Surveillance studies on Infectious diseases: Evidence for action
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Trends in hepatitis A, B, and shigellosis compared with gonorrhea and syphilis in men who have sex with men in Amsterdam, 1992-2006

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Abstract

Background: Since the mid-1990s, sexually transmitted infections (STIs) among men who have sex with men (MSM) have increased and appear to be related to more risky sexual behaviour. We compare trends in hepatitis A acute hepatitis B and shigellosis with the trends of gonorrhea and infectious syphilis in Amsterdam MSM over a period of 15 years.

Methods: We used data of all reported hepatitis A, acute hepatitis B, and shigellosis, and from all patients newly diagnosed with gonorrhea and infectious syphilis who visited the Public Health Service (PHS) STI outpatient department in Amsterdam between January 1, 1992, and December 31, 2006.

Results: Hepatitis A incidence remained unchanged in MSM (mean 0.97 per 1000 MSM, range 0.04-2.27), who had 21 percent of all 1697 infections. Hepatitis B likewise remained unchanged in MSM (mean 0.47 per 1000 MSM, range 0.19-0.77), who had 41 percent of all 448 infections. Most shigellosis is travel-related (657/974), and 16 percent of the infections occurred in MSM. Its incidence dropped in general, but not in MSM. Both gonorrhea and infectious syphilis in MSM show a steep increase, mainly after 1998.

Discussion: Hepatitis A, hepatitis B, and shigellosis do not follow the rising trends of conventional STI in MSM, which are believed to result from increased risky sexual behaviour. This disparity in trends implies differences in transmission dynamics. Recent molecular epidemiological studies suggest that clustered transmission in social MSM networks plays a major role.
Introduction

Since the mid-1990s the number of sexually transmitted infections (STIs) among men who have sex with men (MSM) has increased. Several studies have indicated that the increase of gonorrhea, syphilis, and HIV in MSM is related to more risky sexual behaviour and coincides with the introduction of highly active anti-retroviral therapy (HAART). Although hepatitis A, acute hepatitis B, and shigellosis are not considered conventional STIs, their transmission within groups of MSM is known to be linked to sexual activities. Yet it is not known whether more risky sexual behaviour affects their incidence as it affects the conventional STIs like syphilis.

In the mid-1970s, shigellosis and hepatitis A were recognized as sexual transmitted among MSM, mainly through direct oral-anal contact or digital-anal sex, particularly when practiced in ‘darkrooms’ or saunas, with anonymous partners or in a group. Elevated incidence rates of shigellosis in HIV-infected populations imply that HIV may be an important risk factor for shigella infection. In the Netherlands, the incidence of shigellosis and hepatitis A in the general population is low, and disease mainly appears in groups at high risk of infection, such as travellers returning from endemic areas, migrant children, and MSM. Hepatitis B in MSM is primarily contracted by ano-genital transmission. A relatively high seroprevalence of hepatitis B surface antigen (HBsAg) in MSM, along with risky sexual behaviour, contributes to a higher incidence of acute hepatitis B in MSM compared to the general population.

Methods

Hepatitis A, hepatitis B and shigellosis

In the Netherlands, all new laboratory-confirmed cases of hepatitis A, acute hepatitis B, and shigellosis must be reported to the Public Health Service (PHS). The PHS reports then to the National Institute for Public Health and the Environment (RIVM) which oversees national surveillance. Public health nurses from each PHS approach all its reported patients to collect data on the source of infection, demographic data, and information on specific risk factors, including travel prior to infection and sexual risk behaviour. Health advice is given, and active case finding among contacts is initiated.
We evaluated all hepatitis A, acute hepatitis B, and shigella patients reported to the PHS in Amsterdam in a 15-year period, between January 1, 1992, and December 31, 2006. All patients were classified into groups by their most likely source of infection, using an algorithm based on probable transmission route.

Hepatitis A patients were ranked hierarchically into five transmission groups: (1) patients most likely infected as a result of homosexual activity during the previous 6 weeks; (2) patients most likely infected by horizontal transmission, that is having a symptomatic hepatitis A patient living/working in the immediate environment; (3) patients most likely infected while travelling in a hepatitis A-endemic country during the previous 6 weeks; (4) patients who did not travel abroad and were most likely infected by an asymptomatic peer at primary school; (5) injecting drug users (IDU), and (6) patients with no likely cause of disease.

Only acute hepatitis B patients were included in analysis. Reporting criteria are clinical signs and symptoms, in combination with findings of HBsAg and/or type M immunoglobulin antibodies to hepatitis B in the serum. Acute hepatitis B patients were ranked hierarchically into five transmission groups: (1) sexual transmission-patients with high-risk sexual behaviour specific for hepatitis B transmission with sub-groups to distinguish unprotected homosexual and heterosexual contact with new and/or multiple partners; (2) IDU; (3) horizontal transmission- patients with exposure to a likely source i.e., when a household or other contact is identified as a carrier of HBsAg or when such identification is likely; (4) health care transmission-patients with invasive procedures performed in the six months preceding infection; (5) patients in whom none of the above risks are identified.

Shigella patients are hierarchically classified in three groups, including (1) patients most likely infected while travelling in a shigella-endemic country within the incubation period for shigellosis, i.e., seven days prior to symptomatic disease; (2) patients with no history of travel to a shigella-endemic country, sub-grouped as MSM, contacts of primary patients from the group above, and patients with an unknown cause of infection; (3) patients that can not be classified in group 1 or 2 as data on travel history are missing.

In Amsterdam, the sexual preference of patients has been registered for both hepatitis A and B since 1991. Data on the sexual preference of patients with shigellosis have been collected since 2001. We therefore used a derivative to represent MSM with shigellosis from 1992 to 2000, consisting of all male patients with shigellosis aged 15 and above with no history of travel within the incubation period.
Infectious syphilis and gonorrhea

The PHS in Amsterdam offers free-of-charge examination and treatment for STIs at its outpatient department (STI-OPD). At every consultation, information about socio-demographic characteristics is collected, and all visitors are screened for gonorrhea and syphilis. An individual can have multiple new consultations in one year and/or more than one diagnosis per consultation. For this study, we used data from patients newly diagnosed with gonorrhea and infectious syphilis (primary, secondary, and early latent syphilis) in the period 1992 and 2006.

Analyses

Incidence rates were calculated using an estimate of 26,000 MSM residing in Amsterdam as denominator. This number is based on an estimation of Veugelers in 1993, and Dukers in 2004. There is no indication that the proportion of MSM in the Amsterdam population (about 9% of the male sexual active men) has changed largely over the past fifteen years. Incidence rates for the general Amsterdam population are based on yearly population data from the local government, minus 26,000 MSM. The catchment area for the STD clinic has not changed over time and is the whole population of Amsterdam. Incidence over calendar time was also modelled using Poisson regression. We allowed for smooth time trends via the use of natural splines. In order to allow for over dispersion, the dispersion parameter was estimated from the data (quasi-Poisson model). P values were determined using the F test. For all infections we tested whether the null hypothesis of constant infection rates could be rejected. Analyses were done in the R statistical package version 2.6.2.

Results

Hepatitis A

During the study period, the total number of yearly reported hepatitis A patients dropped greatly, from 184 patients in 1992 to 18 patients in 2006. Of all 1697 reported infections with hepatitis A in Amsterdam, 21 percent (353) were attributed to MSM. Incidence rates in the Amsterdam non-MSM population are low and decreased significantly from 0.23 in 1992 to 0.02 per 1000 inhabitants in 2006 (p <0.0001). Incidence rates in MSM decreased too, but show large fluctuations. This decrease is not significant (p =0.13). The mean incidence rate is 0.97 per 1000 MSM (range 0.04-2.27) (Figure 1a). The trend of MSM shows a remarkable pattern
of peaks every three years, in 1992, 1995, 1998, 2001 and 2004. The incidence rate appears not to be different between MSM younger than 35 years and older than 35 years (data not shown).

**Acute hepatitis B**
A total of 448 patients with acute hepatitis B were reported to the PHS in Amsterdam of which 184 patients (41%) occurred in MSM. Among MSM, the number of new acute hepatitis B patients per year has remained fairly stable with a mean of 12 patients (range 5-20). The incidence rate appears not to be different between MSM younger than 35 years and older than 35 years (data not shown). Figure 1b shows the incidence rates in the last 15 years. Incidence rates in MSM (mean 0.47 per 1000 MSM, range 0.19-0.77, \( p = 0.4 \)) are on average 15 times higher than in non-MSM (mean 0.03 per 1000 persons, range 0.02-0.07, \( p = 0.1 \)). Both trend lines are rather constant.

**Shigellosis**
Since 1992, the total number of yearly reported shigellosis patients has decreased considerably, from 120 patients in 1992 to 40 patients in 2006. In total 974 patients were reported of which 16% (157/974) occurred in MSM. Most shigellosis (67.5% or 657 patients) was most likely imported from shigella-endemic countries. The remaining third (33.5% or 317 patients) had a likely source of infection in the Netherlands, and half of these infections (157/317) occurred in MSM. Figure 1c shows the incidence rates per 1000 persons. The incidence rate in non-MSM dropped significantly from 0.14 in 1992 to 0.04 per 1000 persons in 2006 (\( p < 0.002 \)). Incidence rates in MSM decreased too, but this decrease is not significant (mean 0.41 per 1000 MSM, range 0.0-0.96, \( p = 0.4 \)). The incidence rates in MSM show large fluctuations, with two distinct peaks in 1995 and in 2001 and patients varying from 0 to 25 per year. On average, the incidence in MSM is 5 times higher than the incidence in non-MSM. The incidence rate appears not to be different between MSM younger than 35 years and older than 35 years (data not shown).

**Gonorrhea**
In the fifteen-year study period, more than half (54%) of all 12,693 gonorrhea infections diagnosed at the STI-OPD of the PHS in Amsterdam occurred in MSM. Initially, the majority of diagnoses concerned heterosexuals, but since 1996 the number of diagnoses in MSM exceeds the number of diagnoses in heterosexuals. Figure 1d shows the incidence rates. The incidence rate in the general population
is low and fluctuated over time (mean 0.55 per 1000 persons, range 0.34-0.87, p <0.01). The incidence rate in MSM is much higher and increased from 10 in 1992 to 25.5 per 1000 MSM in 2006 (p <0.0001). An initial increase of infections in MSM is seen in the period 1994-1996, followed by a second steep rise of infections from 1998 onwards. After a peak of over 700 infections in 2001, the yearly number of infections seems to have stabilized around 600 diagnoses. Whereas before 2003 most infections were diagnosed in MSM younger than 35 years, since 2004 gonorrhea is mostly diagnosed in MSM of 35 years and older (data not shown).

**Infectious syphilis**

From 1992 to 2006, a total of 1840 infectious syphilis diagnoses were made at the STI OPD, of which three-quarters (75% or 1391) were in MSM. Figure 1e shows the incidence rates per 1000 persons. The incidence rate in the non-MSM population is low (mean 0.04) and increased only slightly (p =0.2). Before 1999, infectious syphilis in MSM was rare, but a steep increase of infections in MSM set off in 1998, and the incidence rates increased from 0.54 in 1992 to 7.54 in 2006 (p <0.0001). Since 2001, this rise seems to have stabilized, with an average of 199 new infections per year. From 2001 onwards the increase of syphilis amongst MSM ≥35 years is twice as high as amongst MSM <35 years (data not shown).
Figure 1. Incidence rates of (a) hepatitis A, (b) acute hepatitis B, (c) shigella, (d) gonorrhea, and (e) syphilis infections in MSM (black line) and all other patients (non-MSM) (grey line) in Amsterdam 1992-2006.
Discussion

In this study, population-based incidence rates for MSM were calculated, enabling not only comparison of trends in incidence between different STIs, but also between MSM and the general population. Only few analyses of STI trends in MSM have taken this approach.23 The findings in this study confirm the rising incidence of gonorrhea and infectious syphilis infections in Amsterdam MSM since the late 1990s. Syphilis mainly increased in older MSM (35 years and older). A similar trend was seen for gonorrhea in both age groups.24 Both STIs are regarded as re-emerging epidemics among MSM. These trends are not followed by hepatitis A, acute hepatitis B, and shigellosis in MSM. The trend of acute hepatitis B displays a more constant incidence rate, and an ongoing epidemic among MSM compared to the general population. Hepatitis A and shigellosis also show an ongoing epidemic among MSM, but its trend lines show a rather peaky course reflecting (cyclical) outbreaks. The disparity in trends suggests differences in transmission dynamics with the conventional STIs, showing little or no effect from the more risky sexual behaviour seen in MSM communities since the introduction of HAART.1,4,6,25-27 For hepatitis A, it is well-known that the transmission pattern within the homosexual communities differs from the pattern in the general population. In the general population, new hepatitis A infections are usually imported by returning travellers, especially children, originating from endemic countries. Imported infections cause sporadic, common-source outbreaks with seasonal peaks after the summer holidays.28,29 After the introduction of a paediatric vaccine in 1997 and the start of an annual vaccination program for migrant children in 1998, hepatitis A in the general population of Amsterdam declined.30 In contrast, hepatitis A among Amsterdam MSM occurs in year-round micro-epidemics.15,31 Only occasionally are new HAV strains imported into the male homosexual population, where the disease remains endemic and spreads without a seasonal pattern. Recent molecular epidemiological studies show that hepatitis A virus (HAV) is endemic among MSM all over Europe.17,32-34 The homosexual communities within the individual countries are probably too small to maintain HAV in their population over time, whereas the combined homosexual communities across Europe are sufficiently large, to sustain continued circulation of homologous HAV strains for years. This may explain the frequent reports of outbreaks on the continent.16,32,33 The appearance of small epidemics every three years in MSM in Amsterdam is not easily understood. The proportion of immune MSM following an outbreak may decrease over time, and
only when enough non-immune MSM have entered the homosexual community can a new outbreak occur.\textsuperscript{32,33} No systemic efforts have been made to vaccinate MSM against HAV. Combined hepatitis B/hepatitis A vaccination is offered to MSM since the start of the targeted hepatitis B vaccination campaign in 1998. It is unknown how many MSM received vaccination against hepatitis A, or what its overall vaccine coverage is in this group.

For shigellosis social groups of HIV-infected MSM may have an effect on its transmission pattern. HIV infection enhances transmission of shigella species in the immuno-compromised host through an increased susceptibility or a prolonged infectivity.\textsuperscript{1,14,18,35} For example, the peak of 25 patients in 2001 among MSM in Amsterdam was a clustered outbreak in a specific social group of MSM visiting so-called ‘trash parties’.\textsuperscript{36} Almost all patients in this outbreak were HIV-infected. The introduction of a new shigella species by an infected MSM returning from a shigella-endemic area may be the source of a clustered outbreak. However, it may be possible that some shigella species, just as homologous HAV strains, circulate among homosexual transmission networks in Western Europe. Various recent reported outbreaks of shigellosis among MSM in major cities in Europe, and also in the United States and Australia, were caused by either \textit{Shigella flexneri} or \textit{Shigella sonnei} species.\textsuperscript{36-43} More research such as a molecular cluster analysis could confirm whether these shigella species are molecularly linked.

The effect of changed sexual behaviour on hepatitis B incidence in MSM is uncertain. Since the prevalence of hepatitis B surface antigen carriers is relatively high among MSM in Amsterdam,\textsuperscript{44} it seems inevitable that more risky sexual behaviour among MSM should have led to an increase of acute hepatitis B. Also, an increase of STI, especially genito-ulcerative infections, could have led to its increased transmission and incidence.\textsuperscript{45} It is plausible that the negative effects of increased risky sexual behaviour among MSM have been counterbalanced by the positive effects of the targeted vaccination campaign for this group that started in 1998.\textsuperscript{46} The relatively high proportion of hepatitis B infections in MSM confirms that MSM are still a major risk group for acute hepatitis B in Amsterdam. Some limitations should be considered when reviewing the results of this study. Several probably predictive data, such as HIV co-infection, sexual activity or behaviour were not routinely collected in the different data bases. Data for infectious syphilis and gonorrhea are based on clients of a STI clinic only, whereas hepatitis A, B and shigellosis data are based on notified infections. Finally, risky sexual behaviour is not a homogenous concept. Variation in modes of transmission (oral-faecal,
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genital, and genital-anal exposures during sex) may contribute to our varied findings.
One may conclude from the presented results that, apart from the differences between MSM and non-MSM, clear differences in trends among STIs exist as well. Trends in the conventional STIs are soundly dependent on changes in sexual behaviour, whereas hepatitis A, and probably shigella too, show little or no effect from increased risky sexual behaviour. Other factors, such as a co-infection with HIV or introduction from abroad seem to play a more important role. The apparently absent effects of sexual behaviour on a vaccine preventable disease like hepatitis B demonstrate that careful evaluation of findings is needed to detect the positive, negative, and their counterbalancing effects of such an intervention as vaccination. The existence of international MSM-specific transmission networks is essential in understanding the epidemiology of STIs in MSM. More detailed knowledge on social and sexual behaviour among MSM is needed to understand the clustered transmission of infectious diseases. Molecular epidemiological studies are needed to gain insight into these possible transmission networks.
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