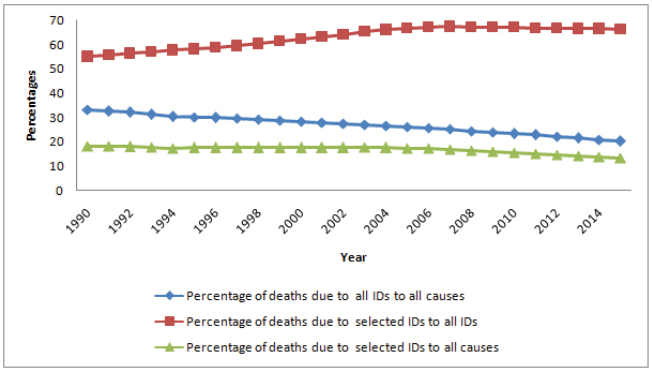

Figure 1: Mortality trend of infectious diseases from 1990-2015.

The study focuses on major infectious diseases like HIV & TB, HIV/ AIDS, Tuberculosis, Lower respiratory infections, Intestinal infectious diseases, Malaria and Diarrheal where these selected infectious diseases accounted for approximately 18 per cent of deaths among the deaths due to all causes (Infectious and Non Infectious diseases) in the year 1990 as shown in figure 1. But this per cent is declined to 13 per cent in the year 2015. We have accounted the deaths due to infectious and parasitic diseases and infectious causes from remaining grouping. Of these diseases, selected seven ID's accounted for approximately 66 per cent in 2015 increased by 11 per cent from the year 1990. Out of all the infectious diseases classified by WHO in the form of International Classification of Diseases (ICD) these seven infectious diseases plays a significance role in mortality rates. Hence it is necessary to study the trends of Mortality rates of these seven ID's global level.

This paper aims to study the trend and pattern of seven selected ID's. First section briefs about the introduction and significance of ID's, section 2 discusses about Methods and Materials used, section 3 focuses on results and discussion and last section concludes the study.

METHODS AND MATERIALS

This paper is attempt to study selected seven major infectious diseases globally viz. Lower respiratory infections, Diarrheal diseases, Tuberculosis, HIV/ AIDS, Malaria, Intestinal infectious diseases and HIV with TB. The data on deaths due to these above mentioned ID's is collected from Institute for Health Matrix and Evaluation (IHME) in the form of time series data from 1990 to 2013.

The assumptions of normality and homogeneity of variance of residuals which are obtained after applying the model are tested using the Shapiro-Wilk test for normality and Standard Normal Homogeneity test respectively. The Joinpoint regression analysis is used in the study to analyze the trends of incidence and mortality rates of any Infectious diseases which give the Annual Percentage Change (APC) and Points of Inflation. This study can fit the joinpoint regression model to the data that allow for testing of whether an apparent change in trend is statistically significant.

Joinpoint Regression Model:

The joinpoint (JP) regression model for the observations: $(x_1,y_1), (x_2,y_2), \ldots, (x_n,y_n)$, where $x_1 < x_2 < \cdots < x_n$ represent the time variable and $y_i, i = 1,2,\ldots,n$ are the response variable, can be written as

$$E[y_i|x_i] = \beta_0 + \beta_1 x_i + \gamma_1 (x_i - \tau_1)^+ + \cdots + \gamma_n (x_i - \tau_k)^+$$

Where $\beta_0, \beta_1, \gamma_1, \ldots \gamma_n$ are regression coefficients and the $\tau_k, k < n$, is the k-th unknown joinpoint in which

$$(x_i - \tau_k)^+ = \begin{cases} (x_i - \tau_k) & f\ (x_i - \tau_k) > 0 \\ 0 & Otherwise \end{cases}$$

This model assumes a linear trend between joinpoints and continuity at the joinpoints. It is mainly used to identify the points of inflation in the trends and to detect the statistical significant change when changes occurred in the trends. This model has also same underlying assumptions as simple regression. If constant variance of error is assumed then estimates the parameters of joinpoint model with ordinary least squares and for non constant variance i.e. variance of errors depends on time then applied the weighted least square method to estimates the parameters.

There are three major decisions in any joinpoint regression analysis

1. The form of the mean function (Data distribution: Normal or Poisson; Equation: linear or log linear)
2. The location of the joinpoints given number of joinpoints, and
3. The optimal joinpoint model

The first step is to find out the form of data. The next step in fitting the model is to determine the range of the number of joinpoints to be tested, usually between 0 and 4. Then locations of the each given number of the joinpoints can be determined by using grid search method. This method creates a "grid" of all possible locations for joinpoints specified by the settings, and tests the error sum of square (SSE) at each one to find the best possible fit. The third step is to find the final model i.e. the optimal number of joinpoints and the optimal locations of related joinpoints using the permutation test method (Jiang et al., 2010).

Kim et al., (2000) proposed a series of permutation tests to determine the best number of change-points in segmented line regression. In choosing the better model between the one with k_0 change-points and the alternated with k_1 change-points, Kim and others proposed the Monte Carlo simulation approach for permutation tests based on F-statistic:

$$F_{(0)} = \frac{SSE(k_1)}{SSE(k_0)}$$

Obtained from the residual sum of squares: $SSE(k_0)$ and $SSE(k_1)$, for the model k_0 and k_1, where the degrees of freedom of the F-distribution is k_0 and k_1 respectively. Then using Monte Carlo simulation approach to calculate the frequency that the event $[F_{(i)} \geq F_{(0)}]$ happened, for the F-statistic: $F_{(i)}, i = 1,2,\ldots, N-1$;

$$p = \frac{number\ of\ times\ that\left[F_{(i)} \geq F_{(0)}\right]}{N}$$

The hypothesis test H_0: model k_0 v/s H_1: model k_1, is implemented by comparing the probability p with the adjusted significant level α', which is defined as the Bonferroni significant value given the significant level α.

The sequential method to determine the optimal model using the permutation test is described below

1. k_0-The minimum number of joinpoints, k_1- maximum number of joinpoints;
   Testing the
   $H_0: k_0$ *is the best model* v/s
   $H_1: k_1$ *is the best model*
   $0 \leq k_0 \leq k_1$, and calculate $\alpha' = \alpha/(k_1 - k_0)$ for a given significant level α
2. If $p > \alpha'$, don't reject H_0 and set $k_1 = k_1 - 1$
   If $p \leq \alpha'$ then H_0 is rejected, set $k_0 = k_0 + 1$ and calculate new $\alpha' = \alpha/(k_1 - k_0)$
3. Go back to do step 1 and step 2 until $k_1 = k_0 + 1$ (Jiang et al., 2010)
   The Annual percent change (APC) is calculated when $(x_1, x_2, \ldots, x_n)$ represents years and $(y_1, y_2, \ldots, y_n)$ represents the log of the observed rate. Then APC between τ_i *and* τ_{i+1} is (Esteve J et al., 1994 and Kim et al., 2004)

$$APC = \frac{y_{n+1} - y_n}{y_n} \times 100$$

Where $y_n = e^{\alpha+\beta x}$, putting $y_n = e^{\alpha+\beta x}$ we get

$APC = 100 * (e^{\beta} - 1)$ Where β is slope.

RESULTS

Trends of mortality rates of selected seven ID are visualized by joinpoint regression analysis and have identified joinpoints with annual percentage change. Table 1 represents the APC's for different time period of the LRI, Diarrheal diseases, TB and IID, there is only one change point occurred in the mortality trend of these four diseases when both sexes combined. During the period 1990 to 2015 for the total (both sexes), LRI disease have accounted highest number of deaths among the all other 7 selected ID's followed by the Diarrheal diseases and HIV/AIDS. The IID's has counted minimum number of deaths during the year 2015 followed by HIV/TB.

When sex wise comparison is made, male mortality is higher than female mortality in the all seven IDs except Malaria as shown in the Table 1 and Table 2. Female death rates have decreased sharply than the male death rates in the study period from 1990 to 2015 but in case of HIV/AIDS and co-infection with TB female death rates increased sharply. Although mortality rates of all ID's showed overall decrement from the year 1990 to 2015 for the both sexes except HIV/AIDS and co-infection with TB.

Table 2 represents the APC's for different time period of the HIV/AIDS, Malaria and HIV with TB co-infection, there are three change points have observed in HIV/AIDS mortality trend and two change points observed in Malaria and HIV with TB co-infection mortality trend when both sexes combined.

Joinpoint regression model identify 3 JP's at HIV/AIDS mortality trend and 2 JP's at malaria and HIV/TB co-infection mortality trend in total (both sex) population. These three diseases approximately followed the same trend during the study period, 1990-2015 i.e., increased mortality rates up to 2004, later decreased. The initial increase of HIV/AIDS mortality may due to unsafe sex, sharing needles and injection drug use. The morality rates have extremely increased with different APCs with statistically significant till the year 2005.

Table 1: Analysis of mortality rates for LRI, Diarrheal, TB and IID by sex and total (Both sexes combined), identified trends, 1990-2015.

Infectious Diseases	Rate of 1990	Rate of 2015	Trend 1		Trend 2		Trend 3	
			Period	APC	Period	APC	Period	APC
Lower Respiratory Infections								
Male	64.26	38.74	1990-2005	-2.4^	2005-2015	-1.3^	–	–
Female	63.76	35.49	1990-2006	-2.7^	2006-2015	-1.7^	–	–
Total (Both sex)	64.01	37.13	1990-2005	-2.58^	2005-2015	-1.53^	–	–
Diarrheal diseases								
Male	42.11	18.13	1990-1998	-4.8^	1998-2010	-2.3^	2010-2015	-3.5^
Female	45.43	17.47	1990-1998	-4.6^	1998-2005	-2.3^	2005-2015	-4.0^
Total (Both sex)	43.76	17.80	1990-1997	-4.6^	1997-2015	-2.9^	–	–
Tuberculosis								
Male	35.33	19.57	1990-1998	-2.3^	1998-2002	-1.5^	2002-2015	-2.7^
Female	22.74	10.57	1990-1998	-2.7^	1998-2002	-2.0^	2002-2015	-3.7^
Total (Both sex)	29.07	15.09	1990-2003	-2.2^	2003-2015	-3.1^	–	–
Intestinal Infectious Diseases								
Male	4.77	2.58	1990-1998	-2.0^	1998-2015	-2.7^	–	–
Female	4.53	2.26	1990-1997	-2.3^	1997-2015	-3.0^	–	–
Total (Both sex)	4.65	2.42	1990-1997	-2.1^	1997-2015	-2.9^	–	–

Rates are no. cases/100000 persons, APC- Annual Percent Change, - not applicable, ^ APC is significantly different from the zero at alpha= 0.05

Table 2: Analysis of mortality rates HIV/AIDS, Malaria and HIV/TB co-infection by sex and total (Both sexes combined), identified trends, 1990-2015.

Infectious Diseases	Rate of 1990	Rate of 2015	Trend 1		Trend 2		Trend 3		Trend 4	
			Period	APC	Period	APC	Period	APC	Period	APC
HIV /AIDS										
Male	6.72	17.14	1990-1994	21.2^	1994-2001	8.5^	2001-2005	2.2^	2005-2015	-4.7^
Female	2.71	15.20	1990-1995	28.8^	1995-2001	15.0^	2001-2006	4.0^	2006-2015	-6.2^
Total (Both sex)	4.73	16.18	1990-1994	24.0^	1994-2000	12.1^	2000-2005	4.9^	2005-2015	-5.2^
Malaria										
Male	17.10	9.75	1990-2003	-0.6^	2003-2007	-2.7^	2007-2015	-6.7^	_	_
Female	18.32	10.07	1990-2003	-0.4^	2003-2007	-3.2^	2007-2015	-6.7^	_	_
Total (Both sex)	17.71	9.91	1990-2003	0.5^	2003-2007	-3.0^	2007-2015	-6.7^	_	_
HIV/TB										
Male	1.65	3.15	1990-1994	16.6^	1994-2000	8.8^	2000-2005	2.6^	2005-2015	-5.7^
Female	0.81	2.58	1991-1995	23.4^	1995-2001	12.2^	2001-2006	1.9	2006-2015	-7.5^
Total (Both sex)	1.24	2.87	1990-1996	17.5^	1996-2004	7.2^	2004-2015	-6.0^	_	_

Rates are no. cases/100000 persons, APC- Annual Percent Change, - not applicable, ^ APC is significantly different from the zero at alpha= 0.05

Gender wise comparison is made; 3 JP's at HIV/AIDS mortality trend and 2 JP's at malaria and HIV/TB co-infection mortality trend in both male and female population. The higher mortality can be seen in male than the female population in case of HIV/AIDS and HIV/TB co-infection. But in case of malaria, female mortality is higher than the male mortality. But both sexes have equally exposed to the malaria disease as per the available evidence but pregnant women and pregnant women with HIV are in high risk.

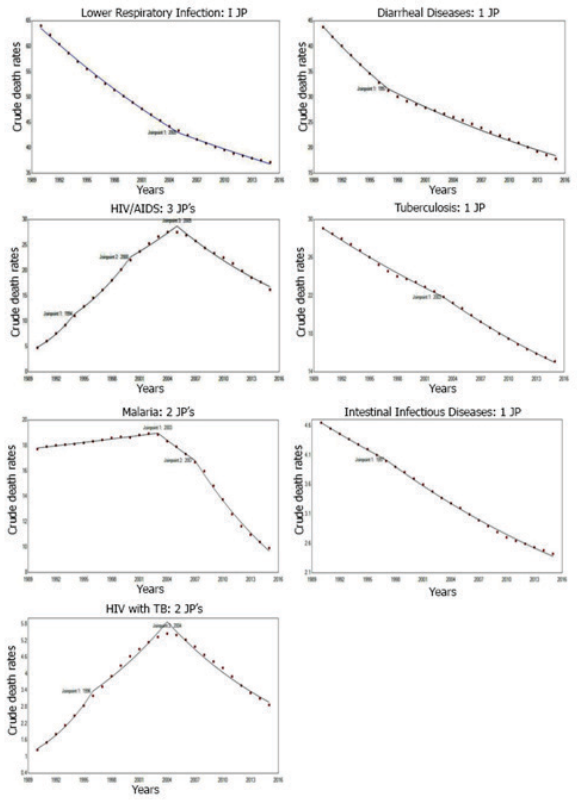

Figure 2: Observed mortality rates and estimated mortality rates through Joinpoint regression model of both sex.

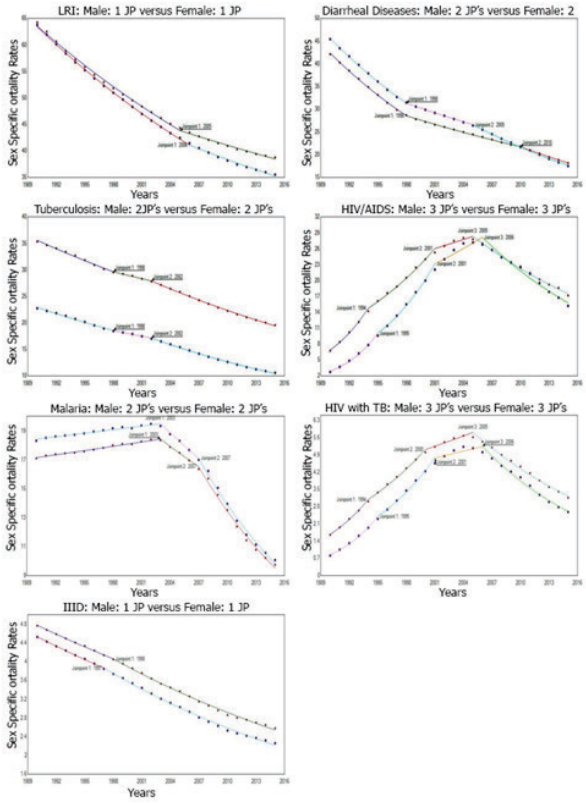

Figure 3: Comparison of sex specific mortality rates and estimated mortality rates through Joinpoint regression model.

♦ Indicates Male mortality rates • Indicates Female mortality rates

DISCUSSION

Joinpoint regression model identifies one JP at LRI, Diarrheal, TB and IID mortality trend in total (both sex) population. All ID's gradually decreased throughout the study period, 1990-2015. All the changes occurred in trends are statistically significant. Gender wise comparison made; LRI and IID mortality trend have two JP's in the both male and female population and one JP at Diarrheal and TB mortality trend. High mortality is observed in the male population than the female mortality.

This gender inequality may be due to lifestyle, behavior and socioeconomic difference between the males and females (Matthew E. F et al., 2007, Neyrolles O et al., 2009, Sevilimedu V et al., 2016).

Late 1990's, introduction of Antiretroviral therapy played a significant role in increasing the life expectancy of HIV/AIDS patients and reducing the risk of TB infection in people living with HIV. The prevention of Mother to child transmission strategy is also great success in reducing the infant mortality due to HIV/AIDS disease.

CONCLUSION

At present, while non-communicable diseases causes more death and disability than communicable diseases in the world as a whole communicable and related disease remain the leading cause of death and disability among the global poor. LRI is leading cause of mortality among under age 5 years and severe impact on the health of populations at all ages also. Lower respiratory infections remained world's deadly infectious disease till to the date followed by the diarrheal disease.

The trends of mortality rates for selected seven ID's are showing decrease through the study period 1990-2015, HIV/AIDS , HIV with TB and malaria mortality rates only increased up to the year 2004, after 2004 this mortality rates also sharply decreasing.

In the late 1990s, highly active antiretroviral therapy was developed. This therapy was able to reduce the HIV viral replication. This new treatment effected in major changes in the mortality rate for AIDS in specific age group. This may be the reason to reduction in mortality rates of ID's trend.

The risk of developing TB is high to who infected by HIV than non HIV population. Currently co-infection leads to more likely to the fatal and so hard to treat. Most of the people living with HIV who are also infected by TB have receiving ART therapy; this may results that decrement in mortality of HIV with TB co-infection in recent years. Directly observed treatment short course (DOTS) strategies by WHO has played a significant role in identification, diagnose, pre-

vention of TB and improvement in longevity of HIV patients who have also TB infection. These may the main reason for reduction in TB mortality rates as well as HIV-TB co-infection mortality rates.

LRI, Diarrheal diseases, IID and Malaria diseases have been prevented by practising good lifestyle and improvement in socioeconomic status, improvement in sanitation, personal hygiene of the people and good food to the society.

Sex is considerable epidemical factor for the numerous diseases. Sex difference played an important role in making adequate health policies and strategies. Both sexes have not equally susceptible to the all infectious diseases because it dependence on the lifestyle, behavioural and socioeconomic factors of males and females. In selected seven IDS, male population is more susceptible to LRI, diarrheal diseases, TB, HIV/AIDS, IID and HIV/TB co-infections.

Decreases in the mortality rates of selected ID's may be because of advancement of Science and Technology which improvement in the medical facilities, awareness about the ID's to the people due to globalization. Proper implementations of health policies by UN and their national Governments led to downfall in the trends of mortality rates. Despite a decrease in deaths caused by infectious diseases that was interrupted by HIV/AIDS at beginning of the 1990s, infectious diseases continue to be a major cause of death, which is a huge challenge to the public health.

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