National and Sub-national Burden of Infectious Diseases in Iran, 1990 to 2013: The Study Protocol

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Abstract

Background: To assess the burden of infectious diseases, it is necessary to utilize a systematic approach for data collection and deploying the sophisticated methods to estimate the burden of infectious diseases for health policy making at national level. The present study protocol is aimed to provide a comprehensive explanation of the general structure and method used in the national and sub-national burden of selected infectious diseases study in Iran from 1990 to 2013.

Methods: The trend, burden, and geographical inequality pattern of infectious diseases will be estimated through a comprehensive review of published and unpublished data. Different sources of data including health surveys, surveillance data, hospital data surveys, death registry system, census, household expenditure survey, and published manuscripts will be synthesized to calculate the estimates. All indicators will be reported by gender, age, and geographic area. Two different statistical models include "Spatio-Temporal" and "Bayesian multilevel autoregressive" will be applied to overcome the scarcity and misalignment of the obtained data.

Discussion: Estimating the prevalence trend and burden of infectious diseases would be helpful to use more cost-effective interventions considering sub-national variations. Additionally, the information obtained from these studies can depict the ability of health system authorities in controlling these types of diseases. Overall, the present applied models can be deployed as a part of inputs in further studies to estimate the burden of diseases, not only in Iran but also all around the Middle East countries.

Keywords: Burden of diseases, DALY, infectious diseases, Iran, study profile, YLD, YLL

Introduction

Infectious diseases impose a huge load of burden on the health care systems globally.[1–4] This is evidenced by the considerable rates of morbidity, mortality, and related costs associated with these types of disease around the whole world.[5] Drawing on the results of the Global Burden of Disease project (GBD) in 2010,[6] infectious diseases such as diarrhea, lower respiratory infectious diseases, HIV/AIDS, and malaria were ranked among the top ten diseases with the highest amount of burden. Continual possibility of wildlife-to-human transmission, as well as being re-emerging over time and consequently deadly human pandemics are among the other parameters introducing infectious diseases as one of the most important worldwide health disasters.[7]

Considering the variety of geographical and socio-economic situations in Iran, infectious diseases are known as a major health concern in this country. Drawing on the Joint United Nations Programme on HIV/AIDS (UNAIDS) global report, it was estimated that roughly 71,000 (53,000 – 100,000) individuals were living with HIV to the end of 2012, while this number is still increasing over time.[8] Being located in the vicinity of endemic countries such as Pakistan and Afghanistan might partly justify the considerable prevalence rate of TB, especially in border cities of east and southeastern of Iran.[9] Approximately 3000 cases of Malaria were reported from Iran in 2010, while 95 % of the patients were living in only three provinces.[10] Brucellosis is one of the other major infectious diseases especially among people in rural areas of Iran, which its considerable prevalence might somehow be related to the economic dependency of rural population on livestock and agriculture activities in Iran.[11] Above-mentioned examples demonstrate that infectious diseases should still be considered as major health problems in Iran.

Estimation of the burden of diseases seems to be necessary to take proper decisions toward healthcare cost management, determination of health priorities, definition of the extension of different diseases, and application the effective interventions to mitigate the consequences of infectious diseases in the communities. In addition, conducting the research projects in national and sub-national scales to estimate the burden and trend of infectious diseases might be helpful to provide a unique opportunity for the policymakers to fill the existing information gaps of the health-

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care system, as well as to compare the national results with the regional and global statistics. As a sub-component of the National and Sub-national Burden of Diseases (NASBOD) research project, the present study is advanced to calculate the burden of infectious diseases in Iran in a 23-year period from 1990 to 2013.

Materials and Methods

In the Burden of Infectious Diseases study (BID), the prevalence, incidence and measures for burden of infectious diseases including Years of Life Lost (YLLs), Years Lived with Disability (YLDs), and Disability Adjusted with Life Years (DALYs) will be estimated. The above-mentioned indicators will be reported by gender, age, and province from 1990 to 2013. Likewise, we will provide the uncertainty levels associated with these estimations.

To make consistency among the entire groups, numerous workshops were held for the team members and researchers based on their educational needs toward burden of diseases and standards of systematic review with a focus on the burden concept. Thereafter, technical team prepared a research proposal for each selected disease. In order to develop a specific and pre-defined study framework, an expert panel was held with the participation of experts consisted of the head of infectious diseases department, Ministry of Health (MOH), infectious diseases specialists, community medicine specialists, public health experts and epidemiologists. The selected diseases were defined according to the list of infectious diseases adopted for the Global Burden of Diseases (GBD) in 2010,[6] as well as numerous experts' points of view. The framework was modified with consideration of the prevalence, incidence, duration and severity, impact of diseases on the people's health, and data availability. Meanwhile, some other diseases including poliomyelitis, rubella, hemorrhagic fevers and brucellosis due to their importance for policy makers or prevalence among Iranian population, these diseases were also added to the current list. However, some other diseases such as dengue fever, varicella, Influenza and hookworm were excluded from the final list due to their low prevalence or not being of the high priority of Iran's ministry of health, or sub-optimal data availability; we reclassified the included diseases into eight categories as shown in the Table 1.

Ethical consideration

The ethical committee of Tehran University of Medical Sciences declared ethical approval and the permission for the publication of results depends on the funder approval.

Data collection sources

The investigators will use a systematic and comprehensive approach to provide comprehensive information about the variety of the prevalence and incidence of infectious diseases, at national, provincial, and district levels among Iranian general population. We will obtain data by searching the names of infectious diseases and the related Medical Subject Headings (MeSH) terms and all subheadings in the international (PubMed , ISI the Web of Science, and Scopus), and national databases (IranMedex ,Irandoc and SID). In addition, congress abstracts, conference proceedings, theses, and reports published in related databases in Persian language, such as IranMedex Irandoc and SID, will be assessed. To find the standard search terms the MeSH terms and Entry Terms (the PubMed thesaurus), and Emtrees (the EMBASE thesaurus) will be used. Details on our search strategy and search terms

which will be used to obtain the needed data is available in the appendix 1. The Persian keywords for searching in domestic search engines will be equivalent to their English words and all probable combinations will be taken into account. We will also review the reference lists of the included article and relevant review articles.

Inclusion and exclusion criteria

The entire cross-sectional studies, results of the baseline of cohort studies and national surveys that estimated prevalence of selected diseases will be included. All national, provincial, district, and community studies conducted from January 1990 to December 2013, which reports prevalence or incidence data, will be included in the study. In the BID study, we don't have any language restriction. Results of the case reports and review articles, studies that have not provide a clear confirmation laboratory test for diagnosis of diseases, as well as the studies which have used convenient or non-random sampling will be excluded.

Study Selection Process

Reviewers will skim the titles. If the title meets inclusion criteria, the article will be evaluated by reviewing the abstract. The abstract review phase is designed to identify studies reporting the prevalence, incidence of diseases and their estimated uncertainty. The abstracts will be reviewed independently by two investigators, and will be excluded if both investigators agree that the article meets one or more of the exclusion criteria. Disagreement between investigators regarding abstract inclusion or exclusion will be resolved through consensus adjudication. In case of missing or vague data, the researchers will send emails to the corresponding authors and ask them to clarify the vague issues. The articles promoted on the basis of abstract review will undergo another independent parallel review to determine if they should be included based on full text review. We will identify additional data sources through personal communications with researchers.

Quality Assessment

A quality assessment form will be designed to screen all extracted articles in order to be scored. The scoring system will be based on the study characteristic sheet. This sheet will be designed according to the Newcastle Ottawa scale[12] with emphasis on the study design, scope, and level of study, sampling method, sample size, study populations, response rate and measurement method. Afterwards the completing quality assessment form by two researchers, disagreements will be discussed to resolve the existed inconsistency. Technical team will develop a data extraction form in which data will be categorized based on age, sex, scale of the study (National, provincial, district or community), scope of the study (urban, rural), and study year. Other main variables are prevalence, incidence, standard deviation (SD), confidence interval (CI) and/or standard error (SE) of the selected diseases.

Other Sources

We will use all infectious diseases surveillance data collected by Iranian CDCs, especially the data about tuberculosis, malaria, sexually transmitted diseases and HIV/AIDS, vaccine preventable diseases, and zoonosis diseases surveillance system. In order to have an estimation of the prevalence of specific diseases such as HIV we will also collect data on the size of the specific sub populations of HIV high risk groups including People Who Inject Drugs (PWIDs), Female Sex Workers (FSWs), and Men who

Table 1. Selected infectious diseases in Iran

	Disease	ICD10 code
Sexually transmitted diseases		
	HIV/AIDS	B20
	Chancroid	A57
	Chlamydia Infections	A56
	Gonorrhea	A54
	Syphilis	A50
	TB	A15
Vaccine preventable diseases		
	Measles	B05
	Rubella	B06
	Tetanus	A33
	Dyphteria	A36
	Pertosis	A37
	Acute poliomyelitis	A80
Zeonosis		
	Rabies	A82
	Brucellosis	A23
	Leishmaniasis	B55
	Hydatid cysts	B67
	Hemorrhagic Fever	A98
	Malaria	B50
	Meningitis	A87
	Encephalitis	A83
Acute upper and lower respiratory infectious diseases		J00 and J20

have Sex with Men (MSMs).

Blood donors' registration system data (the results of both taken and rejected people who volunteered for blood transfusion studies) from Iranian Blood Transfusion Organization (IBTO) as a data sources will be used for our modeling to estimate the general population prevalence and subsequently burden of diseases.

Hospital Data Survey provides inpatient data about the related diseases and morbidity in hospitals in Iran also data of the death registration system of Ministry of Health will be used in order to obtain cause specific mortality records. The prescribed drugs for STIs patients, which acquired by Outpatient Data Survey will be used as an indirect method to estimate the prevalence of these diseases. Census and household expenditure survey are other sources of data, which will be used to calculate the major covariates required to measure the burden of diseases.

We will calculate HIV/AIDS prevalence under several scenarios derived from existing models of Spectrum software (Estimation and Projection Package). The software will be set under a range of assumptions about the relevant sub-epidemics and four epidemiological parameters which will be used to fit a curve to generate the prevalence trend.[13]

Statistical analysis plans

Burden of disease is measured in DALYs. DALYs includes the sum of the Years of Life Lost due to premature death (YLL) and Years Lived with Disability (YLD). YLL will be calculated using age and disease-specific deaths, YLD using estimates of incidence and duration of non-fatal diseases for Iran and disability weights for each disease will be applied from the GBD study.

To access the entire national surveys and address the lack of data or non-informative data (i.e., those with large uncertainty) in some regions, we will use Spatio-temporal and Bayesian multilevel autoregressive models. Moreover, for some of the provinces

which were separated in the specified period of study, the problem of misaligned areal units arise that will settled by both models. In order to verify the model independency of the estimations, we will apply the two mentioned models.

Spatio-temporal model

As mentioned before, one of the models to overcome the data scarcity is Spatio-temporal Bayesian hierarchical modeling with conditional autoregressive (CAR) prior for spatial random effects (Spatio-temporal article). As the first assumption in this model, the nearby areas are more linked together than those farther away. This assumption allows model to improve estimations for the areas with incomplete or missing observations through borrowing information from the neighboring areas. Additionally, to join incompatible areal units among various data sources or over the years, spatio-temporal misalignment modeling will be utilized.

Bayesian Autoregressive Multilevel model

In this model observations are nested in more than one level, including provinces, sub-regions, regions, and national levels respectively. The hierarchical nature of the model allows higher levels to borrow information to the lower levels depending on the degree of data availability. Also units of each level borrow information to each other in case of data scarcity. The model considers a number of components including nonlinearity associated with age and variation over time, heterogeneity among data sources, linear time trend and covariate effects.

Actually, both models are best handled within a Bayesian framework, and statistical inference is carried out using Markov Chain Monte Carlo (MCMC) simulation. Besides, using regression models provides an opportunity to crosswalk between categorical and continuous variables, for dealing with the problem of different classification of measurement.

Discussion

The study of the burden of infectious diseases as a sub-component of a comprehensive project named NASBOD has been designed to fill out the information gaps of Iranian health system. The first global burden of diseases (GBD) study was performed in 1990,[14] and recently the results of GBD was updated for 2010.[6] The GBD 1990 study generated comprehensive estimates of mortality and morbidity, and documented the health consequences of 107 diseases by age, sex, and region. A comprehensive update of diseases burden has been done as of the 1990 study and the burden of 291 causes, 20 age groups and for 21 regions in 1990, 2005 and 2010 was performed.[6] The 2010 GBD study determined YLL, YLD, and consequently calculated the DALY as a single measure to quantify the burden of diseases, injuries and risk factors. Generally, burden studies have been conducted in several countries such as USA,[15,16] Australia,[17–19] Netherlands,[20] New Zealand,[21] Mexico,[22,23] Iran,[24] Pakistan,[25] Ghana,[26] Kenya,[27] Nairobi[28] and South Africa,[29] to estimate the burden of infectious diseases.

In a study conducted by Christie and Tobias (1998) in New Zealand, the mortality data was obtained from the Ministry of Health to measure the burden of infectious diseases from 1980 to 1993.[21] They applied the "cause of death" analysis as well as sub group analyses by sex, age, and ethnicity. As a considerable limitation, since they only included mortality data in their study, the researchers were not able to estimate the burden of non-fatal outcomes.

Health surveys, mortality data, vital statistics, national censuses, and published epidemiological studies were used as data sources in Mexico and Australia burden of diseases studies.[17,23] The Mexican researchers assessed all their results based on age; sex and selected regions, while six geographical regions were classified for all analyses based on the socioeconomic status of the population and total mortality numbers.

Naghavi, et al.[24] estimated DALY for diseases in six selected provinces and at national level in 2003 in Iran. After more than a decade, it seems to be essential to conduct a new study with more comprehensive methodology to fulfill the gaps and rectify lack of data regarding the burden of diseases in Iran. The BID study will describe and present the causes, origins, backgrounds and burden of important infectious diseases over a 23-year period. Acquisition of available national data sources and different methodologies provide certain advantages for this study comparing with the previous study in Iran [24] and sub-national studies in other countries.[23,30,31]

Trends of various diseases and pattern of geographical and socioeconomic inequalities at national and provincial levels will be another advantage of the BID study. Likewise, one of the most important strengths of the burden of infectious diseases study can be the consistent assessment of prevalence, incidence, mortality, duration, and severity, as well as a comprehensive list of infectious diseases, which are among the most important health priorities in Iran.

Burden of infectious disease study has also some limitations. First, in case of using the surveillance system reports of the MOH, we will face lack of annual data for our specific categorized years. Besides, it should be considered that acquired data might be influenced by over-reporting or under-reporting. Second, there is limited access to the grey literatures especially for sexually transmitted diseases due to lack of grey sources in Iran. Finally, for some diseases such as STIs and HIV, stigma inevitably leads to the scarcity of available valid data. However, the research team will apply the statistical models to deal with data scarcity and misalignment problems.

The policy implications are worth emphasizing at both national and sub-national levels. Regional differences in estimated burden would be helpful for highlighting the health concerns, evaluating the prevention interventions, and applying the most effective health policies. Geographical inequalities of diseases can be estimated as background dissimilarity and these results can also be considered as a guideline for resource allocation at sub-national level. Additionally, it seems that trend analysis and consequently the feasibility of further projections are among the most important characteristics of the burden of infectious diseases study.

Results of the BID study might be helpful to find the defects of the existing healthcare system in Iran, monitor the burden and trend of infectious diseases, and manage the relevant costs in the country. Moreover, it should be mentioned that BID study would help the researchers who are going to conduct similar studies not only at national and sub-national levels in Iran, but also around the whole developing world.

Author's Contribution

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Approval: *All authors have read and approved the content and the authorship of the final version of the submitted manuscript.*

Acknowledgments

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Appendix 1. Search strategies for infectious diseases

• Iran [Mesh] OR "I.R.Iran" OR "IR Iran" OR "Islamic Republic of Iran" OR "Iran (Islamic Republic of) OR "Iran (Islamic Republic)" OR "Iranian" OR "Iranians OR Persia*

AND

• All related terms of each disease separately

  AND

• Incidence OR prevalence

Sexually Transmitted Diseases

"Disease, Sexually Transmitted" OR "Diseases, Sexually Transmitted" OR" Sexually Transmitted Disease" OR" Sexually Transmitted Diseases" OR STDs OR "Venereal Diseases" OR "Disease, Venereal" OR "Diseases, Venereal" OR "Venereal Disease"

• **HIV**
"human immunodeficiency virus" OR "Acquired Immunodeficiency Syndrome" OR "AIDS-Related Complex" OR "AIDS-Related Opportunistic Infections" OR "HIV Infections" OR "HIV Seropositivity" OR "AIDS-Related Complex" OR "HIV Seroprevalence" OR "HIV-1" OR "HIV-2"

• **Chancroid**
Chancroid*

• **Chlamydia Infections**
"Infections, Chlamydia" OR "Chlamydia Infection" OR "Chlamydia Infections" OR "Infection, Chlamydia"

• **Gonorrhea**
Gonorrhea*

• **Granuloma Inguinale**
"Granuloma Venereum" OR Donovanosis OR "Granuloma Inguinale"

• **Syphilis**
"Great Pox" OR "Pox, Great" OR syphilis

• **Condylomata Acuminata**
"Venereal Warts"OR "Condylomata Acuminata" OR "Venereal Wart" OR" Wart, Venereal" OR "Warts, Venereal" OR "Genital Warts" OR "Genital Wart" OR "Wart, Genital" OR" Warts, Genital"

• **Herpes Genitalis**
"Genital Herpes" OR "Herpes, Genital" OR" Herpes Genitalis" OR "Herpes Simplex Virus Genital Infection" OR"Herpes Simplex, Genital" OR "Genital Herpes Simplex"

• **Urogenital Diseases**
"Urogenital Disease"OR "Urogenital Diseases"OR " Genitourinary Diseases"OR"Genitourinary Disease"

• **Genital Diseases**
"Gynecologic Diseases" OR " Diseases, Gynecologic" OR" Gynecologic Disease" OR" Genital Diseases"OR" Diseases, Genital" OR"Genital Disease"

• **Lymphogranuloma Venereum**
"Lymphogranuloma Inguinale" OR" Lymphogranuloma Venereum"
• **Chancre**
Chancre*

• **Trichomonas**
Trichomona*

Zoonosis

• Malaria

Remittent Fever OR Fever, Remittent OR Paludism OR Plasmodium Infections OR Infections, Plasmodium OR Infection, Plasmodium OR Plasmodium Infection OR Marsh Fever OR Fever, Marsh OR Malaria, Avian OR Avian Malaria OR Avian Malarias OR Plasmodium falciparum Malaria OR Malaria, Plasmodium falciparum OR Vivax Malaria Plasmodium OR vivax Malaria Malaria, OR Plasmodium vivax

• Brucellosis

Brucelloses OR Gibraltar Fever OR Fever, Gibraltar OR Rock Fever OR Fever, Rock OR Fevers, Rock OR Rock Fevers OR Undulant Fever OR Fever, Undulant OR Fevers, Undulant OR Undulant Fevers OR Cyprus Fever OR Cyprus Fevers OR Fever, Cyprus OR Fevers, Cyprus OR Malta Fever OR Fever, Malta OR Brucellosis, Pulmonary OR Brucelloses, Pulmonary OR Pulmonary Brucelloses OR Pulmonary Brucellosis

• Brucellosis, Bovine

Bovine Brucelloses OR Bovine Brucellosis OR Brucelloses, Bovine OR Bang's Disease OR Bangs Disease OR Disease, Bang's OR Bang Disease

• Leishmaniasis

Cutaneous Leishmaniases OR Cutaneous Leishmaniasis OR Leishmaniases, Cutaneous OR Oriental Sore OR Leishmaniasis, Cutaneous OR Visceral Leishmaniasis OR Kala-Azar OR Kala Azar OR Black Fever Fever, Black

• Hidatid cystics

Echinococcoses, Hepatic OR Hepatic Echinococcoses OR Echinococcosis, Hepatic OR Parovarian Cyst OR Hepatic Echinococcosis OR Echinococcosis, Hepatic Alveolar OR Alveolar Echinococcoses, Hepatic OR Alveolar Echinococcosis, Hepatic OR Echinococcoses, Hepatic Alveolar OR Hepatic Alveolar Echinococcoses OR Hepatic Alveolar Echinococcosis OR Hydatidosis, Hepatic OR Hepatic Hydatidoses OR Hepatic Hydatidosis OR Hydatidoses, Hepatic OR Alveolar Echinococcis, Hepatic OR Echinococcis, Hepatic Alveolar OR Hepatic Alveolar Echinococcis OR Hydatid Cyst, Hepatic OR Cyst, Hepatic Hydatid OR Cysts, Hepatic Hydatid OR Hepatic Hydatid Cyst OR Hepatic Hydatid Cysts OR Hydatid Cysts, Hepatic OR Hydatid Cyst of Morgagni OR Morgagni Hydatid Cyst OR Morgagni Hydatid Cysts OR Echinococcoses OR Hydatid Cyst OR Hydatidosis OR Hydatidoses OR Cysts, Hydatid OR Cyst, Hydatid OR Hydatid Cysts OR Echinococcosis

Vaccine preventable diseases

• Measles

Rubellas OR Three Day Measles OR Measle, OR Three Day Measles, OR Three Day OR Three Day Measle OR German Measles Syndrome OR Congenital Rubella OR Rubella Syndrome, Congenital OR Congenital Rubella Syndromes

• Rubella

Rubella virus OR Rubellas OR Three Day Measles OR Measle, Three Day OR Measles, Three Day OR Three Day Measle OR Measles, German OR German Measles

• Tetanus

Tetanus Toxoid

• Diphtheria

Diphtherias OR Bacterial Infections and Mycoses
Gram-Positive Bacterial Infections
Gram Positive Bacterial Infections OR Infections, Gram-Positive Bacterial OR Bacterial Infection, Gram-Positive OR Gram-Positive Bacterial Infection OR Infection, Gram-Positive Bacterial OR Infections, Gram Positive Bacterial OR Bacterial Infections, Gram-Positive OR Bacterial Infections, Gram Positive

• Bordetella pertussis

Hemophilus pertussis OR Haemophilus pertussis OR Bordetella OR Bordetella avium OR Bordetella bronchiseptica OR Bordetella parapertussis

• Poliomyelitis

Epidemic Acute Poliomyelitis OR Acute Poliomyelitis, Epidemic OR Poliomyelitis, Epidemic Acute OR Poliomyelitis, Acute OR Acute Poliomyelitis OR Polio OR Polios OR Poliomyelitis, Preparalytic OR Poliomyelitides, Preparalytic OR Preparalytic Poliomyelitis OR Poliomyelitis, Nonpoliovirus OR Nonpoliovirus Poliomyelitis OR Encephalitis, Polio OR Polio Encephalitis OR Infantile Paralysis OR Paralysis, Infantile OR Poliomyelitis, Bulbar OR Bulbar Poliomyelitis OR Poliomyelitis, Medullary Involvement OR Medullary Involvement Poliomyelitis OR Bulbar Polio OR Polio, Bulbar OR Postpoliomyelitis Syndrome OR Post-Polio Syndrome OR Post-Polio Syndromes OR Post-Poliomyelitis Syndrome OR Post Poliomyelitis Syndrome

Respiratory Tract Infections

Infection, Respiratory Tract OR Respiratory Tract Infection OR Respiratory Infections OR Infections, Respiratory OR Infections, Respiratory Tract OR Upper Respiratory Tract Infections
Infections, Upper Respiratory Tract OR Upper Respiratory Infections OR Infections, Upper Respiratory OR Respiratory Infection, Upper