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HSV-2 serology can be predictive of HIV epidemic potential and hidden sexual risk behavior in the Middle East and North Africa

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ABSTRACT

Background: HIV prevalence is low in the Middle East and North Africa (MENA) region, though the risk or potential for further spread in the future is not well understood. Behavioral surveys are limited in this region and when available have serious limitations in assessing the risk of HIV acquisition. We demonstrate the potential use of herpes simplex virus-2 (HSV-2) seroprevalence as a marker for HIV risk within MENA.

Methods: We designed a mathematical model to assess whether HSV-2 prevalence can be predictive of future HIV spread. We also conducted a systematic literature review of HSV-2 seroprevalence studies within MENA.

Results: We found that HSV-2 prevalence data are rather limited in this region. Prevalence is typically low among the general population but high in established core groups prone to sexually transmitted infections such as men who have sex with men and female sex workers. Our model predicts that if HSV-2 prevalence is low and stable, then the risk of future HIV epidemics is low. However, expanding or high HSV-2 prevalence (greater than about 20%), implies a risk for a considerable HIV epidemic. Based on available HSV-2 prevalence data, it is not likely that the general population in MENA is experiencing or will experience such a considerable HIV epidemic. Nevertheless, the risk for concentrated HIV epidemics among several high-risk core groups is present.

Conclusions: HSV-2 prevalence surveys provide a useful mechanism for identifying and corroborating populations at risk for HIV within MENA. HSV-2 serology offers an effective tool for probing hidden sexual risk behaviors in a region where quality behavioral data are limited.

Introduction

The Middle East and North Africa (MENA) region is perceived as "a real hole in terms of HIV/AIDS epidemiological data" (Mark Kline) (Bohannon, 2005). Despite emerging data revealing low HIV prevalence, surveys suggest pockets of high risk (Abu-Raddad et al., 2010a,b; Egypt Ministry of Health and Population National AIDS Program, 2006; Elrashied, 2006; Jahani et al., 2009; Khattabi and Alami, 2005; Kriitmaa et al., 2010; Mahfoud et al., 2010; Marcelin et al., 2002; Pakistan National AIDS Control Program, 2008). There is a notion that risky sexual practices do occur in MENA but these practices are hidden due to the conservative nature of MENA societies (Kelley and Eberstadt, 2005).

Though there has been an increase in the number of studies assessing sexual risk behavior among populations within MENA (Abu-Raddad et al., 2010a,b), the representation, quality, and reproducibility of these data are open to question. Sexual measures in MENA tend to be limited due to minimal surveillance efforts, methodological limitations, conservative nature of MENA societies, and stigma and illegality associated with some forms of sexual practices (Abu-Raddad et al., 2010a). Several integrated bio-behavioral surveillance surveys were recently conducted in MENA among men who have sex with men (MSM), including male sex workers (MSWs), and among female sex workers (FSWs), and injecting drug users (IDUs) (Abu-Raddad et al., 2010a,b). Most surveys revealed low or absent HIV infection despite

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significant reported risk behaviors (Abu-Raddad et al., 2010a,b). Though these results might reinforce a perception that this region is immune to HIV due to its socio-cultural fabric (Gray, 2004; Khawaja et al., 1997; Lenton, 1997), these populations may be at risk for potentially extensive HIV epidemics. Current low HIV prevalence may be due to initial isolation of hard to reach populations in MENA from high-risk networks in other parts of the world. Indeed, several recent studies show rapidly escalating HIV epidemics among IDUs and MSM in MENA (Abu-Raddad et al., 2010a,b). Alternatively, different sexual networking patterns and universal circumcision status may be limiting the sexual spread of HIV.

Even when accurate risk behavior measures exist, they may not establish a precise assessment of the true risk of HIV exposure. Questionnaires, interviews, and focus groups provide only indirect information regarding sexual activity (Obasi et al., 1999). The sensitive nature of sexual behavior, informational limitations of egocentric data, and non-random social desirability and recall biases, can introduce invalidity or inaccuracy of estimates for associations or effects (Caldwell, 1989; Lee and Renzetti, 1990; Morris, 1993; Wadsworth et al., 1993). Women may underreport sexual activity while men may over-report (Catania et al., 1990). Validity of reported risk behaviors that are illegal is likewise difficult to ascertain (Pisani et al., 2003).

It is also challenging to precisely quantify the multitude of facets that define sexual behavior including rate of partnership formation, contact with sex workers, heterogeneity in partner change rates, and risk group and age cohort mixing (Abu-Raddad et al., 2006). Network structure and concurrency of partnerships play a major role in HIV transmission (Farjadian et al., 2003; Kretzschmar and Morris, 1996; Morris, 1997; Watts and May, 1992): a monogamous member of a stable sexual partnership can be at high risk of infection because of connection through a primary partner, or a partner of a primary partner, to a high-risk sexual network. Conversely, a person with frequent partnership change remains at low risk if his/her network is closed with low risk of HIV penetration.

Faced with these barriers, population data for other sexually transmitted infections (STIs) take on importance as objective measures of HIV risk. Herpes simplex virus type-2 (HSV-2) is particularly relevant to the dynamics of HIV transmission (Corey et al., 2004). Genital herpes caused by HSV-2 is one of the most widespread sexually transmitted infections (O'Farrell, 1999; Smith and Robinson, 2002; Weiss, 2004), and is currently the leading cause of genital ulcer disease (GUD) in developed and developing countries (Ahmed et al., 2003; Mertz et al., 1998; Morse, 1999). An estimated 536 million people were living with this infection and 23.6 million new infections occurred in 2003 (Looker et al., 2008). HSV-2 is transmitted almost exclusively by sexual contact and results in production of lifelong antibodies (van de Laar et al., 2001). There is repeatedly a very strong observed correlation between HSV-2 infection and sexual risk behavior as well as HSV-2 infection and HIV infection (Abu-Raddad et al., 2008; Cowan et al., 1994; Cunningham et al., 1993; Obasi et al., 1999; van de Laar et al., 2001). Measurement of HSV-2 antibodies in the blood is therefore a convenient method to assess hidden levels of sexual risk behavior (Nahmias et al., 1990).

There is also extensive observational evidence that HSV-2 infection substantially increases HIV acquisition and transmission risk due to enhanced genital inflammation in HSV-2 infected persons (Freeman et al., 2006). At the population level, HSV-2, may have played an important role in fueling the HIV epidemic in sub-Saharan Africa (Abu-Raddad et al., 2008; Corey et al., 2004). The majority of HIV infected persons are infected with HSV-2, and at an individual level, HSV-2 is usually acquired before HIV (Corey et al., 2004). As such, HSV-2 spreads along the paths of sexual risk and delineates potential avenues of future sexual HIV spread in the population. In a sense, HSV-2 infection may act as a "tour guide" for future HIV infection, even when conventional behavioral measures such as partnership change rates fail to predict the risk posed by the structure of sexual networks (Nagelkerke et al., 2006). In a study of four cities in Africa, only circumcision and HSV-2 prevalence were determinants of large differences in HIV-1 prevalence (Buve et al., 2001). Because circumcision is widespread in MENA, HSV-2 may take on primary importance as a risk factor for HIV-1 infection in the region.

In this article, we use a mathematical model that estimates the spread of HIV and HSV-2 to illustrate how the extent of future HIV epidemics can be inferred by measuring endemic prevalence of HSV-2 within different subpopulations. We also review HSV-2 prevalence data from MENA, and conclude that strategically implemented HSV-2 serosurveys are critical in mapping HIV-1 risk among different populations within MENA.

Methods

Mathematical modeling

We used a compartmental modeling formalism to simulate the potential course of HIV and HSV-2 epidemics in a high-risk population in MENA (Online Supporting Appendix). The model is based on extensions of earlier HIV and HSV-2 transmission models (Abu-Raddad and Longini, 2008; Abu-Raddad et al., 2006; Garnett and Anderson, 1993), but is applied, with no loss of generality, to a prototype MSM population, that is a group of MSM individuals at heterogeneous levels of risk behavior and where there is mixing between the different risk groups through proportional as well as assortative components (Online Supporting Appendix).

The formalism was built accommodating both deterministic and stochastic solutions to allow for wider applicability of the modeling framework. The deterministic version of the framework consists of a system of four differential equations for each risk group of ten MSM risk groups in the population. The stochastic version of the framework assumes the same transition rates (hazard rates) as in the deterministic version, but uses these transition rates to generate the stochastic process. The deterministic framework can be used whenever the population size in each risk group is large enough so that stochastic effects are not influential. The stochastic framework can be used at any arbitrary population size, but the computing time increases exponentially with the population size leading to impracticality at large population sizes. In this article we focused on the predictions for an MSM population where some of the risk groups within the MSM community can be small enough to necessitate the use of the stochastic framework. Accordingly, all reported results apart from Fig. 1 were generated using the stochastic version of the model. Nevertheless, our modeling framework is general enough to be used for large populations using the deterministic version. We have also used the deterministic version to provide checks on the results generated using the stochastic framework.

We chose model parameters for an MSM population since MSM is a leading group at risk of HIV sexual transmission in MENA (Abu-Raddad et al., 2010a,b); but the model and its key inferences apply

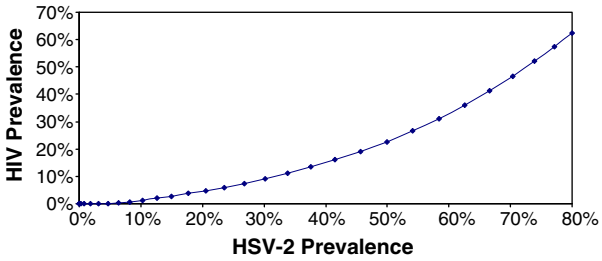

Fig. 1. The link between HIV and HSV-2 epidemiologies. The relationship between the endemic saturated levels of HIV prevalence and HSV-2 prevalence in a prototype high-risk population of men who have sex with men in the Middle East and North Africa. Both infections are spreading in the same sexual network, but reach different prevalence levels due to the biological differences between the two infections.

generally to other risk populations where sexual contact is the dominant mode of transmission. The model's biological input, including HIV and HSV-2 natural history and transmission probabilities, is described in the Online Supporting Appendix and in more detailed form elsewhere (Abu-Raddad and Longini, 2008). Parameter values of the HSV-2 sub-model are chosen according to the best available evidence of HSV-2 biology including detailed data about the pattern of HSV-2 reactivation in its clinical and subclinical forms (Abu-Raddad et al., 2008; Mark et al., 2008) (supplementary information appendix for Ref (Abu-Raddad et al., 2008)). Behavioral parameters in the model are informed by data from the MENA HIV/AIDS Epidemiology Synthesis Project as will be described later (Abu-Raddad et al., 2010a, b), and are chosen to provide a representative heterogeneous risk behavior structure typical of that of MSM as well as other risk groups (Garnett and Anderson, 1993). We altered risk behavior in different simulations to account for discrepant values of HSV-2 prevalence in different populations and then observed the dynamics of HIV-1 spread. To disentangle sexual risk behavior from biological interactions of HIV and HSV-2, we assumed no enhanced acquisition or transmission probability of one infection due to the biology of the other infection. Therefore, the only assumed link between HIV and HSV-2 in this model is the common mode of transmission.

HSV-2 in MENA systematic review

We conducted a systematic review of HSV-2 epidemiology in MENA by undertaking a literature search of Medline (PubMed) using both free text and MeSH headings: (Herpesvirus 2, Human OR Herpes Genitalis) AND (Middle East OR Islam OR Arabs OR Arab World OR Africa, Northern OR Mauritania OR Sudan OR Somalia OR Djibouti OR Pakistan). No language or year limitation was imposed. The inclusion criterion was any publication with a serological measurement of HSV-2 prevalence in any population group. We identified 30 publications for inclusion as of August 17, 2010. The countries included in our systematic review are Afghanistan, Algeria, Bahrain, Djibouti, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Pakistan, Palestine, Qatar, Saudi Arabia, Somalia, Sudan, Syria, Tunisia, United Arab Emirates, and Yemen (Fig. S1 of the Online Supporting Appendix shows a map of the region).

We supplemented our HSV-2 Medline systematic review by the data identified through the MENA HIV/AIDS Epidemiology Synthesis Project (Abu-Raddad et al., 2010a,b). The Synthesis Project mandate was to systematically collect, review, and synthesize all available data in MENA on HIV, STIs, and sexual behavior, and was conducted through a partnership with the World Bank, the MENA Regional Support Team (RST) of Joint United Nations Programme on HIV/AIDS (UNAIDS), and the Eastern Mediterranean Regional Office (EMRO) of the World Health Organization (WHO) (Abu-Raddad et al., 2010a). Detailed description of the Synthesis Project systematic review can be found in (Abu-Raddad et al., 2010a,b). The identified studies and data sources include, in addition to nearly 4000 scientific sources of literature, hundreds of country-level reports, governmental studies and publications, non-governmental organizations' studies and publications, international organizations' reports and databases, and other institutional reports related to HIV and STIs in MENA (Abu-Raddad et al., 2010a,b). We also searched the WHO/EMRO databases of notified HIV/AIDS cases and STIs (WHO/EMRO), and consulted with public health officials, and key experts in the region and beyond.

Results

HSV-2 prevalence as a predictor of the distribution, evolution, and size of future HIV epidemics

To illustrate the link between HIV and HSV-2 epidemiologies, we calculated the relationship between HSV-2 prevalence and the potential size of an HIV epidemic within an MSM sexual risk contact structure of different risk groups mixing with each other. We varied HSV-2 infection prevalence by altering the average level of sexual risk behavior practiced in the sexual risk contact structure. We achieved different levels of risk by varying the rate of partner change in the whole population by the same multiplicative factor. Both viral infections spread within the same contact structure, but at different rates reflecting biological differences between the two infections.

Our model demonstrates that HSV-2 prevalence is predictive of the size of future endemic HIV prevalence, but the relationship is non-linear (Fig. 1). A sexual risk contact structure where a low level of risk behavior supports an HSV-2 prevalence of about 10%, cannot sustain much endemic HIV transmission. Though HIV can be introduced into such a sexual risk contact structure, HIV prevalence is not likely to exceed 1%. In order for an HIV epidemic to reach greater than 5% in a population (a concentrated HIV epidemic, Pisani et al., 2003), the level of sexual risk behavior in the population must support an HSV-2 prevalence of about 20%. In settings where the level of risk behavior supports an HSV-2 prevalence exceeding 60%, HIV prevalence is predicted to exceed 35%. At very high levels of HSV-2 prevalence, HIV prevalence values approach those of HSV-2. This non-linear relationship between the two total-population prevalence levels for each infection is also qualitatively seen for each risk group in the population (Fig. S2). It must be noted here that these quantitative results provide rough estimates to demonstrate this concept of the link between the epidemiologies of the two infections rather than strictly literal quantitative predictions.

Case scenarios illustrating HSV-2 prevalence as a biomarker of risk behavior and potential HIV expansion

Fig. 2A shows the time course of an HIV epidemic in a prototype MSM population whose endemic HSV-2 prevalence is 45%. HIV infection is introduced into this population in the year 2000: it takes several years before HIV infection sustains a considerable transmission. The epidemic peaks at approximately 20% prevalence following two decades of expansion. In the simulation in Fig. 2B, HSV-2 prevalence is 10%. When HIV is introduced into this population, the level of sexual risk behavior does not sustain infectious spread. Fig. 2C shows the average of 100 simulations of HIV and HSV-2 epidemics assuming that the two infections are introduced concurrently into an MSM population. The HSV-2 infectious spread in its epidemic phase grows more slowly than that of HIV, but eventually achieves a larger endemic prevalence than that of HIV.

HSV-2 prevalence in MENA

We identified 14 references including HSV-2 prevalence measures out of the 30 references identified through the Medline search. We also identified another 14 relevant references through the wide umbrella of the Synthesis Project search. Through this extensive review, we found that HSV-2 research remains limited in MENA. The majority of data were from the peer-reviewed literature, but some of which were not indexed in Medline. Table 1 lists HSV-2 prevalence measurements in MENA and related cultural settings. There is a pattern of low prevalence among the general population, but substantial prevalence among groups with identifiable risk factors such as FSWs, MSM, “bar girls”, and STD clinic attendees. HSV-2 prevalence is lower overall than in all other regions of the world (Table 2).

Several studies found higher HSV-2 prevalence levels (27%–54%) among the general population, but there is reason to doubt the accuracy of these studies. Diagnostic tests used in these publications often suffered from high levels of cross-reactivity with herpes simplex virus type 1 (HSV-1) antibodies (Ashley et al., 1991). In other studies, we were unable to clarify, despite repeated attempts to contact the

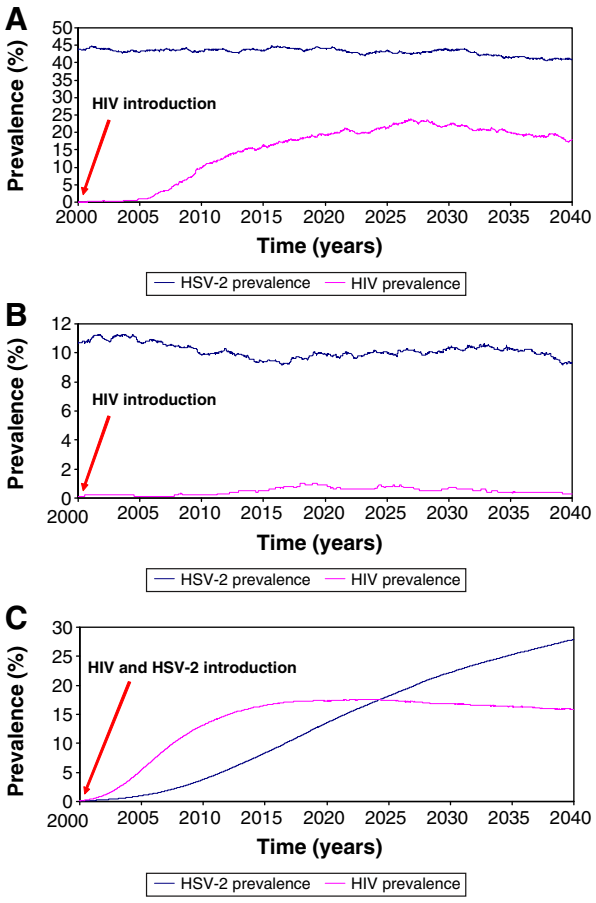

Fig. 2. A case scenario for HIV epidemic expansion in a prototype high-risk population of men who have sex with men in the Middle East and North Africa. HIV infection is introduced in year 2000 by one infected person with latent infection. A) HSV-2 prevalence is at about 45% prevalence reflecting high levels of sexual risk practices in this population. B) HSV-2 prevalence is at about 10% prevalence reflecting relatively low levels of sexual risk practices in this population. C) The two infections are introduced concurrently in year 2000 by one infected person with latent infection of both diseases. The HIV and HSV-2 prevalence curves shown reflect the average over 100 simulations for each epidemic.

authors, the type of HSV-2 serology test performed. Thus, the actual prevalence of HSV-2 in these reports is in doubt.

In certain countries, HSV-2 seroprevalence among certain age groups achieves reasonably considerable levels. Fig. 3 shows age stratified prevalence in a study from Morocco (Cowan et al., 2003). Prevalence grows slowly for males and females in comparison to other regions (see multiple data in Cowan et al., 2003 and Smith and Robinson, 2002) suggesting that it takes a long time after sexual debut for the risk of exposure to this STI to become appreciable.

Discussion

HSV-2 versus other biomarkers of risk

HSV-2 serology is a powerful marker of sexual risk that bypasses shortcomings of risk behavior measures gathered through surveys, and can be used in a similar manner to the use of hepatitis C infection as a proxy for HIV risk of acquisition among IDUs (Vickerman et al., 2010). HSV-2 is also a more powerful marker of sexual risk behavior than other STIs in relation to HIV epidemic potential. Bacterial STIs tend to cluster among populations at highly elevated risk behavior and are therefore not as representative as HSV-2 to HIV infectious spread which can affect a larger segment of the population (Abu-Raddad et al., 2008; Boily and Masse, 1997; Brunham and Plummer, 1990; Yorke et al., 1978). On the other hand, other viral STIs such as human papilloma virus (HPV), are much more infectious than HIV and HSV-2, and can affect a much larger part of the population than HIV and HSV-2 (Abu-Raddad et al., 2010a, 2008; Trottier and Franco, 2006). HSV-2 epidemiology is the most relevant of all STIs to HIV epidemiology. This fact is manifested in the consistently strong association between these two infections in multiple studies in diverse settings and populations (Corey et al., 2004; Freeman et al., 2006). Other infections such as hepatitis B and hepatitis C have modes of transmission other than sexual intercourse and their epidemiologies reflect multiple risk factors beyond sexual behavior.

Prevalence of HSV-2 in MENA and prediction of HIV epidemic potential

Using a mathematical model, we described how forthcoming HSV-2 prevalence data could help identify the potential size of HIV epidemics in MENA. Our literature review documents low levels of HSV-2 infection in the general population suggesting that although sexual risk practices are present, they may be at low levels compared to other regions (Table 2). Low levels of cervical cancer (Abu-Raddad et al., 2010a; Drain et al., 2002), which suggest low circulating levels of oncogenic human papilloma virus, as well as the very low HIV prevalence among the general population (Abu-Raddad et al., 2010a), attest to this conclusion. Yet, HSV-2 prevalence appears to be considerably higher among core groups for sexually transmitted infections, indicating a higher level of risk behavior.

MENA populations, for cultural reasons, are unlikely to self-identify as high risk for STIs or HIV infection. Tables 1, 3, and 4 illustrate how HSV-2 prevalence can identify populations with elevated sexual risk behavior such as MSM, FSWs, “bar girls”, and STD clinic attendees. In order to prioritize the limited HIV prevention resources in this region, it is critical to finely map elevated risk behaviors. In Pakistan, surveillance work among different types of MSWs shows widely variable HSV-2 prevalence, but very limited HIV prevalence (Table 5) (Hawkes et al., 2009). The *khusra* MSWs (often known as *hijra*) have much higher HSV-2 prevalence than the *bantha* or *khotki* MSWs, and must be prioritized for HIV prevention interventions. Though HIV prevalence continues to be low among *hijra* MSWs in Pakistan (Hawkes et al., 2009; Pakistan National AIDS Control Program, 2005; Pakistan National AIDS Control Program, 2006–07; Pakistan National AIDS Control Program, 2008), it is probably only a matter of few years before a substantial upsurge in HIV incidence occurs in this population leading to a prevalence that possibly could reach 20% (Fig. 2A). Recent rapid rise in HIV prevalence among *hijras* in Pakistan affirms this conjecture (HIV prevalence increased from 0.8% in 2005 to 1.8% in 2006, and to 6.4% in 2008, Pakistan National AIDS Control Program, 2005; Pakistan National AIDS Control Program, 2006–07; Pakistan National AIDS Control Program, 2008). Meanwhile, HIV prevalence is more likely to stay at low levels among *bantha* and FSWs where HSV-2 prevalence is below 10% (Fig. 2B). Any group in MENA with high HSV-2 seroprevalence should be prioritized for HIV prevention interventions.

Despite overall low levels of HSV-2 prevalence, there is a considerable heterogeneity, with some sub-regions showing higher prevalence (such as Sudan and Morocco). Age stratified analyses of a Moroccan cohort reveal a typical increase in prevalence with age, though infection appears to be less commonly acquired during adolescence than in other regions of the world (Cowan et al., 2003; Smith and Robinson, 2002). Increasing prevalence in successive age cohorts reflects cumulative acquisition of HSV-2 through adulthood. Men in particular could be engaging in repeated episodes of high-risk practices throughout their sexual activity lifespan, such as contacts with FSWs. An alternative explanation might be a changing likelihood of successive birth cohorts to be exposed to HSV-2 infection during different eras (Burchell et al., 2006), or a low force of infection that increases average age at infection (Anderson and May, 1991). The former explanation seems unlikely as recent trends suggest increasing

Table 1
HSV-2 prevalence in different Middle East and North Africa populations as well as culturally related populations.

Country	HSV-2 prevalence	Assay	Accuracy and reproducibility of measurement[a]
Bangladesh	12% (women attending primary care clinic) (Bogaerts et al., 2001)	HSV-2 specific IgG ELISA (Gull Laboratories Inc., Salt Lake City, USA)	Good
Djibouti	2% (general population women), 5% (male blood donors), 49% (luxury bar FSWs), 81% (street-based FSWs) (Marcelin et al., 2001)	Unknown	Unknown
Egypt	32% (women, obstetric outpatient clinic) (el-Sayed Zaki and Goda, 2007)	HSV-2 qualitative specific IgM ELISA (Equipar Via G, Ferrari, Saronno, Italy)	Poor
Iran	28% (women, primary health care centers) (Kasraeian et al.)	HSV-2 specific IgG ELISA (unknown; commercial test)	Unknown
	8.25% (pregnant women) (Ziyaeyan et al., 2007)	Serum neutralization test	Poor
	23.3% (university students) (Tayyebi et al., 2010)	HSV-2 specific IgG ELISA (Dia-pro, Italy)	Good
Israel	9% (Arab and Jewish non-Soviet immigrants: pregnant women) (Dan et al., 2003)	HSV-2 specific IgG ELISA (Savyon Diagnostics Ltd., Ashdod, Israel) (Ohana et al., 2000)	Good
	2.4% (Arab STD clinic attendees) (Feldman et al., 2003)	HSV-2 specific IgG ELISA (EIA-gG; Gull, USA) (Ashley et al., 1998)	Good
Jordan	53% (male university students), 42% (female university students) (Abuharfeil and Meqdam, 2000)	HSV-2 IgG ELISA (Ismunit, Italian Institute of Immunology, Rome, Italy)	Fair
Lebanon	0.027% (general population women) (Karam et al., 2007)	Unknown	Unknown
Morocco	16.2% (ANC attendees), 13% (general population women), 10% (general population men), 6.7% (STD clinic attendees) (WHO/EMRO)	Unknown	Unknown
	26% (urban women with a median age of 40 years) (Patnaik et al., 2007)	Western blot (reference gold standard) (Ashley, 1998; Ashley et al., 1988; Ashley and Wald, 1999)	Excellent
	12.9% (ANC attendees), 9.2% (male HIV sentinel surveillance), 6.5% (military personnel) (Cowan et al., 2003)	HSV-2-specific IgG ELISA (HerpesSelect; Focus Technologies, CA, USA)	Good
Pakistan	3.4% (urban men) (Mir et al., 2009)	HSV-2 specific IgG ELISA (unknown; commercial test)	Unknown
	11.0% (IDUs), 6.0% (IDUs) (Platt et al., 2009)	HSV-2-specific IgG ELISA (HerpesSelect; Focus Technologies, Cypress, CA, USA)	Good
	8% (FSWs), 4.7% (FSWs), 7.4% (MSWs; *bantha*), 2.5% (MSWs; *bantha*), 14% (MSWs; *khotki*), 25% (MSWs; *khotki*), 54% (MSWs; *khusra*), 31.3% (MSWs; *khusra*) (Hawkes et al., 2009)	HSV-2-specific IgG ELISA (HerpesSelect; Focus Technologies, Cypress, CA, USA)	Good
Saudi Arabia	27% (pregnant women) (Ghazi et al., 2002)	HSV-2-specific IgG ELISA (Wampole Laboratories, New Jersey, USA)	Poor.
Sudan	27% (women Sudanese refugees in Ethiopia), 26% (men Sudanese refugees in Ethiopia) (Holt et al., 2003)	Glycoprotein G-based immunoblot assays (Centers for Disease Control and Prevention laboratory, Atlanta, USA) (Schmid et al., 1999)	Fair
	5.5% (household cluster survey; South Sudan), 4.5% (household cluster survey; South Sudan), 6.1% (household cluster survey; South Sudan) (Kaiser et al., 2006)	Glycoprotein G-based immunoblot assays (Centers for Disease Control and Prevention laboratory, Atlanta, USA).	Fair
Syria	0% (pregnant women), 0% (general population women), 0.3% (general population men), 0% (neonates), 9.5% (STD clinic attendees), 8.0% (women with cervical cancer), 20% ("bar girls"), 34% FSWs (Ibrahim et al., 2000)	HSV-2-specific IgG ELISA (Radim company, Sulzbach, Germany)	Good
Turkey	89% (women with pregnancy complication) (Cengiz et al., 1993b)	HSV-2 IgG ELISA (Unknown)	Unknown
	63.1% (pregnant women) (Duran, 2004; Duran et al., 2004)	IgG antibodies	Poor
	5.0% (pregnant women)	HSV-2-specific IgG ELISA (Euroimmun, Germany) (Aksözek et al., 2004; Eing et al., 2002)	Good
	5.5% (blood donors), 4.8% (sexually active adults), 8.3% (hotel staff), 17.3% (patients with genital warts), 60% (FSWs) (Dolar et al., 2006)		
	26% (MSM) (Cengiz et al., 1992; Cengiz et al., 1993a)	HSV-2-specific IgG ELISA (Unknown)	Unknown
	53.5% (rural general population women) (Maral et al., 2009)	EIAgen Herpes Simplex 2 IgG Code 08.1007.2 (ADALTIS ItaliaS.p.A. Via Magnanelli, 2-40033 Casalecchio di Reno)	Unknown.
	80% (FSWs) (Gul et al., 2008)	HSV-2-specific IgG ELISA (Euroimmun, Germany) (Aksözek et al., 2004; Eing et al., 2002)	Good
United Arab Emirates	17.7% (blood donors including migrant workers), 7.3% (migrant workers), 9.7% (migrant workers) [N.J. Nagelkerke, personal communication]	HSV-2-specific IgG ELISA (Kalon Biological, Ltd., Surrey, United Kingdom)	Good, but relatively insensitive to new diagnosis.

FSW = female sex worker, MSW = male sex workers, MSM = men who have sex with men, ANC = ante-natal clinic, STD = sexually transmitted diseases, IDU = injecting drug user, *bantha* = biological males with a male gender identity, *khotki* = biological males who dress as men but have "female soul" and feminized traits, *khusra* = transgenders who dress as women (also known as *hijra*).

[a] Criteria used to judge the confidence in the serology measurements were the robustness of the serology test used, procedures used to conduct the serology test, and amount of available information on the serology test. We labeled any test with greater than 95% specificity and sensitivity *excellent*; tests with greater than 90% sensitivity and specificity *good*; tests with greater than 75% sensitivity and specificity *fair*; all other tests were considered *poor*. Poor tests tend to suffer from cross-reactivity with other infections, particularly HSV-1. We also judged a test to be *poor* if authors used or described tests that have not been validated in the medical literature. In several cases, we were not able to identify the test used from manuscripts and numerous attempts to contact authors: these were labeled *unknown*.

sexual risk behavior in the young population (Abu-Raddad et al., 2010a).

HSV-2 research and trends in sexual risk behavior in MENA

The use of age cohorts will be critical to study the nature of HSV-2 prevalence in MENA. Rates of HSV-2 prevalence often change most rapidly among adolescents and young adults, suggesting that HSV-2 can be used to gauge recent changes in risk behavior among young age cohorts (Obasi et al., 1999; Slomka, 1996; van de Laar et al., 2001; Xu et al., 2006). MENA is characterized by a massive youth bulge. One-fifth of the population, 95 million people, are in the 15–24 years age group (Assaad et al., 2007; Roudi-Fahimi and Ashford, 2008; UNAIDS RST MENA, 2007) which is normally the age of initiation of sexual

Table 2
HSV-2 prevalence in the general population in different regions of the world (O'Farrell, 1999; Paz-Bailey et al., 2007; Pebody et al., 2004; Smith and Robinson, 2002; Weiss, 2004).

Region	HSV-2 prevalence
Asia	10% to 30%
Europe	4% to 24%
Latin America	20% to 40%
Middle East and North Africa	0% to 15%
North America	18% to 26%
Sub-Saharan Africa	10% to 80%

activities (Roudi-Fahimi and Ashford, 2008). This youth cohort represents the largest potentially-vulnerable population to HIV in MENA (Assaad et al., 2007). Youth are experiencing high rates of unemployment, delayed marital age, increased premarital sex, conflict morbidity, increased mobility, peer pressure to engage in risk behavior, and changing lifestyle norms (Busulwa, 2003; UNAIDS RST MENA, 2007, 2008). Population-based data of HSV-2 among youth collected sequentially in time would be valuable to determine trends of sexual risk behavior.

Epidemic growth and endemicity of HSV-2 and HIV infections

Though overall HSV-2 transmission probability per coital act during shedding is larger than that of HIV (Abu-Raddad et al., 2008; Wald et al., 2006, 2001), HSV-2 transmission occurs only during HSV-2 primary infection and reactivations, thereby slowing growth of HSV-2 epidemics. HIV transmission probability is considerable throughout the natural history of infection (Wawer et al., 2005) allowing for more rapid epidemic expansion. However, the infectious period for HIV is limited by disease mortality after about ten years, whereas the infectious period of HSV-2 persists for the duration of sexual activity of the infected host. Therefore, HIV cannot sustain as high a prevalence as that of HSV-2 in the population. HSV-2 prevalence reaches high levels but may need as much as several decades to reach its peak. Once HSV-2 reaches its endemic saturation, the HSV-2 force of infection becomes substantially larger than that of HIV and it is much more likely for a susceptible person entering the sexually active population to be infected with HSV-2 prior to HIV.

There are no longitudinal data of HSV-2 prevalence in MENA and it is not known whether HSV-2 prevalence has saturated its epidemic potential among the different populations in the region. Based on data from other regions (Korenromp et al., 2002a,b,c; O'Farrell, 1999; Smith and Robinson, 2002; Weiss, 2004), HSV-2 prevalence may have reached endemic levels within MSM in MENA. In most of Africa for example, the HSV-2 epidemic started no later than the first half of the twentieth century (Nahmias et al., 1990), and reached its peak prior to

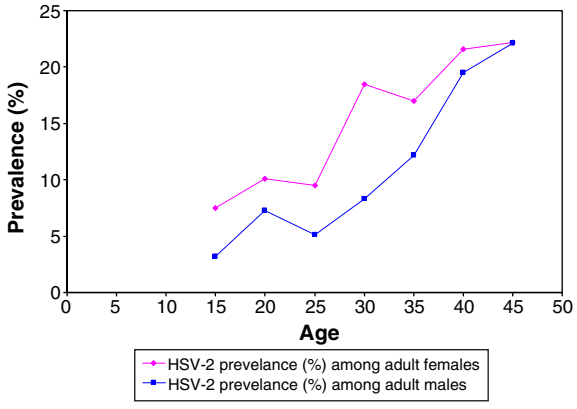

Fig. 3. HSV-2 prevalence for selected populations by age group in Morocco (Cowan et al., 2003).

Table 3
HSV-2 prevalence in different population groups in a study from Syria (Ibrahim et al., 2000).

Population	Population size	Prevalence HSV-2 (%)
Healthy men	305	0.3
Healthy women	349	0.0
Pregnant women	55	0.0
Neonates	101	0.0
Sexually transmitted disease patients	21	9.5
Cervical cancer patients	51	8.0
Bar girls	125	20.0
Female sex workers	101	34.0

the HIV epidemic (Abu-Raddad et al., 2008). However some high-risk populations in MENA have HSV-2 prevalence measures (Table 1) that are considerably lower than those in corresponding populations in other regions (Corey et al., 2004; O'Farrell, 1999; Smith and Robinson, 2002; Weiss, 2004). One cannot exclude that HSV-2 could be in the midst of early epidemic expansion in some high-risk populations in MENA.

If HSV-2 has only recently been introduced into a high-risk population in MENA, its use as a proxy to map levels of existing risk behaviors may be limited. Indeed, if risk behavior is increasing within certain subpopulations in MENA, then this may allow for conditions that promote both HSV-2 and HIV expansion. Because our model suggests that HSV-2 prevalence is best predictive of HIV spread when an endemic HSV-2 level is established, serial measures of HSV-2 prevalence will be necessary to rule out an enlarging HSV-2 epidemic. A related conclusion of our simulations among MSM is that a cross-sectional study that reveals an HIV-1 prevalence greater than or equivalent to that of HSV-2 suggests that both HSV-2 and HIV prevalence may be in an expansion phase.

Potential study limitations and limitations of available HSV-2 evidence in MENA

Our study has several limitations. First, our model's quantitative predictions are generated for a specific sexual risk contact structure and cannot be generalized for all populations. Sexual networks vary in structure (Ghani and Garnett, 2000; Morris, 1997) and this variation may affect HIV and HSV-2 infectious spread differently. It is not our aim to explore the complexity of links between HIV and HSV-2 epidemiologies. For this reason, we also did not include biological interactions between HSV-2 and HIV in our model. Rather, we explored generic conclusions regarding the predictive nature of HSV-2 prevalence as a measure of risk for HIV epidemic propagation. These findings do not apply for an HIV epidemic fueled by non-sexual modes of transmission such as injecting drug use. We also did not incorporate the overlap of risk behaviors such as part of the MSM population engaging in sexual risk behavior and injecting drug use at the same time. Existing evidence in MENA suggests a considerable overlap of risk factors between different risk groups (Abu-Raddad et al., 2010a, b). For example, often as much as 15% of MSM inject drugs and 30% report anal sex with injecting drug users (Mumtaz et al., 2010).

Table 4
HSV-2 prevalence in different population groups in a study from Turkey (Dolar et al., 2006).

Population	Population size	Prevalence of HSV-2 (%)
Sexually active adults	725	4.8
Pregnant women	300	5.0
Blood donors	200	5.5
Patients with genital warts	110	17.3
Hotel staff	264	8.3
Female sex workers	483	60.0

Table 5
Prevalence of HSV-2 and HIV in different high-risk populations in a study from Pakistan (Hawkes et al., 2009).

Type of population	Rawalpindi		Abbottabad	
	HSV-2 prevalence (%)	HIV prevalence (%)	HSV-2 prevalence (%)	HIV prevalence (%)
Bantha MSWs	7.4	0.5	2.5	0
Khotki MSWs	14	0	25	0
Khusra MSWs	54	2.4	31.3	0
FSWs	8.0	0	4.7	0

HSV-2 seroprevalence is a marker of lifetime sexual risk, not necessarily of current risk behaviors, and therefore HSV-2 prevalence may reflect current or recent risk behavior only among youth (Obasi et al., 1999; Slomka, 1996; van de Laar et al., 2001; Xu et al., 2006). However, this limitation should not affect the utility of using HSV-2 prevalence as a powerful marker of risk behavior and HIV epidemic potential in MENA. The populations for which this methodology is suggested are either young in age (high-risk populations), or populations with variable age structure (general population) but whose HSV-2 prevalence appears, given the aforementioned data, to be at low levels. A low HSV-2 prevalence in a population suggests that this population, irrespective of its age structure, may not have practiced high levels of sexual risk behaviors in the past.

Multiple studies on MSM in MENA in different countries have shown that the majority of sexually active MSM are young in their 20s and that these young MSM changed their sexual partners most often (Abu-Raddad et al., 2010a; El-Rahman, 2004; El-Sayyed et al., 2008; Elrashied, 2006; Mishwar, 2008). In Pakistan, MSWs had an average age of 22.3 (Pakistan National AIDS Control Program, 2005), 21.3 (Pakistan National AIDS Control Program, 2006–07), and 21.7 (Pakistan National AIDS Control Program, 2008) years, and started commercial sex at an average age of 16.9 (Pakistan National AIDS Control Program, 2005), 15.9 (Pakistan National AIDS Control Program, 2006–07), and 16.2 (Pakistan National AIDS Control Program, 2008) years. Furthermore, the vast majority of FSWs in MENA have been identified in multiple studies in different countries to be well below age 30, and young FSWs most often had the highest client volume (Abu-Raddad et al., 2010a; ACCORD, 2005, 2006; Ati, 2005; Syria National AIDS Programme, 2004; Yousif, 2006). Lastly, multiple studies in different countries show also that the dominant profile of IDUs, who engage in multiple sexual risk behaviors (Abu-Raddad et al., 2010a,b), is that of young men raised in large families shattered by unemployment, economic hardship, and urban–rural migration (Abu-Raddad et al., 2010a; Afifi and El-Sousi, 2004; Bolhari and Mirzamani, 2002; Michael et al., 2003; Mishwar, 2008; Pakistan National AIDS Control Program, 2005; Pakistan National AIDS Control Program, 2006–07; Shareef et al., 2006; Tiouiri et al., 1999; Zamani et al., 2006).

We assumed no enhanced acquisition or transmission probability of one infection due to the biology of the other infection in order to disentangle sexual risk behavior from biological interactions of HIV and HSV-2. In light of the fact that recent clinical trials have failed to document effects of HSV-2 suppressive therapy on HIV incidence, the degree of epidemiological synergy between HSV-2 and HIV-1 incidence remains uncertain (Celum et al., 2008; Lingappa et al., 2010; Watson-Jones et al., 2008). If such biological synergy between HIV and HSV-2 exists (Abu-Raddad et al., 2008), it can affect the epidemic spread and heterogeneity of disease burden, but at the same time, it would strengthen our argument for using HSV-2 as a predictor of the HIV epidemic potential since HSV-2 prevalence would reflect levels of risk behavior as well as the additional biological susceptibility to HIV infection arising from the biology of HSV-2 infection. HIV mortality may also affect, as a matter of principle, HSV-2 prevalence complicating the relationship between the epidemiologies of the two infections. However earlier work has suggested that this effect is very minor (Abu-Raddad et al., 2008).

Our focus in this article was on the qualitative findings linking the epidemiologies of HIV and HSV-2 rather than on precise quantitative estimates. Therefore we did not incorporate uncertainty analyses on the parameters of the model. Incorporation of such analyses would produce a range of estimates around the point estimates of our predictions presented here. Though we presented results for an MSM population, our qualitative results are of general nature and apply to heterosexual sex networks. Heterogeneities in the HIV transmission process due to variability in risk behavior, transmission probability and gender, can influence the distribution of the infection burden, but maintain the predictive effect of HSV-2 as a proxy of the risk of HIV acquisition for each subpopulation as can be seen in Fig. S2 of the Online Supporting Appendix.

Many HSV-2 seroprevalence studies to date in MENA suffer from methodological limitations due to use of inappropriate whole virus based assays that do not distinguish antibodies to HSV-2 from those against HSV-1. Due to the wide burden of HSV-1 infection in the region (Cowan et al., 2003; Smith and Robinson, 2002), assays that accurately differentiate chronic HSV-1 from HSV-2 infection are imperative. HSV-1 infection that is usually acquired during childhood through oral but not sexual contact, has a very high prevalence in MENA (Cowan et al., 2003; Smith and Robinson, 2002), and shows extensive sequence homology with HSV-2 (Gentry et al., 1988). HSV-1 causes a high proportion of incident genital herpes in some populations due to oro-genital as opposed to purely genital transmission (Lafferty et al., 2000; Langenberg et al., 1999; Lowhagen et al., 2000; Nilsen and Myrmel, 2000; Ribes et al., 2001; Roberts et al., 2003; Scoular et al., 2002; Tran et al., 2004). This trend has been observed regionally only in Israel (Samra et al., 2003), but could become more widespread if there is a trend of increased oral sex. Clinical exam is of no utility in differentiating HSV-1 and HSV-2 lesions, and up to 90% of HSV-2 seropositive persons do not recall having genital herpes (Corey and Handsfield, 2000; Cowan et al., 1994; Fleming et al., 1997). For these reasons, monitoring of HSV-2 infection must include accurate serologic assays. Several available serological assays have high specificity and sensitivity, though their results still need to be validated by population with Western blot assay (WBA) because of variable performance characteristics in different regions (Ashley-Morrow et al., 2004; Ashley and Wald, 1999). For these reasons our classification of serology tests as excellent, good, fair or poor should be interpreted cautiously as assay utility may vary regionally.

Finally, HSV-1 infection could hypothetically have a protective effect against HSV-2 acquisition (Cowan et al., 1994; Mertz et al., 1985), thereby partially contributing to lower regional prevalence of HSV-2. However, evidence for a protective effect is conflicting (Brown et al., 1997; Cowan et al., 2003; Langenberg et al., 1999), and in many settings, high HSV-1 prevalence (Cowan et al., 2003; Smith and Robinson, 2002) has not tainted the predictive power of HSV-2 as a proxy for sexual risk behavior. In fact, overwhelming evidence affirms the utility of HSV-2 as a marker of risk behavior irrespective of HSV-1 prevalence (Cowan et al., 2003,1994; Cunningham et al., 1993; Dan et al., 2003; Obasi et al., 1999; van de Laar et al., 2001). Near universal male circumcision coverage in MENA is also not likely to explain low HSV-2 prevalence as male circumcision reduces HSV-2 sero-incidence by at most 30% (Bailey, 2007; Tobian et al., 2009; Weiss et al., 2006).

Summary of findings

In conclusion, we identify HSV-2 serology as a powerful marker of sexual risk behavior that should be a standard component in any proposed HIV surveillance efforts in MENA. This is particularly true for studies incorporating integrated bio-behavioral surveillance surveys

among high-risk populations. At present, HSV-2 prevalence in the general population in MENA is among the lowest globally (Table 2) (O'Farrell, 1999; Paz-Bailey et al., 2007; Pebody et al., 2004; Smith and Robinson, 2002; Weiss, 2004). This provides an indication that sexual risk behavior in the general population in MENA is low, and that HIV infection will have limited inroads into this population. Yet, HSV-2 prevalence levels in MENA populations with identifiable risk behaviors are substantial and on occasion comparable to those in other regions (Smith and Robinson, 2002). Our model suggests that in a population where HSV-2 is already at a relatively high endemic level, HIV prevalence may continue at low levels for many years. However, there exists a potential for rapid exponential spread. Such populations should be a priority for early public health interventions including surveillance mechanisms for more intensive data collection to track the potential for further spread.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.epidem.2010.08.003.

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