







Original article

Estimation of Prevalence and Incidence of Sexually Transmitted Infections in Iran; A model-based approach

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ABSTRACT

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Background: Routine reporting of sexually transmitted infections (STIs) in Iran is one of the main information sources on STIs, endures some diminution under influence of several factors. We aimed to adjust registered STI data with a model-based approach and estimate the incidence and prevalence of STIs in Iran.

Methods: In this cross-sectional study, we developed a stochastic compartmental model considering effects of influential factors on STI reporting process to adjust registered STI data. We reviewed literature and used Delphi method to collect data and estimate model parameters. We calibrated the model using Monte Carol simulation with 95% confidence interval (CI). Finally, we validated the models by comparing their output with investigational data.

Results: The estimated prevalence of male urethral discharge was 0.40% (95% CI: 0.26%, 0.65%); the prevalence of genital ulcers was 3.68% (95% CI: 2.31%, 6.43%) in women and 0.16% (95% CI: 0.10%, 0.27%) in men. The estimated incidence for *Neisseria gonorrhoeae*, *Chlamydia trachoma* and *syphilis* per 1000 women was 2.44 (95% CI: 1.17, 6.65), 5.02 (95% CI: 2.78, 10.16) and 0.04 (95% CI: 0.02, 0.05) respectively; the corresponding figures per 1000 men were 0.43 (95% CI: 0.26, 0.80), 0.82 (95% CI: 0.42, 1.92) and 0.005 (95% CI: 0.003, 0.008).

Conclusions: Various factors are responsible for the obvious underestimation in the number of STIs registered in Iran. Notwithstanding this underestimation, our models offer an indirect method of estimating the prevalence of STIs in the country. Providing policymakers and STI experts with more realistic estimates might prompt policymakers and STI experts to recognize the importance of STIs in Iran and help them to develop appropriate prevention and control programs.

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Introduction

ccording to WHO, there are globally over 90 million new cases of *Chlamydia trachoma* (CT), over 62 million cases of *Neisseria gonorrhoeae* (NG), and 12 million cases of syphilis annually in men and women aged 15-49 years¹. Accurate data is essential to a good understanding of the epidemiology of Sexually Transmitted Infections (STIs) and planning appropriate interventions and arguing for resources. Epidemiological surveys in the community and routine reporting of STIs as two cornerstones of STI surveillance systems are the main sources of information on STIs².

There have been no epidemiological surveys of STIs in Iran owing to technical, economic, and social barriers ³ and local studies are infrequent and uneven in their coverage of various groups. A systematic review of studies on STIs in Iran⁴ revealed the range of estimates for the prevalence of STIs in Iran. For example, estimates of the prevalence of

syphilis amongst symptomatic patients attending clinics varied between zero and 4.66%; the estimated prevalence of NG ranged from 0.2 to 5.27% and there was a similarly wide range of estimates for the prevalence of CT, 9.3-69.4%⁴. These examples illustrate the diversity of current studies in Iran and hence why the findings cannot be generalized to entire population⁴.

Routine reporting of STIs provides precious information. STI surveillance guidelines in Iran state that all healthcare providers who manage STI cases at the primary health care level (i.e. public or private sector) are required to report cases of certain STIs on a monthly basis using both syndromic and etiologic approaches⁵. However, the system for the routine reporting of STIs in Iran has not been successful. The sensitivity of routine reporting was around 25%⁶. STI reporting data in Iran is influenced by various factors, which come into play at various points, from the point of infection to the final phase of data reporting ⁷, e.g., some STIs are asymptomatic⁸ and only 41.3% of women and 50.2% of men in Iran seek treatment when their symptoms first appear ⁹. These factors make the data inaccurate and unreliable, thus posing an additional challenge to efforts to prevent and control STIs in the country.

In view of the shortcomings of the routine reporting data for STIs in Iran, we aimed to develop a stochastic compartmental model considering effects of influential factors on STI reporting process to adjust registered STI data and estimate the prevalence and incidence of STIs in the Iranian adult population. Our estimates should provide a more realistic picture of the STI situation in Iran and thus prompt the allocation of more resources to this healthcare sector as well as enabling the development of STI polices, which are more appropriate to the Iranian context.

Methods

In 2015 winter, in a cross-sectional study, we developed a stochastic compartmental model using the back-calculation method, which would take into account the impact of various factors on the STI data registration process. We used adjusted routine STI reporting data to estimate STI prevalence and incidence for the Iranian adult population (15 to 59 yr) for 2013.

Using a compartmental model allowed us to divide the population into subgroups¹⁰; e.g., symptomatic and asymptomatic cases, cases treated in the private and public services etc. A stochastic model allowed us to take into account random variation. We used Monte Carlo simulation because it is considered the most rigorous method of modeling events affected by random variation¹⁰.

Study setting

Iran, located in the Middle East and North Africa (MENA) region, has a population of 75,149,669; 64% are in 15-59 yr-old age group and 50.3% are male ¹¹.

Source of data

We used registered STI data from 2013 in Center for Disease Control (CDC) as the starting point in which we applied our model parameters to adjust it.

The registered data on STIs comes from routine STI reporting, which consists of reports based on both syndromal and etiological criteria. Syndromal reports comprise data on episodes of male urethral discharge (MUD) and genital ulcers (GUs) in both sexes whereas etiological reports comprise data on confirmed cases of NG and CT, and probable and confirmed primary as well as secondary syphilis in both sexes. Reports were collected monthly for 15 to 59 yr–old in the general population (both urban and rural areas) and combined to give a dataset covering a one-year period 5 .

These data underestimate the incidence of STIs as a number of cases are missing owing to various factors as following, used as model parameters (Figures 1 and 2).

Some STI infections are asymptomatic; however, the proportion of cases, which are asymptomatic, varies according to the agent⁸. 2) Only about half of Iranians who acquire a STI seek treatment after the onset of disease ^{9,12}. 3) The sensitivity and specificity of clinical and etiological diagnoses of STIs is not 100%; in addition, some cases are reported as confirmed etiological diagnoses although in fact they have been diagnosed based on less accurate clinical criteria. 4) Some patients prefer to use private healthcare providers whereas others use public services. 5) Some healthcare providers do not participate in routine STI reporting and there are differences on the routine reporting handled in the private and public sectors. 6) Not all cases of STIs are reported. 7) It is also possible that some patients are double-counted because they present for treatment as 'new' cases on several occasions owing to recurrence of symptoms, partial treatment of them or their partners or re-infection. Detecting and removing repeated cases is not possible under the current STI surveillance protocol, so we included a 'median number of episode' parameter for each syndrome or infection in the models to adjust for over-reporting (Table 1).

Table 1: Final model par	ameters and used source of data
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Notation of			-	
parameters	Model	Description	Source of data	
P _A	1	reported prevalence of NG ^a ,CT ^b , primary and secondary syphilis based on registered data as starting point in model 1	Routine STI case reporting	
\mathbf{P}_{cd}	1	proportion of infections that were clinically diagnosed	Delphi method	
SP_{cd}/SE_{cd}	1	specificity and sensitivity of clinical diagnosis respectively for each infection	Literature review and Delphi method	
$P_{\rm L}$	1	proportion of infections that were diagnosed on the basis of laboratory tests	Delphi method	
SP_t/SE_t	1	specificity and sensitivity of diagnosis tests	Literature review	
Pc	1,2	proportion of patients seeking treatment	Intervening the general population through a cross-sectional study ⁹	
Pc_1/Pc_2	1,2	proportion of patients seeking treatment in the public and private sectors respectively	Delphi method	
Pp_1/Pp_2	1,2	probability of participating in the national STI reporting system for public and private health care providers	Delphi method	
$\mathbf{P}_{\mathbf{u}}$	1,2	probability that a case is not reported	Delphi method	
P _{asy}	1	proportion of asymptomatic infection	Literature review	
Me	1, 2	Median number of episode for syndromes or infections	Literature review and Delphi method	
D	1	duration of infection	WHO guideline	
Ps	2	reported prevalence of MUD^{c} and GU^{d} in both gender based on registered data as starting point of model 2	Routine STI case reporting	
SP_{cd}/SE_{cd}	2	sensitivity and specificity of syndromal diagnosis respectively	Literature review and Delphi method	
ρ		correlation coefficient between sensitivity and specificity of diagnosis	Literature review	
^a Neisseria gonorrhoeae (NG), ^b Chlamydia trachoma (CT), and estimated weighted sensitivity and specificity for each test, ^c Male Urethral				

^a Neisseria gonorrhoeae (NG), ^bChlamydia trachoma (CT), and estimated weighted sensitivity and specificity for each test, ^cMale Urethral charge, ^dGenital Ulcer

Data Collection

We used two sources of data to obtain values for model parameters.

Literature review

Two reviewers searched international and national databases such as PubMed; Ovid; Scopus, Cochrane; Sign; Nice; CDC; GOV; WHO; IUSTI; UNAIDS; Magiran; SID; Irandoc and Iranmedex using keywords such as STI; STD; sex; etiology; syndrome; sensitivity; specificity; genital ulcer; urethral discharge; diagnosis; test; laboratory; *Neisseria gonorrhoeae*; *Chlamydia trachomatis; Treponema pallidum* and syphilis with connective words (or; and). We also searched grey literature including unpublished WHO and Ministry of Health and Medical Education (MOHME) reports and statistics. The search procedure was completed through three months, and 1100 related subjects were found in primary research. Quality of evidences was assessed by standard checklists¹³ and then 62 evidence were included.

Delphi method

To estimate the parameters for which accurate Iranian data were not available we conducted a three-round Classic Delphi study with key individuals involved in STI programs. We included 25 participants using purposive sampling. We started semi-structured interview with some open-ended questions. After each phase, we explored and summarized the results, presented them to participants and asked them to review the information about the results of the previous round and revise their judgments accordingly. Participants were approached by E-mail in the first and second phase and telephone in the third phase.

Statistical analysis method

Data from various sources were combined and summarized. Owing to discrepancies in the data, for certain variables we provided a range for each parameter (i.e. minimum and maximum values) based on the summarized data. Next, we explored and validated parameter values through an expert focus group. Then, to apply an exclusive normal distribution for each parameters, using dedicated maximum and minimum values, we estimated the mean and SD for each parameter (Equation 1)¹⁴.

$$SD = \frac{(maximum value-minimum value)}{6}$$

Model

Regarding two syndromic and etiologic approaches, we developed two stochastic compartmental submodels to estimate A) prevalence and incidence of NG, CT and primary and secondary syphilis and B) prevalence of GU in both sexes and MUD. The models were based on probabilistic trees (Figures 1 and 2) in which the branches represented effects of influential factors on STI reporting process (equation 2 and 3).

Equation 2- Estimation of incidence of NG, CT and primary and secondary syphilis based on sudmodel 1 (Figure 1)



Figure 1: Model-based estimates of the prevalence and incidence of *Neisseria gonorrhoeae* (NG), *Chlamydia trachoma* (CT), and primary and secondary syphilis

Pc1 and Pc2: proportion of patients seeking treatment in the public and private sectors respectively; Pcd: proportion of infections that were clinically diagnosed; PL: proportion of infections that were diagnosed on the basis of laboratory tests; SE, SP: sensitivity and specificity of diagnosis respectively; Pp1 and Pp2: probability of participating in the national STI reporting system for public and private health care providers; Pu: probability that a case is not reported.



Figure 2: Model-based estimates of the prevalence of genital ulcers in women (FGU) and men (MGU) and male urethral discharge (MUD) Pc1 and Pc2: proportion of patients seeking treatment in the public and private sectors respectively; SE, SP: sensitivity and specificity of diagnosis respectively; Pp_1 and Pp_2 : probability of participating in the national STI reporting system for public and private health care providers; Pu: probability that a case is not reported. Equation 3- Estimation of prevalence of GU in both sexes and MUD based on submodel 2 (Figure 2)

$$P = \frac{\left(\frac{(P_{s}+SP_{cd}-1)}{(SE_{cd}+SP_{cd}-1)}\right) \times \left(\frac{1}{Pc}\right) \times \left(\frac{1}{(Pc_{1\times}Pp_{1})+(Pc_{2\times}Pp_{2})}\right) \times \left(\frac{1}{(1-Pu)}\right)}{M_{e}}$$

In addition, we considered the correlation between sensitivity and specificity of diagnoses (i.e. etiological or clinical) using equation 4.

Equation 4- adjusted specificity of a diagnosis in correlation with its sensitivity¹⁵

Adj SP=
$$\rho \times SE + \sqrt[2]{1-\rho^2} \times SP$$

Calibration

The models were calibrated using Monte Carlo simulation; thousands of random cases were generated based on the probability distribution functions. We calculated means and the upper and lower ranges of outputs to enhance the accuracy of the analysis and present the 95% confidence interval (CI) for estimates. For each parameter, we constructed a random variable with a normal distribution (i.e. with specific mean and SD). The simulation generated 10,000 cases using the specified formula for models one and two. After the iteration process, we computed the mean and 95% CI based on the 2.5 and 97.5 percentiles for each output.

We used Stata (version 11, StataCorp) for the statistical analysis and crosschecked the output by repeating procedures in Microsoft Excel 2007.

Validation

As there was no suitable dataset against which we could compare the model outputs to cross-validate them we recruited focus groups to explore and validate our results. As previous studies estimated low sensitivity for STI case registry ⁶, we assumed that if the models were valid the estimated incidence and prevalence of the various syndromes and STIs would be higher than the corresponding figures in the registered data. In addition, outputs were compared with the results of a systematic review of Iranian studies on STIs ⁴. We also evaluated our results using the 2012 Global AIDS Response Progress Reporting (GARPR) system and the 2008 WHO estimation ^{16,17}. If the models were valid, the confidence interval of our outputs would cover the results of those studies.

Assumptions of models

We assumed that median number of episode for each infection or syndrome was similar for all ages. We assumed that cases of STIs among high-risk groups were accurately represented in the registered data for the Iranian population. As we estimated prevalence and incidence at a single point in time, we did not omit the infected people from the denominator in our incidence formula. The models were static and ignored changes in variables over time. We assumed that all parameters were normally distributed. The models were linear in which all variables were simple functions of one another. We assumed no correlation between variables excepting correlation between sensitivity and specificity of diagnosis.

Ethical consideration

The Ethics Committee of Kerman University of Medical Sciences approved the study protocol via ethical code of 'IR.KMU.REC.1394.171'.

Results

Some of model Inputs in the context of Iran

Approximately, 68% of Iranian patients prefer to use private healthcare providers while the proportion of private providers involved in the program for routine STI reporting is incredibly small (10%). The estimated level of under-

reporting varied between syndromes and etiological diagnoses; it ranged from at least 22% for syphilis to a maximum of 77% for MUD. The sensitivity and specificity of diagnosis of syndromes (GU and MUD) appears to vary by patient sex. Our experts' opinion was that the specificity of GU diagnosis in women is relatively low. Although healthcare providers were asked to report laboratory-confirmed CT, NG and syphilis it was estimated that only 15% of reported NG cases and less than 0.1% of reported CT cases were diagnosed via laboratory tests (Table 2).

Table 2: Estimated influence of some parameters on routine STI reporting in the context of Iran

Parameters		Min %	Max %
Location of patients seeking treatment	Public sectors	30.1	35.3
	Private sectors	64.8	71.4
Probability of participating in the national STI reporting system	Public sectors	45.1	61.6
	Private sectors	5.0	14.4
Probability that a case is not reported	Female Genital Ulcer	49.1	64.5
	Male Genital Ulcer	66.4	85.1
	Male Urethral Discharge	58.2	76.8
	Chlamydia trachoma	45.0	61.0
	Neisseria gonorrhoeae	44.9	60.8
	Primary and secondary syphilis	22.1	36.7
Proportion of infections that were diagnosed on the basis of laboratory tests	Chlamydia trachoma	0.0	0.07
	Neisseria gonorrhoeae	10.6	19.1
	Primary and secondary syphilis	70.0	87.1

Prevalence and incidence estimates

A total of 114,731 episodes of syndromes (GU and MUD) and etiologically diagnosed STIs (NG, CT, primary and sec-

ondary syphilis) among Iranian men and women between 15 and 59 years old were reported to CDC in 2013 (Table 3).

Table 3: Registered episodes, estimated number of cases, incidence and prevalence of STIs in Iran

		Model Estimation (95% CI)		
Syndrome/Agent	Registered episodes	Number (*1000)	Prevalence (%)	Incidence (per 1000 person)
Male				
Genital Ulcer	3050	38 (25, 63)	0.16 (0.10, 0.27)	-
Urethral discharge	9012	98 (66, 151)	0.40 (0.26, 0.65)	-
Neisseria gonorrhoeae	649	31 (21, 55)	0.13 (0.08, 0.22)	0.43 (0.26, 0.80)
Chlamydia trachoma	422	188 (102, 422)	0.78 (0.41, 1.79)	0.82 (0.42, 1.92)
Primary and secondary syphilis	109 ^a	4 (3, 5)	0.02 (0.01, 0.02)	0.01 (0.00, 0.01)
Female				
Genital Ulcer	93621	876 (570, 1475)	3.68 (2.31, 6.43)	-
Neisseria gonorrhoeae	1725	284 (144, 729)	1.19 (0.59, 3.16)	2.44 (1.17, 6.65)
Chlamydia trachoma	5449	1582 (921, 3016)	6.65 (3.78, 13.09)	5.02 (2.78, 10.16)
Primary and secondary syphilis	694 ^a	25 (17, 37)	0.10 (0.07, 0.16)	0.04 (0.02, 0.05)

^a Confirmed and probable reported cases of Primary and secondary syphilis

For 2013, the model estimated the numbers of GU cases in women and men as around 876,000 and 38,000 respectively while the estimated number of MUD cases was estimated at about 98,000. The prevalence of GUs was 3.68% in women and 0.16% in men, whilst the prevalence of MUD was 0.40%. The estimated number of NG cases in women and men was around 286,000 and 31,000 respectively, while the corresponding estimated prevalences were 1.19% and 0.13%. The number new cases of NG occurred per 100,000 was 244 for women and 43 for men; the estimated numbers of new syphilis cases were 25,000 for women and 3,600 (95% CI: 2,600, 5,200) for men. In men the prevalence of syphilis was 0.015% (95% CI: 0.01, 0.022), but the incidence was 0.005 (95% CI: 0.003, 0.008); however the incidence of new cases among women was higher. The estimated number of cases of CT was more than one million for women; prevalence and incidence were 6.65% and 5.02 per 1000 women respectively. Estimates of number of new cases, prevalence, and incidence of CT were lower for men (Table 3).

The model-based estimates of prevalence of syndromes and confirmed infections were higher than those based on registered data. However, the ratio of estimated prevalence to reported prevalence varied between syndromes and infections.

Discussion

There is a noticeable underestimation in the number of STIs cases in Iran. CDC-registered data fail to include some cases for a variety of reasons. We designed a model to adjust for the effects of these factors and estimate actual figures for the incidence and prevalence of GU, MUD, NG, CT and primary and secondary syphilis in Iranian adult men and women.

According to our model, more than one million Iranian adult women experienced GUs in 2013. The prevalence of GUs in women was about 4% while in men it was less than 0.2%. Based on WHO reports on STIs, the incidence rate of GU in men in Morocco, Jordan, Sudan and Bahrain (other MENA countries) in 2012 was 9.6%, 0.0%, 3.4% and 0.8% respectively; the corresponding rates in women were 1.5%, 1.1%, 0.4% and 2.9%¹⁷. The incidence of GU in women and men in Djibouti was 3 per 100,000 people in 2009¹⁷. It seems that the sex ratio of GU incidence and prevalence varies between countries. The estimated prevalence of MUD in Iran was less than 0.5%. In the 2012, GARPR report the prevalence of MUD as 27.5 cases per 100,000 people 17 . As GARPR reports are usually based on registered STI data, it is unsurprising that this estimate is lower than that of our model. The incidence of MUD in Oman was 8 per 100,000 people

in 2010¹⁷. The limited data available for Iran meant that we could not estimate the incidence of MUD and GU in men and women.

Our results demonstrated that more than one million Iranian adult women were infected with CT in 2013; a prevalence and incidence of about 6.7% and 5%. The results of a systematic review of STI studies in Iran conformed to our models' estimates of the prevalence of CT in women (i.e. a range of 8-11%)⁴. According to our model, the prevalence of CT in men was less than 1%. The WHO estimated the prevalence of CT in the MENA region was 1.1% and 0.9% in women and men respectively, with 9.8 and 10.9 new cases per 1000 for women and men respectively¹⁶. These rates partly cover confidence interval of our estimates.

The model estimated the incidence of NG in 2013 as 0.13% and 1.19% in men and women respectively. The reported prevalence of NG was 0.2–5.27% for both sexes in Iran ⁴. In the 2012 GARPR, the rate of NG among Iranian men was 2.3 cases per 100,000 ¹⁷. The estimated rate of NG was higher than the reported rate in the 2012 GARPR which is usually based on registered STI data. According to WHO, the prevalence of NG in the MENA region was similar in men and women, at 0.3%, the incidence rate is 8.1 and 11.6 per 1000 in women and men respectively ¹⁶. The incidence of NG in men living in low- or middle-income countries was 5.8 per 100,000 ¹⁸. It seems that in Iran the incidence and prevalence of NG are different in men and women.

The incidence rate of primary and secondary syphilis in Iran was estimated at near to zero for both sexes. The results of a study on blood donors in Tehran in 2007¹⁹, and the 2012 GARPR reported rates in Iranian adults fall within the 95% CIs for the estimates for the prevalence and incidence of syphilis produced by our models. The prevalence of syphilis among blood donors and pregnant women in Iran, two groups assumed to be representative of the general population, was near to zero ¹⁷. The WHO estimated that in 2008 the prevalence of syphilis in the MENA regions was 0.5%, and the incidence was 2.1 per 1000 and that these figures were similar for men and women ¹⁶. Although syphilis has a high prevalence among high-risk groups, such as female sex workers, in Iran^{17,20} it seems that the prevalence in the general population is lower than in other countries. To date there has been no analysis of the reasons for the internationally low incidence and prevalence of syphilis in Iran; future research should address this issue.

In general, more STI cases are reported and estimated in women than men; future investigations suggested to explore the reasons.

The models presented here provide indirect estimates of the real prevalence and incidence of STIs. The publication of more realistic estimates should help to convince policymakers and STI experts of the importance of STIs to public health in Iran. More epidemiological data that are accurate will enable the development of appropriate prevention and control programs. The results of this study should pave the way for further research on STIs.

One of the major limitations in this study, like other modeling studies, was related to the absence of reliable data needed as input for the model. As a result, the model outputs will be associated with a certain degree of uncertainty and this should be kept in mind when interpreting model outputs ²¹. Although STI data are registered by age groups in CDC, we were not able to estimate age-specific incidence and prevalence for the various STIs because of data limitations affecting some input parameters. There was no information on STI treatment, patient follow-up and partner notification in Iran and so we were not able to include theses influential parameters in our models. We were unable to determine what tests the various Iranian laboratories used for each pathogen and so we assumed that all laboratories used the WHO-recommended tests²².

Conclusions

According to our estimates, the incidence and prevalence of STIs in Iran are much higher than the registered data suggest. Several factors affect the reliability of the registered data and we suggest that an effort should be made to eliminate or reduce their impact. We hope that providing more realistic estimates of the incidence of STIs will enable experts and policymakers to develop better plans to tackle STIs in Iran.

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Conflict of interest statement

Kianoosh Kamali was supported by CDC and MOHME. The rest of authors declare that they have no conflicts of interest.

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