Practical Insights for Public Health Decision-Makers: Using Time Series Models with NTD Disease Counts (Selected) for Myanmar, Nepal, and Timor-Leste

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ABSTRACT

The effort to provide medical and public health services in order to eliminate (or bring to near-zero) the burden of neglected tropical diseases (NTDs) on global populations is a public health issue that can be aided through managerial epidemiologic practice. The use of epidemiology (including statistical methods) to study the health history of a population, diagnose the health of a community, and/or examine the work of health services can be enacted in a way to better understand the health status of a population and matters related to health service utilization within a population or community. This paper describes the use of time series methods from managerial epidemiology to provide additional insights for public health decision-makers seeking to reduce NTD counts in the WHO South-East Asia Region, specifically, the countries of Myanmar, Nepal, and Timor-Leste. The examination of leprosy and visceral leishmaniasis disease counts for the three countries revealed interesting patterns. ARIMA models were used and included the calculation of the 95% CI around forecasted values that had public health significance for public health decision-makers. An important consideration for these decision-makers is to take steps that will control specific neglected tropical diseases and not allow the diseases to get out of control.

INTRODUCTION

The use of epidemiology to study the health history of a population, diagnose the health of a community, and/or examine the work of health services can be assembled in a way to better understand the health status of a population and matters related to health service utilization within a population or community.[1-7] This focus on health status and the utilization of health services by a given population point to a specialized concentration of epidemiology called, managerial epidemiology [5] whose functional definition is the use of epidemiology for designing and managing the health care of populations; the study of the distribution and determinants of health and disease, including injuries and accidents, in specified populations; and the application of this study to the promotion of health, the prevention and control of disease, the design of health care services to meet population needs, and health policy.

Within this context, epidemiological data and information will be important for public health and health care managers when considering the design, operations, and evaluation of health service utilization for a population: [3-5]

- Chronic disease management in population healthcare management
- Healthcare-associated infections in a healthcare system
- Public health surveillance
- Reimbursement methods associated with population health management
- Population health outcomes
- Measuring and managing health outcomes in a healthcare system
- Promoting patient safety in a health organization
- Economic analysis of healthcare for populations
- Expanding delivery of hospital health care services for the elderly

The point of the list is to illustrate that these current topics are focused on understanding the health of a population and the utilization of health services by the community or population with an eye toward improvement. The global effort to provide medical and public health services to eliminate (or bring to near-zero) the impact of neglected tropical diseases (NTDs) on global populations is one that can be aided by managerial epidemiologic practice for guiding the efforts of public health decision-makers.[8] NTDs are diseases associated with poverty,[8,9] and several of them were identified for eradication in the late 1980s.[10]

Actions to control or eliminate NTDs depend on an understanding of the burden of disease.[11,12] Health planning[13] for the reduction of NTDs requires the measurement of health status and prevalence of disease in the population. Epidemiologic information allows health planners to work toward the improvement of the health status of the population while also decreasing inequalities in health status among various groups in a population or between different geographic areas.[14] Statistical trends in the analysis of diseases provide some indication of the success of existing disease control efforts or point to the need for additional actions.[15]

The World Health Organization South-East Asia Region (WHO-SEAR) accounts for the second highest burden of NTDs across the globe.[16] The countries of this area include Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand, and Timor-Leste. At least one NTD is present in eleven countries in the region. Additionally, it has been reported that "59% of the global population requiring interventions against lymphatic filariasis (LF), 66.5% of new cases of leprosy, and 56% of children requiring regular deworming against soil-transmitted helminthiases" were accounted for in the WHO South-East Asia Region while public health efforts of the Region accounted for a 20% reduction in the total population requiring NTD interventions.[16]

Were any of the analytic methods of managerial epidemiology used to provide additional insights on the trends regarding disease counts in WHO-SEAR? A PubMed search including publications over the past five years (2019-2023) did not reveal any works for the following search terms: neglected tropical diseases + time series + forecasting + South-East Asia Region; neglected tropical diseases + trend analysis + South-East Asia; neglected tropical diseases + time series + Indian subcontinent. Thus, this paper demonstrates the use of time series methods from managerial epidemiology to provide additional insights for public health decision-makers seeking to reduce NTD counts in the WHO South-East Asia Region.

MATERIALS & METHODS

Aims

The purpose of this secondary data analysis project was to demonstrate that an ARIMA time series model could predict a reasonable number of counts (along with 95% CI) beyond the original time series for specific NTDs (leprosy, visceral leishmaniasis) in each of the comparative WHO SEAR countries (with similar HDI) for public health programming. The main, statistical hypothesis (Ho) was that no trend in NTD counts would be found in each of the comparative countries for the time period in question.

Study design

A time series ecologic study design [17,18] was used in cases where the aggregate reported counts for a specific NTD were examined over time in comparative countries.

Definitions of key concepts/variables

Neglected Tropical Disease. The World Health Organization (WHO) described these diseases, among them leprosy and visceral leishmaniasis, as "a diverse group of 20 conditions that are mainly prevalent in tropical areas, where they affect more than 1 billion people who live in impoverished communities. They are caused by a variety of pathogens including viruses, bacteria, parasites, fungi and toxins. These diseases cause devastating health, social and economic consequences to more than one billion people." [19]

Leprosy is caused by the bacteria Mycobacterium leprae and affects the skin, peripheral nerves, mucosa of the upper respiratory tract, and the eyes. The WHO described the burden of leprosy as follows:[20]

Leprosy is a neglected tropical disease (NTD) which still occurs in more than 120 countries, with more than 200 000 new cases reported every year. Elimination of leprosy as a public health problem globally (defined as prevalence of less than 1 per 10 000 population) was achieved in 2000 (as per World Health Assembly resolution 44.9) and in most countries by 2010. The reduction in the number of new cases has been gradual, both globally and in the WHO regions.

Additionally, leishmaniasis is caused by a protozoa parasite from over 20 Leishmania species that is transmitted by the bite of an infected female phlebotomine sandfly. The WHO described the burden of visceral leishmaniasis (VL) as follows:[21]

Visceral leishmaniasis (VL), also known as kala-azar, is fatal if left untreated in over 95% of cases. It is characterized by irregular bouts of fever, weight loss, enlargement of the spleen and liver, and anemia. Most cases occur in Brazil, east Africa and India. An estimated 50 000 to 90 000 new cases of VL occur worldwide annually, with only 25–45% reported to WHO. It has outbreak and mortality potential.

Human Development Index (HDI). The United Nations Development Program (UNDP) described the index as follows:[22]
The HDI was created to emphasize that people and their capabilities should be the ultimate criteria for assessing the development of a country, not economic growth alone. The Human Development Index (HDI) is a summary measure of average achievement in key dimensions of human development: a long and healthy life, being knowledgeable and having a decent standard of living. The HDI is the geometric mean of normalized indices for each of the three dimensions.

Population to be studied

Aggregate disease counts for leprosy and visceral leishmaniasis from the populations of Myanmar (HDI-2021: 0.585), Nepal (HDI-2021: 0.602), and Timor-Leste (HDI-2021: 0.607) were reported to the WHO by the health ministries of each country. The

WHO processed these data along with similar data from other countries.

The selected countries (Myanmar, Nepal, and Timor-Leste in the WHO South-East Asia Region) had population HDI values that were characterized as "medium human development" with HDI Ranks of 149, 143, and 140, respectively, and with a small population size.

Data sources

The data were downloaded from the WHO Global Health Observatory:[23] "The GHO data repository is WHO's gateway to health-related statistics for its 194 Member States. It provides access to over 1000 indicators on priority health topics including mortality and burden of diseases, the Millennium Development Goals (child nutrition, child health, maternal and reproductive health, immunization, HIV/AIDS, tuberculosis, malaria, neglected diseases, water and sanitation), non-communicable diseases and risk factors, epidemic-prone diseases, health systems, environmental health, violence and injuries, equity among others."

The specific data sources included:

Public-use leprosy data (years 2012 thru 2021) for Myanmar, Nepal, and Timor-Leste were found at this location: https://apps.who.int/gho/data/node.main-searo.NTDLEPR3?lang=en

Public-use visceral leishmaniasis data (years 2005 thru 2021) for Nepal were found at this location: https://apps.who.int/gho/data/node.main-searo.NTDLEISHVNUM?lang=en

Public-use HDI (2021) data were downloaded from the UNDP at this location: https://hdr.undp.org/data-center/human-development-index#/indicies/HDI

Data management

The aggregate counts for each disease by country and year were entered into a small desktop, MS-Access database for organization and storage. Datafiles were then exported in CSV format for analysis in statistical software or data science workbench software.

Statistical Analysis:

A time series analysis examines changes in data from a specific event over time.[12] Any data collected over time can be considered a time series which usually takes the form of aggregated numerical data collected over time and at regular intervals.[24] A time series analysis often forecasts or predicts data values into the future.

The autoregressive integrated moving average (ARIMA) model is one type of time series analysis model. The general formula for the ARIMA model is as follows:[25]

$$F_t = L_t + \Omega_1 D'_{t-1} + \ldots + \Omega_p D'_{t-p} + \beta_q E_{t-1} + \ldots + \beta_q E_{t-q}, \text{ where}$$

F_t = forecast point at time t

L_t = Level at time t (straight line approximation of all your data at one time point - calculated in ARIMA, it uses the mean of differenced data times smoothing constants)

D'_{t-p} = previous differenced observed data points

E_{t-q} = Error in prediction on previous data points

Ω and β are smoothing constants

ARIMA has been previously described, [18,24,26-29] and the model can be understood using three parts:

- Autoregressive (AR)
- Integrated (I) or Difference
- Moving Average (MA)

The ARIMA model was used to forecast the aggregate counts of leprosy, and, separately, visceral leishmaniasis in the countries included in this project using the processes found in NCSS. The forecast extended 1/3 of the distance beyond the original time series dataset with the 95% confidence interval (LL, lower limit and UL, upper limit) around the forecast. Model Estimation and Autocorrelation Plots were reviewed. The analytic software used in this study was

NCSS 2023 Statistical Software (2023). NCSS, LLC. Kaysville, Utah, USA. URL: ncss.com/software/ncss.

Limitations

A key assumption is that the aggregate data were completed by the health ministry and, subsequently, processed for public use by the WHO. There are well-recognized limitations to the use of the ecologic study design in epidemiology, including the ecologic fallacy and the presence of confounders. While the annual counts of data from some countries is small, there is no universally accepted rule[24] regarding the number of records needed for a time series analysis. Therefore, the rule of thumb to not extend the forecast beyond 1/3 of the length of the time series dataset will be employed.[27]

NTD-Leprosy

Myanmar

Ethical considerations

A JSPHE organizational ethics team reviewed and approved the study protocol (5 June 2023). The committee confirmed that this data analysis project would employ public-use data from the WHO and the UNDP. No human interviews or medical data would be required, and the protocol, as described, was likely to yield useful information for public health practice.

RESULTS

Patterns in disease counts for leprosy were examined using data (2012-2021) from Myanmar, Nepal, and Timor-Leste. The disease counts for leprosy were plotted for each country, and then, an ARIMA time series model was used to forecast possible disease counts into the future, yielding a 95% confidence interval for the forecasted values.
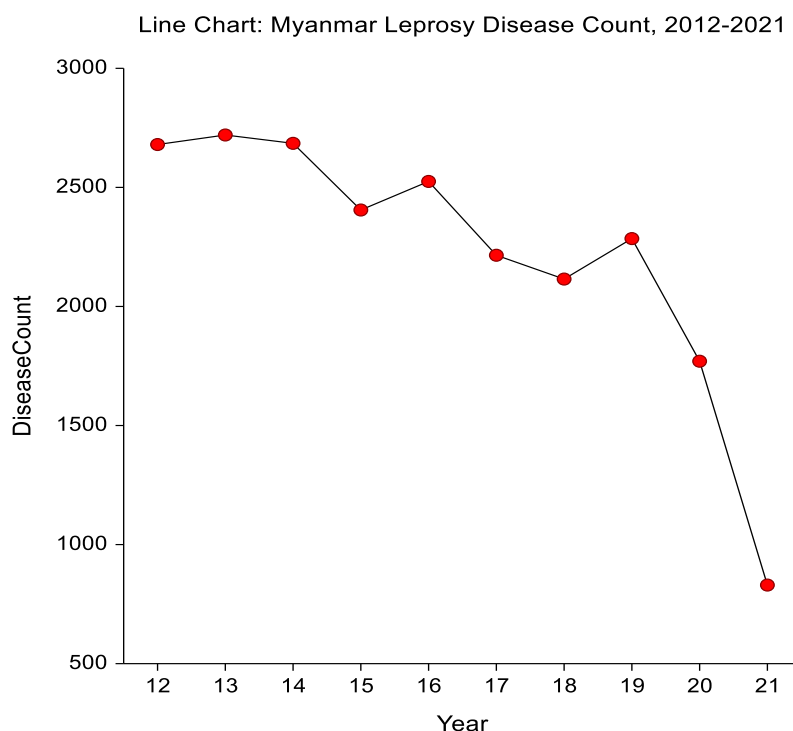
Fig 1: Leprosy Disease Counts for Myanmar, 2012-2021.
NCSS 2023 Statistical Software (2023). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/ncss.

The disease counts were plotted to explore the pattern of disease counts reported by each country over a decade. The counts of lep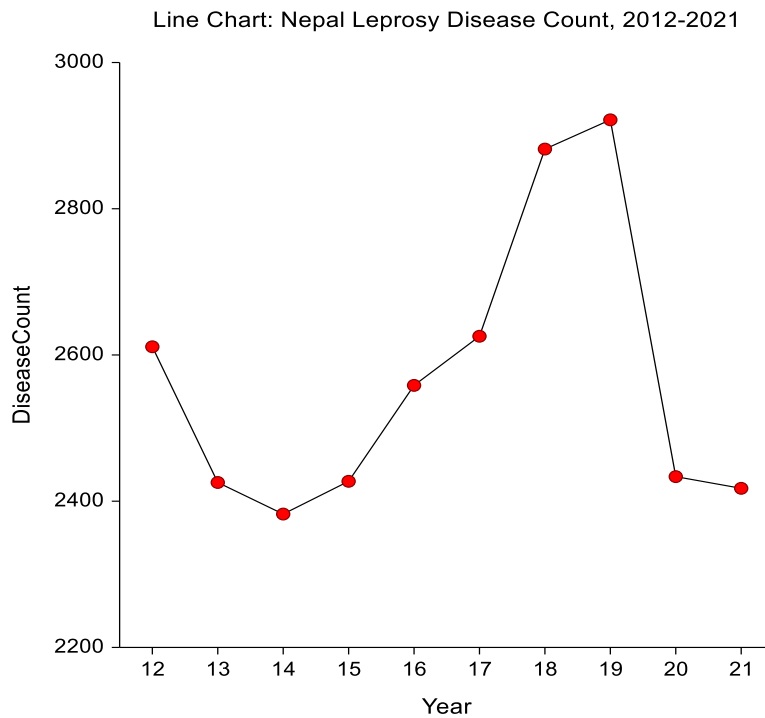rosy reported in Myanmar showed a downward pattern from 2012 to 2021, and there was a steep decline in the counts reported beginning in 2019.

Nepal

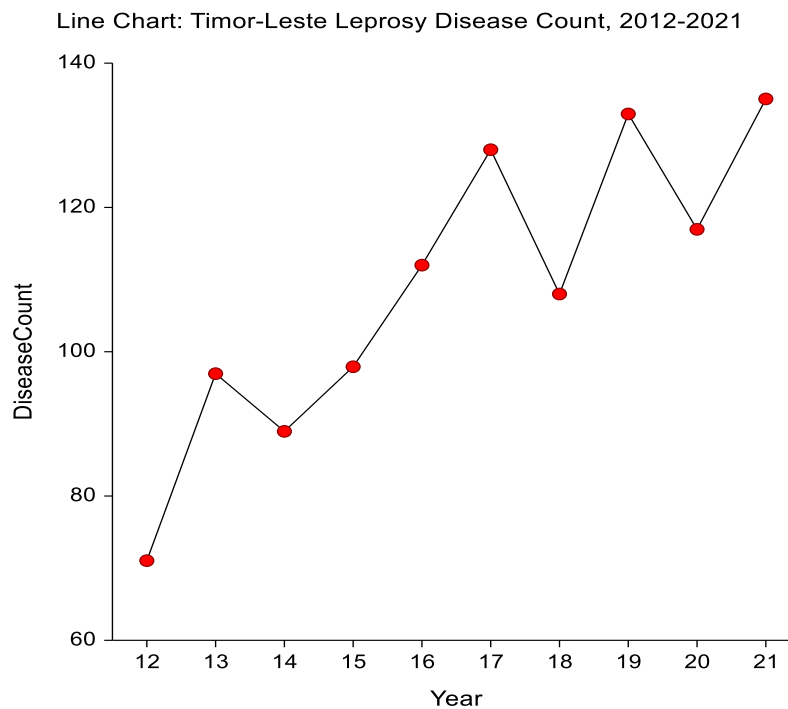The counts of leprosy reported in Nepal from 2012 to 2021 show an irregular pattern. There was a U-shape in reports of leprosy from 2012 to 2019. After 2019, the counts of leprosy showed a decline.

Fig 2: Leprosy Disease Counts for Nepal, 2012-2021.
NCSS 2023 Statistical Software (2023). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/ncss.

Timor-Leste

Fig 3: Leprosy Disease Counts for Timor-Leste, 2012-2021.
NCSS 2023 Statistical Software (2023). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/ncss.

The counts of leprosy reported in Timor-Leste showed an upward pattern from 2012 to 2021. Notice the jagged shape of the reporting of leprosy in the country represented in the line chart. The overall counts of leprosy in Timor-Leste were smaller compared to the counts in Myanmar and Nepal. Given the available time series data from each country, an ARIMA statistical model was used to forecast possible disease counts, and a 95% confidence interval was reported for the forecasted values (see Table 1).

Table 1: NTD (Leprosy) Time series Forecast: Myanmar, Nepal, Timor-Leste, 2012-2023

	Myanmar ARIMA (2,0,0) Pseudo R-sq 61.274 MSE 143517.2 Autocorr Plot: No pattern				**Nepal** ARIMA (2,0,0) Pseudo R-sq 43.951 MSE 24098.35 Autocorr Plot: No pattern				**Timor-Leste** ARIMA (2,0,0) Pseudo R-sq 48.425 MSE 244.696 Autocorr Plot: No pattern			
	Actual	Forecast	95% CI LL	95% CI UL	Actual	Forecast	95% CI LL	95% CI UL	Actual	Forecast	95% CI LL	95% CI UL
2012	2680				2612	2618			71			
2013	2721				2425	2529			97			
2014	2687				2382	2439			89			
2015	2403				2427	2520			98			
2016	2526				2559	2578			112			
2017	2216				2626	2646			128			
2018	2117				2882	2615			108			
2019	2287				2921	2759			133			
2020	1768				2434	2634			117			
2021	828	1400	0	2867	2418	2260	1885	2635	135	125	93	157
2022		183	0	1650		2541	2166	2915		121	89	153
2023		0	0	1958		2639	2263	3014		128	90	166

NCSS 2023 Statistical Software (2023). NCSS, LLC. Kaysville, Utah, USA

The time series models forecasted future leprosy counts using the existing data. The statistical results showed that the path to under 200 counts of leprosy is possible in Myanmar. By contrast, the forecasted counts of leprosy for Nepal and Timor-Leste showed different results.

NTD-Visceral leishmaniasis
Nepal
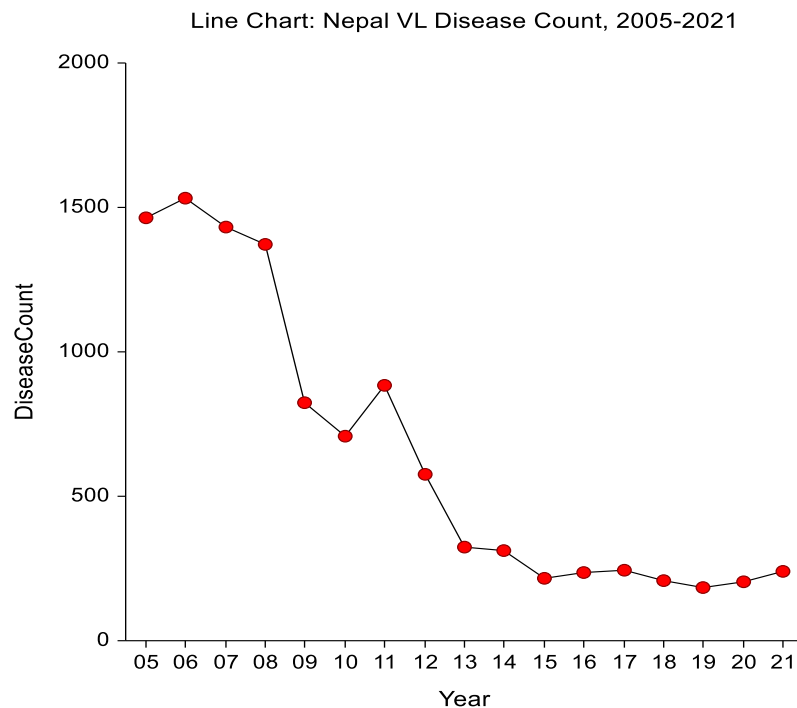
Fig 4: Visceral Leishmaniasis (VL) Disease Counts for Nepal, 2005-2021.
NCSS 2023 Statistical Software (2023). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/ncss.

Visceral leishmaniasis (VL) counts were reported for Nepal but not for Myanmar or Timor-Leste. From 2005 to 2021, VL counts decreased from approximately 1500 cases to a value as low as 185. A particularly steep decline can be seen from 2008 to 2018. Given the slightly longer time series of available data, an ARIMA statistical model was used to forecast possible disease counts, and a 95% confidence interval was reported for the forecasted values (see Table 2). The possible counts of VL cases were forecasted to 2025.

Table 2: NTD (Visceral Leishmaniasis) Time series Forecast: Nepal, 2005-2025

	Nepal ARIMA (2,0,0) Pseudo R-sq 87.952 MSE 33611.43 Autocorr Plot: No pattern			
	Actual	Forecast	95% CI LL	95% CI UL
2005	1463			
2006	1531			
2007	1433			
2008	1371			
2009	824			
2010	708			
2011	886			
2012	575			
2013	325			
2014	311			
2015	217			
2016	237			
2017	244			
2018	208			
2019	185			
2020	206			
2021	240	225	0	767
2022		260	0	802
2023		277	0	950
2024		293	0	1067
2025		308	0	1165

NCSS 2023 Statistical Software (2023). NCSS, LLC. Kaysville, Utah, USA

DISCUSSION

The disease counts for the selected countries reveals interesting patterns. For leprosy disease counts over a decade, a downward pattern was seen in the data from Myanmar and Nepal (Fig. 1 and Fig. 2). However, there was a slight upward pattern in leprosy reports from Timor-Leste (Fig. 3). These patterns were uncovered in the line charts that were plotted, trends were identified, and forecasted values calculated. The ARIMA models for each country also forecasted possible values with a 95% confidence interval around these data values for leprosy (Table 1). The model for Myanmar was the strongest of the three countries (Pseudo R-sq = 61.274); notice the scale on the vertical axis.

Nepal was the only country able to report visceral leishmaniasis cases and the 15-year time span of data from Nepal showed a general downward pattern (Fig. 4). The ARIMA model for Nepal forecasted possible values with a 95% confidence interval around these VL data values (Table 2). This was a strong ARIMA model (Pseudo R-sq = 87.952). There was no pattern detected in the autocorrelation plots for ARIMA models.

These results were particularly interesting from a technical point of view. The results also had public health significance. The patterns found in each figure (Figs. 1-4) may indicate both the prevalence of disease counts over the time series and, also, remind public health decision-makers of temporal events that could have occurred to account for those patterns.

The forecasted disease counts with a 95% confidence interval (LL, UL) are especially useful to public health decision-makers. If no meaningful change in public health intervention is applied to the experience of disease in each country, then excess disease counts could be as high as the UL. However, an effective public health intervention could reduce the disease counts to the LL.[30] Collectively, public health decision-makers could discuss the public health significance of the patterns of disease counts and the forecasted values when considering public health actions to address the cases of leprosy and visceral leishmaniasis reported in each country (or geographic area within a specific country) on the way to reaching both national and regional goals for the reduction of these diseases.

The World Health Organization has already identified treatment and prevention strategies for leprosy and visceral leishmaniasis:[31,32]

Leprosy
Treatment
Leprosy is a curable disease. The currently recommended treatment regimen consists of three drugs: dapsone, rifampicin, and clofazimine. The combination is referred to as multi-drug therapy (MDT). The duration of treatment is six months for Paucibacillary (PB) and 12 months for Multibacillary (MB) cases. MDT kills the pathogen and cures the patient. Early diagnosis and prompt treatment can help prevent disabilities. WHO has been providing MDT free of cost. Free MDT was initially funded by The Nippon Foundation and since 2000 it has been donated through an agreement with Novartis.

Prevention
Case detection and treatment with MDT alone have proven insufficient to interrupt transmission. To boost the prevention of leprosy, with the consent of the index case, WHO recommends tracing household contacts along with the neighborhood and social contacts of each patient, accompanied by the administration of a single dose of rifampicin as preventive chemotherapy.

Visceral Leishmaniasis
Diagnosis and treatment
People suspected of suffering from visceral leishmaniasis should seek medical care immediately. Diagnosis is made by combining clinical signs with parasitological or serological tests (such as rapid diagnostic tests). In cutaneous and mucocutaneous leishmaniasis serological tests have limited value and clinical manifestation with parasitological tests confirms the diagnosis.

The treatment of leishmaniasis depends on several factors including type of disease, concomitant pathologies, parasite species and geographic location. Leishmaniasis is a treatable and curable disease, which requires an immunocompetent system because medicines will not rid the body of the parasite, thus there is a risk of relapse if immunosuppression occurs. All patients diagnosed with visceral leishmaniasis require prompt and complete treatment. Detailed information on the treatment is available in the WHO technical report series 949, Control of leishmaniasis and the latest guidelines published on HIV-VL in east Africa and South-East Asia and the guideline for the treatment of leishmaniasis in the Americas.

Prevention and control
Preventing and controlling the spread of leishmaniasis is complex and requires many tools. Key strategies include:

- **Early diagnosis and effective prompt treatment** reduce the prevalence of the disease and prevents disabilities and death. It also helps to reduce transmission and to monitor the spread and burden of disease. There are highly effective and safe anti-leishmanial medicines particularly for visceral leishmaniasis, although they can be difficult to use. Access to medicines has significantly improved thanks to a WHO-negotiated price scheme and a medicine donation program through the WHO.

- **Vector control** helps to reduce or interrupt transmission of disease by decreasing the number of sandflies. Control methods include insecticide spray, use of insecticide-treated nets, environmental management and personal protection.

- **Effective disease surveillance** is important in order to promptly monitor and act during epidemics and situations with high case fatality rates under treatment.

- **Control of animal reservoir hosts** is complex and should be tailored to the local situation.

- **Social mobilization and strengthening partnerships** along with education of the community with effective behavioral change interventions must always be

locally adapted. Partnership and collaboration with various stakeholders and other vector-borne disease control programs is also critical.

Public health decision-makers in each country could review the data for both disease counts and discuss treatment and prevention options. The outcome of such a discussion could aid medical and public health interventions, namely in terms of reducing the incidence of leprosy and visceral leishmaniasis. Additionally, issues of resource availability, reporting of accurate data, and community engagement are topics that could also be considered. The key concern for public health decision-makers is to take steps that will control these neglected tropical diseases and not let them get out of control, because the upper limits of disease forecasts indicate the possible burden that excess counts of leprosy and visceral leishmaniasis would place both on clinical care teams and the public health system of a particular geographic area.

As cited earlier, poverty in a population is a common factor of all forms of NTDs [8,9]. Other factors associated with NTD are as follows:[33]

- NTDs are chronic, debilitating infectious diseases that are not necessarily fatal.
- These diseases carry social stigma for those impacted by them that makes it nearly impossible for the individuals to find employment.
- The NTD burden is largely confined to resource-limited/Third World countries with poor economies.

In general, these diseases are often absent in wealthy countries. Because countries impacted by NTDs often have poorly functioning economies, there is little financial incentive for the biopharma industry to develop new drugs or vaccines in the absence of an economic market. Countries with poor economies do not have

individuals who are able to purchase the products created by these biopharmaceutical companies.[33]

Despite these conditions, the WHO and its global partners have identified broad NTD control and reduction strategies in the following areas:[34]

- Innovative and intensified disease management
- Preventive chemotherapy
- Vector control
- Veterinary public health
- Provision of safe water, sanitation, and hygiene

Public health decision-makers could engage with communities in the countries included in this report. Discussing the data related to leprosy and visceral leishmaniasis, along with disease control and reduction strategies, can help to identify which strategies would be appropriate for each country. Ideally, the activities that flow from the selected strategies could be deployed, supported by country, civil society, and international resources, and monitored as part of the WHO Country Cooperation Strategy (most recent) for each country.

CONCLUSION

The international effort to provide medical and public health services to eliminate (or bring to near-zero) the burden of neglected tropical diseases (NTDs) on populations in various countries around the world is a global public health goal that can be aided by managerial epidemiologic practice in terms of positively guiding the efforts of public health decision-makers (WHO 2020). This study used public-use data with statistical methods to examine the forecasts (95% CI) for leprosy and visceral leishmaniasis counts over time in selected countries in the WHO South-East Asia Region. The statistical analysis revealed additional insights from the available data and suggested that public health decision-makers and their partners could engage with

community representatives to identify the next steps for the control and reduction of leprosy and visceral leishmaniasis in these countries.

Biographical Statement: Dr GV Fant is a public health epidemiologist, public health consultant, and visiting faculty member at JSPH, Rajasthan, India, having taught subjects in epidemiology, biostatistics, field epidemiology, and health database concepts to Indian MPH-degree students and public health professionals since 2013. He is, also, the Executive Director of the Society for Epidemiology at JSPH. Dr Fant earned his doctorate (PhD) from University of Nebraska in 1997 and doctorate (PhD-h.c.) in health sciences and public service from Poornima University in 2021. Dr. Fant earned professional recognition as an Epidemiologist from the American College of Epidemiology (MACE) in 2002, the Society for Epidemiology at JSPH (MSEpi) in 2019, CIMP-Data Science in 2021, and CEHRS in 2022. Beginning in 1997, Dr. Fant has served as a U.S. civil servant and epidemiologist in Northern Virginia, USA.

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