Hepatitis A incidence, seroprevalence, and vaccination decision among MSM in Amsterdam, the Netherlands

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Vaccine 37 (2019) 2849–2856

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

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ARTICLE INFO

Article history:
Received 3 October 2018
Received in revised form 18 March 2019
Accepted 21 March 2019
Available online 13 April 2019

Keywords:
Hepatitis A virus
the Netherlands
Men who have sex with men
Sexual transmission
Epidemiology
HAV IgG seroprevalence

ABSTRACT

Background: Several outbreaks of Hepatitis A virus (HAV) were recently documented among men who have sex with men (MSM) in Europe. We investigated the HAV incidence among MSM in Amsterdam, the Netherlands; and HAV seroprevalence and HAV vaccination decision among MSM visiting the Sexually Transmitted Infection (STI) clinic in Amsterdam.

Methods: Using surveillance data from 1992 to 2017 of MSM with acute HAV in Amsterdam, we estimated the incidence by calendar year and age. We explored HAV seroprevalence by calendar year and age, determinants for HAV seropositivity, and opting-in/out for HAV vaccination using data collected among MSM that visited the STI clinic between 2006 and 2017 and were included in a nationwide Hepatitis B virus (HBV) vaccination programme. Offering HAV vaccination at the STI clinic differed over three consecutive periods: not offered, offered for free, or offered for 75 euros. Logistic regression analyses were used to explore determinants.

Results: HAV incidence increased in 2016/17 after 4 years of absence and peaked in MSM around 35 years of age. Among MSM visiting the STI clinic, HAV seroprevalence was 37% (95%CI = 35–40%), which was constant over the period 2006–2017, and increased with age ($p < 0.001$). Determinants for HAV seropositivity in multivariable analysis were: older age ($p < 0.001$), originating from an HAV endemic country ($p < 0.001$), and being HBV seropositive ($p = 0.001$). MSM opted-in more frequently when HAV vaccination was offered for free versus paid (89% versus 11%, respectively; $p < 0.001$). Younger MSM were less inclined to vaccinate when payment was required ($p = 0.010$). *Post-hoc* analyses showed that 98% versus 46% of MSM visiting the Amsterdam STI clinic would be protected against HAV infection if HAV vaccination was offered for free or for 75 euros, respectively.

Conclusions: The MSM population of Amsterdam is vulnerable to a new HAV outbreak. We strongly recommend that MSM have access to free hepatitis A vaccination.

1. Background

Hepatitis A virus (HAV) causes self-limiting liver disease and is acquired by faecal-oral transmission through ingesting contaminated food and water or via person-to-person contact [1,2]. With increasing hygiene measures and access to clean water, the incidence of acute HAV infection in Europe has declined, resulting in an increase in the proportion of susceptible individuals in recent decades [1–3]. Currently, HAV endemicity in European countries can be categorized as low (HAV seroprevalence < 50% by age 15 and ≥ 50% by age 30) or very low (<50% by age 30 years) [4]. For low and very low endemic countries, the World Health

Abbreviations: MSM, Men who have sex with men; HAV, Hepatitis A virus; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HEV, Hepatitis E virus; HIV, Human immunodeficiency virus; IgG, Immunoglobulin G; IgM, Immunoglobulin M; IQR, Interquartile range; aRR, Adjusted relative risk; 95% CI, 95% confidence interval.

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https://doi.org/10.1016/j.vaccine.2019.03.048
0264-410X/

Organization recommends providing HAV vaccination to high-risk groups (e.g., travellers going to higher endemic countries, MSM, or injecting drug users) [5].

Low endemic areas in Europe are susceptible for HAV outbreaks [2,6], as demonstrated in the past decade by travel-related [7], community-wide [8], and food-borne related [9–12] outbreaks. In Amsterdam, the Netherlands, two main routes of transmission have been identified: travel-related transmission with limited secondary spread usually peaking after the summer holidays, and transmission among MSM, among whom new HAV strains are occasionally imported, become endemic, and slowly spread to a large number of individuals without a seasonal pattern [13–15]. Surprisingly, after decades of transmission, HAV outbreaks in the Netherlands among MSM have been nearly absent between 2012 and 2016. Yet an increase in HAV infections in the Netherlands - as part of a worldwide outbreak [16,17] centred in Europe [18–25]- has been reported since 2016 [20,26,27]. A recent study in the Netherlands showed that about one-third of individuals infected with an MSM HAV-strain were women or men who did not self-identify as MSM; suggesting spread from the MSM-community to the general population [26]. Furthermore, genome sequencing of the HAV strain circulating among MSM revealed three independently circulating strains (VRD 521 2016, RIVM-HAV16-090, and V16-25801), all of which were of genotype IA [26].

It is unknown what the actual HAV immunity level is in the MSM population in the Netherlands, and whether the outbreak occurring after four years of low transmission rates may be caused by a decline of HAV immunity among MSM. In Australia, for example, the contrary occurred with a decrease in the HAV susceptible population, likely caused by HAV vaccination and immigration from HAV endemic countries, which resulted in a decrease of HAV incidence [28]. In the Netherlands, a similar decrease in an HBV susceptible population was observed after the national introduction of hepatitis B vaccination among high-risk groups, resulting in a decrease of hepatitis B incidence among MSM [29]. In the Netherlands, no national HAV vaccination programme is currently in place, although MSM are advised to get vaccinated against HAV [2].

In this study, we estimated the incidence of reported acute HAV infections by calendar-year and by individual age-year, among MSM in Amsterdam, the Netherlands, using surveillance data between 1992 and 2017 (study population 1). Using data collected among MSM who were included in a nationwide Hepatitis B virus (HBV) vaccination programme and who visited the Sexually Transmitted Infection (STI) clinic in Amsterdam over the period May 2006 - February 2017 (study population 2), we explored HAV seroprevalence by calendar year and age. In this same study population we also looked for determinants of HAV seropositivity and opting-in/out for HAV vaccination. Attention was given to periods of changing HAV vaccination policy at the Amsterdam STI clinic: not offered (but referred to the vaccination travel-clinic within the Public Health Service) between May 2006 and May 2009 (period 1); offered free-of-charge between June 2009 and April 2013 (period 2); and offered for €75 (3-dose series) between May 2013 and March 2017 (period 3).

2. Methods

2.1. Study design

Data from two different study populations were used: (1) all HAV acute infections in Amsterdam during the period 1992 and 2017 (study population 1) were used to study the incidence of new HAV infections in MSM in Amsterdam; and (2) MSM visitors of the STI clinic at the Public Health Service (PHS) of Amsterdam who were eligible for hepatitis B vaccination and visited the STI clinic between May 2006 and March 2017 (study population 2) were used to study HAV seroprevalence, determinants of HAV seropositivity, and reasons for opting-in/out for HAV vaccination. Table 1 describes the data source, study period, and outcomes studied in these two populations.

2.2. Study population 1 – HAV incidence

2.2.1. Study design

For study population 1, surveillance data of acute HAV infections in MSM reported to the PHS of Amsterdam over the period 1992–2017 were used. Hepatitis A is a disease for which notification is mandatory in the Netherlands. All new patients with acute HAV infection must be reported to the PHS in the Netherlands. Cases of HAV infection are defined by the following criteria: (1) clinical signs and symptoms of infection (e.g., fever or jaundice) combined with (2) presence of anti-HAV IgM antibodies in serum, or (3) detection of HAV RNA in serum or stool by means of RT-PCR or epidemiological linkage to a confirmed case [13–15,20]. Individual age was available for all participants from 1996 onwards.

2.2.2. Statistical analysis

HAV incidence was plotted by calendar year and by individual age-year using HAV acute infections reported to the PHS (study population 1). Yearly incidence was estimated by dividing the number of acute HAV cases among MSM by the number of MSM residing in Amsterdam per year. Yearly incidence was also strati-

Table 1
Summary of the source, study period, and outcomes studied in two different populations among men who have sex with men (MSM), on the epidemiology of Hepatitis A virus (HAV) in Amsterdam, the Netherlands.

Name	Source	Study period	Outcome
Study population 1	Surveillance data of all acute HAV infections reported to the Public Health Service of Amsterdam	1992–2017	- HAV incidence over time in Amsterdam*¥ - HAV incidence by age in Amsterdam*
Study population 2	MSM who visited the STI clinic at the PHS of Amsterdam and were recruited within an ongoing Dutch nationwide hepatitis B virus (HBV) vaccination programme.	May 2006 - March 2017	- HAV seroprevalence over time - HAV seroprevalence by age - Determinants of HAV seropositivity
		May 2006 - March 2017, stratified by HAV vaccination period**: - period 2 (free): June 2009 - April 2013 - period 3 (€75): May 2013 - March 2017	- Proportion opted-in/out for HAV vaccination - Risk-groups for opting-in/out for HAV vaccination

* Denominator of total numbers of MSM obtained from Statistics Netherlands based on 10% of the male population aged 15–69 years and registered as of January of each calendar year.
¥ HAV incidence among MSM and the general population was also analysed and depicted in Supplementary Fig. 1.
** No HAV vaccination was offered in the period between May 2006 and May 2009 and hence was not included in outcome analysis.

fied by age, taking the average incidence over the period 1996 to 2017 within a specific age-year. The number of MSM residing in Amsterdam was estimated as 10% (constant over time) of the male population aged 15–69 years [29] registered as of January of each calendar year (data downloaded from Statistics Netherlands on 5 June 2018) [30]. HAV incidence was estimated as a function of age in years and as a function of calendar year using Poisson regression with restricted cubic splines at 4 knots (5th percentile, 35th percentile, 65th percentile, and 95th percentile).

2.3. Study population 2 – HAV seroprevalence and HAV vaccination decision

2.3.1. Study design

For the second study population, data from an ongoing Dutch nationwide hepatitis B virus (HBV) vaccination programme targeting high-risk groups [29,31] were used. During this programme, high-risk groups, including MSM, were offered free HBV vaccination (HB-Vax®, MSD or Engerix-B®, GlaxoSmithKline). Of all individuals included in this HBV programme, blood samples were drawn at inclusion (before vaccination) and tested for antibodies against Hepatitis B core antigen (anti-HBc). All further samples were frozen and stored at −20 °C. Within this nationwide HBV vaccination programme anonymised samples were selected from visitors who visited the STI clinic at the PHS of Amsterdam between May 2006 and March 2017, were 16 years or older, and MSM.

Demographics, risk behaviour data, and laboratory results were routinely collected in an electronic patient database. Selected serum samples were tested for IgG anti-HAV antibodies using the qualitative Liaison Anti-HAV IgG chemiluminescence immunoassay (DiaSorin, Saluggia, Italy). All samples were taken prior to vaccination. The presence of anti-HAV IgG is indicative of past or present infection with hepatitis A virus (HAV) or vaccination against HAV. The other extracted laboratory results concerned: HBV status (tested during the HBV programme for anti-HBc), serological syphilis, human immunodeficiency virus (HIV-1) test results, DNA positivity for *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and herpes simplex virus-1 and 2. All tests were performed using standardized protocols [29,32]. STI data was obtained at the same visit as inclusion in the HBV programme.

In addition to the free HBV vaccination offered within the nationwide HBV programme, the Amsterdam STI clinic also offered a combined HAV/HBV vaccination (Twinrix®, GlaxoSmithKline) during certain periods. HAV/HBV vaccination practices at the Amsterdam STI clinic varied over time as follows: it was not offered at the STI clinic (but those interested in the HAV vaccination were referred to the vaccination travel-clinic within the Public Health Service) between May 2006 and May 2009 (period 1); offered free-of-charge between June 2009 and April 2013 (periods 2); and offered for €75 (3-dose series) between May 2013 and March 2017 (period 3). In periods 2 and 3, visitors could choose between the two vaccines: (1) HBV vaccine alone (which was always free of charge independent of the period), or (2) the combined HAV/HBV vaccine. Since the focus of this study is on HAV, we will refer to 'opted-in for HAV vaccination' when a person opted in for HAV/HBV vaccination, and 'opted-out for HAV vaccination' when a person opted in for HBV vaccination only. Persons selected for this study agreed to participate in the nationwide HBV vaccination programme, thus all included individuals received at least one dose of the HBV vaccine.

2.3.2. Statistical analyses

A single-stage 25% random sample without replacement and stratified by calendar year was taken among participants from study population 2. To determine whether any selection bias resulted from the sampling procedure (study population 2), the selected population was compared with the non-selected population. Furthermore, the selected study population was compared over the three different HAV vaccination periods.

Descriptive statistics were used to summarize socio-demographic characteristics, sexual behaviour, and laboratory test results at visit. A risk-factor analysis was conducted using two separate end-points: (i) HAV seropositivity at time of visit, and (ii) opt-in or -out for HAV vaccination (Table 1). Odds ratios (OR) comparing levels of risk-factors and their 95% confidence intervals (CIs) were calculated using a logistic regression model. Risk-factor analysis using opt-in or -out for HAV vaccination was executed separately for period 2 (free) and period 3 (75 euro). Interaction was assessed between identified risk-factors and HAV vaccination period to test whether the effect of these risk-factors was significantly different between periods 2 and 3. Risk-factor analysis was done by initially adding all variables associated at the level of $p < 0.25$ and using a backward-selection procedure to obtain a parsimonious model. Risk-factor analyses accounted for the stratification of sampling by calendar year. In a *post-hoc* analysis, we estimated the impact of offering HAV vaccination on HAV immunity during period 2 (free) and period 3 (75 euros). HAV immunity in this study is defined as a combination of the end-point of being HAV seropositive or having opted-in for the HAV vaccination.

The probability of HAV seropositivity was estimated as a function of age in years and as a function of calendar year using logistic regression models with restricted cubic splines at 4 knots (5th percentile, 35th percentile, 65th percentile, and 95th percentile).

All statistical analyses were performed using Stata 14 (Stata Intercooled, College Station, TX, USA). Significance was determined as p-value < 0.05.

3. Results

3.1. Incidence of acute HAV infection among MSM in Amsterdam (study population 1)

In Fig. 1a the incidence of acute HAV infection among MSM in Amsterdam is presented during the period 1992–2017. HAV incidence fluctuated between 18 and 218 per 100.000 MSM between 1992 and 2004, and between 4 and 44 per 100.000 MSM between 2005 and 2011, was zero between 2012 and 2015, and increased in the last two years (2016 and 2017). Supplementary Fig. 1 depicts the incidence among MSM and the general population. Fig. 1b shows the incidence of acute HAV infection by individual age-years in MSM in Amsterdam during the period 1996–2017. There were no reported HAV infections for MSM under the age of 20 years. The HAV incidence peaked around the age of 35 years and was low after the age of 55 years. Median age of diagnosis with HAV infection was 35 years (interquartile range [IQR] = 30–41) and was not significantly different over the period 1996–2017 ($p = 0.272$).

3.2. Baseline characteristics (study population 2)

Between May 2006 and March 2017, 5,974 visitors of the Amsterdam STI clinic agreed to participate in the nationwide HBV vaccination programme. Of these, 32 were excluded because they were not MSM (women, heterosexual men, or sexual orientation unknown) and another 1,283 were excluded because no serum sample was available or socio-demographic data could not be matched to the serum sample identifier (Supplementary Fig. 2). The target population consisted of 4,657 individuals, and 1,152 (24.7%) were randomly selected for anti-HAV antibody testing. Of these, 18 had unknown HAV status (8 had equivocal results and 10 had insufficient serum available for testing), resulting in 1,134

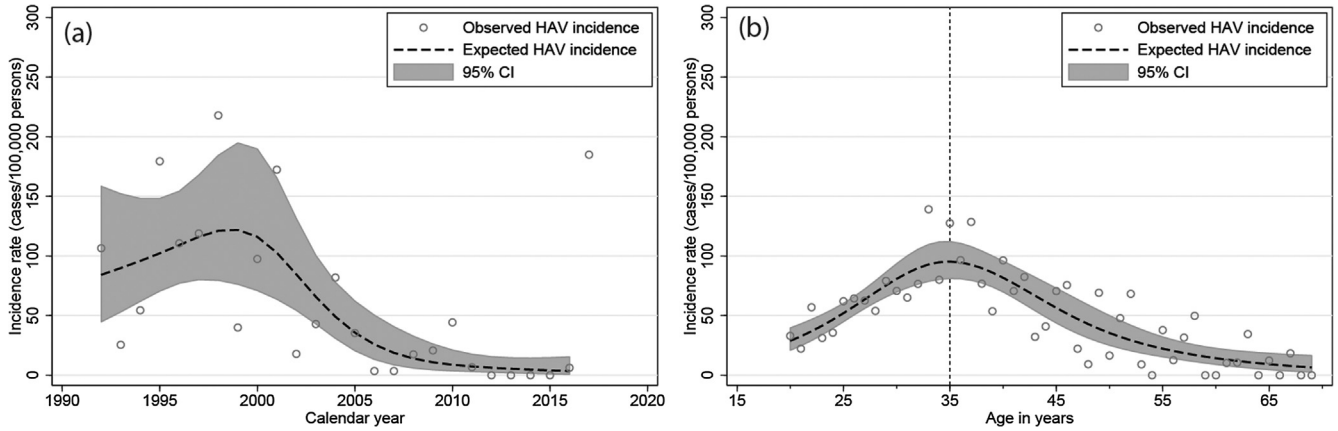

Fig. 1. Acute Hepatitis A incidence in the total MSM population in Amsterdam (1992–2017) by (a) calendar year, and (b) age in years. Incidence (per 100,000 MSM) per calendar year. Calendar year 2017 was not used in the prediction model in Fig. 1a and for Fig. 1b, only data from the period 1996–2017 was used (no individual age data was reported before 1996). Expected hepatitis A incidence was estimated using Poisson regression with restricted cubic splines at 4 knots (5th percentile, 35th percentile, 65th percentile, and 95th percentile) (dashed line).

individuals included in the analysis (Supplementary Fig. 2). There were no observable differences in study characteristics between the 1,134 individuals selected for analysis, 18 individuals selected but excluded from analysis, and 3,505 unselected individuals (Supplementary Table 2).

In the final population (n = 1,134), the median age was 29 years (IQR = 23–37). Most visitors were born in the Netherlands or other low/very low HAV endemic areas, 37% (n = 427) had a high socio-economic status, 24% (n = 272) indicated being bi-sexual, 85% (n = 952) indicated having had anal sex in the preceding six months, 1% (n = 12) reported being a sex worker, and 3% (n = 38) indicated being a client of a sex worker. Twenty-two percent (n = 251) was found to be positive for at least one genital STI and 7% (n = 72) was HIV seropositive (previously known or newly diagnosed). As a reason for visit, 20% (n = 230) indicated that a sexual partner had an STI, and 27% (n = 312) reported having STI related symptoms (Supplementary Table 2).

Over the three HAV vaccination periods, baseline characteristics were similar with some exceptions: visitors from period 1 were slightly older (24% ≤24 years old in period 1 versus 34% and 36% in period 2 and 3, respectively, overall p = 0.005), visitors from period 3 were significantly more often born in an 'intermediate/high endemic area' (19% in period 3 versus 8% and 10% in period 1 and 2, respectively, overall p < 0.001), and visitors from period 3 more often reported anal sex in the preceding six months (89% in period 3 versus 82% in both periods 1 and 2, overall p = 0.011) (Supplementary Table 2). HBV seroprevalence was significantly higher in the first period compared to the other two periods (16% in period 1, 8% in period 2, and 6% in period 3, overall p < 0.001). HIV status and STI diagnoses were not significantly different over the three periods.

3.3. HAV seroprevalence (study population 2)

Overall, the weighed HAV seroprevalence was 37% (95% CI = 35%-40%) and constant over time (p = 0.954) (Fig. 2a), while the apparent low seroprevalence observed in 2017 was likely due to the small number of individuals included in that year (n = 15) (Fig. 2a). Furthermore, HAV seroprevalence was not significantly different over the three HAV vaccination periods (p = 0.704, Supplementary Table 2) respectively 39%, 36%, and 37% for study period 1, 2, and 3. HAV seropositivity increased with age (p < 0.001) and was 35% (95%CI = 33%-42%) at 30 years old (Fig. 2b).

3.4. Determinants for HAV seropositivity (study population 2)

Using probability-weighted multivariable logistic regression, we found that older age (aOR [≥45 years versus ≤ 24 years]: 2.86, 95%CI:1.98–4.14), being from an HAV endemic country (aOR: 2.50, 95%CI: 1.72–3.62), and being anti-HBc seropositive (aOR: 2.00, 95%CI: 1.33–3.03) increased the odds of being HAV seropositive (Supplementary Table 3).

3.5. Groups opting-in or -out for HAV vaccination during period 2 (HAV vaccination offered free of charge)

When HAV vaccination was free of charge, 89% opted-in for the HAV vaccination and 11% opted-out (variable 'Hepatitis A vaccination decision', Supplementary Table 2). HAV seropositive individuals opted-out of HAV vaccination significantly more often than HAV seronegative individuals (25%[=100%-75% of opt-in] versus 3%[=100%-97% of opt-in], respectively) (p < 0.001), and individuals diagnosed with an STI at visit opted-out of HAV vaccination significantly more often than individuals without a diagnosed STI (19% [=100%-81% of opt-in] versus 9%[=100%-91% of opt-in], respectively) (p = 0.007) (Supplementary Table 4).

3.6. Groups for opting-in or -out for HAV vaccination during period 3 (HAV vaccination offered for 75 euros)

During the period in which vaccination was offered for 75 Euros, 11% opted-in for HAV vaccination, and 89% opted-out (variable 'Hepatitis A vaccination decision', Supplementary Table 2). Younger participants opted-out of HAV vaccination more often (p = 0.010) and, as in period 2, HAV seropositive individuals opted-out of HAV vaccination more often than HAV seronegative individuals (p = 0.003) (Supplementary Table 5).

3.7. Differences in groups opting-in or -out for HAV vaccination between periods 2 and 3

To test whether the effects of the above-mentioned risk-factors were significantly different between periods 2 and 3, we tested for interaction. We found that the effects of the identified risk factors on opting-in/-out for the HAV vaccination were significantly different between the two vaccination periods: age (p for interac-

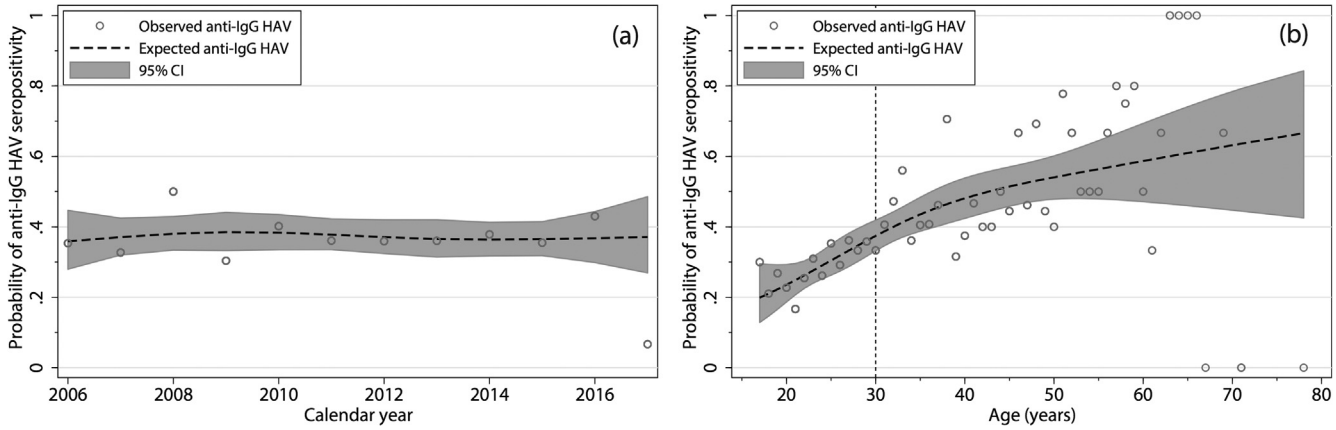

Fig. 2. Hepatitis A seroprevalence among MSM visitors of the Amsterdam STI clinic (2007–2017) by (a) calendar year, and (b) age in years. Expected hepatitis A seroprevalence was estimated from a 4-knot restricted cubic spline standard logistic regression model using default knot values (dashed line). Of note, only 15 individuals were included in 2017.

tion = 0.025), HAV seropositivity status (p for interaction = 0.017), and diagnosis with an STI at visit (p for interaction = 0.009).

3.8. Post-hoc analyses (study population 2)

During the period in which HAV vaccination was offered for free, HAV seroprevalence was 82% among those who opted-out for HAV vaccination, and, prior to vaccination, 31% among those who opted-in for HAV vaccination (Fig. 3). Considering that 89% of visitors opted-in for HAV vaccination, the prevalence of HAV immunity would result in 98% during the period in which HAV vaccination was offered free of charge (Fig. 3).

During the period in which the HAV vaccination was offered for a 75 euro out-of-pocket payment, HAV seroprevalence was 39% among those who opted-out for HAV vaccination, and, prior to vaccination, 19% among those who opted-in for HAV vaccination (Fig. 3). Considering that 11% of visitors opted-in for HAV vaccination, the prevalence for HAV immunity would result in 46% during the period in which HAV vaccination was offered for 75 euros (Fig. 3).

4. Discussion

After decades of endemic transmission, no HAV cases were reported between 2012 and 2016 among MSM in Amsterdam. In 2016, HAV was re-introduced in the Amsterdam MSM population as part of a worldwide outbreak with most cases in European countries [18–25,27]. Subsequently in 2017, HAV incidence among MSM became the highest since the 1990′s. Until now, HAV susceptibility levels among MSM in the Netherlands were unknown. In this study among MSM visiting the Amsterdam STI clinic who agreed to participate in the nationwide HBV vaccination programme, we found an overall HAV IgG seroprevalence of 37%, which did not change over time (2006–2017). Older age, being from an HAV endemic country, and being HBV seropositive were independently associated with HAV seropositivity. A dramatic

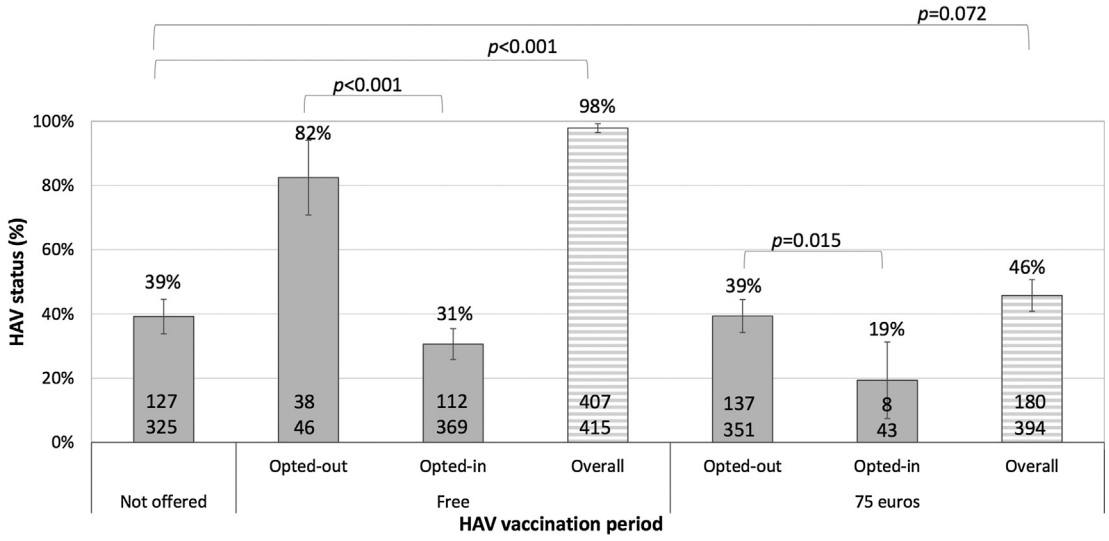

Fig. 3. Hepatitis A status among MSM visitors of the Amsterdam STI clinic (2007–2017). Grey bars represent HAV seroprevalence stratified by HAV vaccination period and HAV vaccination choice. Striped bars represent the proportion of individuals that would be immune for HAV infection, defined as a combination end-point of being HAV seropositive or having opted-in for HAV vaccination. For example, when the HAV vaccination was offered free of charge, 38 individuals who opted-out for HAV vaccination were already HAV seropositive, and 369 individuals opted-in for HAV vaccination, resulting in 407 individuals being protected for HAV infection after their visit at the STI clinic. Percentages represent probability-weighed HAV seroprevalence, and numbers within the bar represent the crude numbers of individuals HAV seropositive (numerator) and number of individuals within that group (denominator). Percentages cannot directly be estimated from the raw numbers, as these percentages were estimated by accounting for random sampling stratified by calendar year.

reduction from 89% to 11% in HAV vaccination opt-in was observed when HAV vaccination was no longer offered for free (versus having to pay 75 euros).

4.1. HAV incidence in MSM in Amsterdam

The peak in HAV incidence observed among younger MSM (~35 years) is in line with previous studies among MSM in the Netherlands [26] and can possibly be explained by a larger proportion of HAV immune individuals among older MSM (in agreement with our results). Another reason could be lower risk of infection by less risky sexual behaviour among older MSM. However, the fact that incidence of other STIs, including HIV, is elevated among older MSM suggests that this is less likely [33].

4.2. Proportion HAV susceptible and potential outbreak in this MSM population

The WHO currently recommends providing HAV vaccination to high-risk groups in low or very low endemic countries [4]. A previous study from Australia among MSM showed that maintaining HAV seroprevalence levels over 40–50% may be enough to prevent future outbreaks [34]. A modelling study from Australia, also among MSM, showed that when the proportion of HAV immunity reaches > 70%, outbreaks simply will not occur [35]. The overall HAV seroprevalence of 37% observed in this study, combined with only 35% being HAV immune at 30 years of age, leads us to conclude that the proportion of MSM susceptible for HAV is quite high in this population. These results support the notion of recent HAV outbreaks among MSM in Amsterdam, but also show the potential for new outbreaks in the absence of effective HAV vaccination programmes.

4.3. Determinants for HAV seropositivity

We observed that a higher proportion of young MSM is susceptible (i.e., not HAV seropositive) to HAV compared to older MSM. As expected, we found that the proportion of HAV susceptible MSM originating from an endemic country is much lower compared to MSM from non-endemic countries, reflecting exposure to HAV in the country of origin. We are unable to explain why HBV seropositive individuals were also more often HAV seropositive, even after controlling for confounding factors (demographic, sexual behavioural characteristics, and calendar year). The few sexual behaviour variables that we explored were not associated with HAV seropositivity. It is unfortunate that the number of sexual partners and anal-oral contact were not (routinely) collected, as we hypothesize that these factors could be more appropriate sexual markers for HAV seropositivity. Since HAV is transmitted by contaminated faeces, we expected an association of HAV seropositivity and anal intercourse, yet our results do not support this. HIV infection was significantly associated with HAV seropositivity in bivariable analysis, yet this association was no longer significant after correcting for age.

4.4. Risk groups for opting out of HAV vaccination

When HAV vaccination was offered for free, we found that HAV seropositive individuals were less likely to opt-in for HAV vaccination. A possible explanation could simply be that participants were aware of their HAV status (i.e., that they were immune) and therefore opted-out of HAV vaccination. Unfortunately, this hypothesis was difficult to evaluate as HAV vaccination history was not routinely collected at the STI clinic. Another explanation could be that these individuals have higher risk behaviour overall (i.e., were less inclined to take vaccination, higher sexual risk behaviour, and hence the chance to contract HAV was increased). This is corroborated by the higher risk of opting-out of the HAV vaccination when individuals were diagnosed with an STI at visit. However, it is important to note that this study concerns a selected study population that opted-in for HBV vaccination, therefore the former explanation is probably more plausible.

Furthermore, we found that younger MSM were less inclined to vaccinate against HAV when they had to pay 75 euros. The lower uptake among younger MSM compared to older MSM, may reflect younger men having less financial resources and indicates that their vaccination uptake would dramatically decrease if vaccination had to be paid out-of-pocket. Given that HAV incidence peaks at younger ages (i.e., 35 years), offering HAV vaccination for 75 euros is clearly ineffective to reach those groups most in need of vaccination.

4.5. The effect of HAV vaccination policy on vaccination uptake and immunity

We found that HAV vaccination uptake was dramatically reduced when HAV vaccination was offered for 75 euros. This is in line with a previous study at the Amsterdam STI clinic in which HPV vaccination intention was dramatically lower when vaccination had to be paid out of the pocket [36]. In our *post-hoc* analyses, we found that 98% of all MSM visiting the STI clinic would be immune for HAV when HAV vaccination was offered for free. This proportion was only 46% when HAV vaccination was offered for 75 euros and this was not statistically different compared to the 39% HAV seroprevalence observed in the period in which no HAV vaccination was offered. Therefore, reducing the vaccination price to, in this case, 75 euros will probably not have a strong effect on the HAV susceptible population, and thus may not prevent future HAV outbreaks in this MSM population. Assuming that these vaccination scenarios were projected to the general MSM population in Amsterdam, and that the proportions of HAV immune populations are reflecting those achieved during these scenarios, HAV outbreaks would be very unlikely to occur if HAV vaccination is offered for free, as 70% is enough to prevent any future outbreaks [35].

4.6. Limitations

HAV seroprevalence was measured among MSM who were included in a national HBV vaccination programme who visited the STI clinic in Amsterdam between 2006 and 2017. It is difficult to generalize these results to a broader MSM population in Amsterdam and/or the Netherlands. On the other hand, we may expect that this group would have higher HAV seroprevalence levels compared to the general population, as they are seeking care for sexually transmitted infections and therefore would result in an overestimation of the true HAV seroprevalence. Furthermore, the fact that these MSM participated in a nationwide HBV vaccination programme suggests that they are more inclined to vaccination.

When executing our post-hoc analyses, we assumed that all MSM opting-in for HAV vaccination would be fully protected for HAV infection. This is substantiated by several clinical trials in the USA finding that a single HAV dose may be sufficient to prime immune response and interrupt the spread in communities at risk [37]. However, cases of acute hepatitis A have been reported in vaccinated individuals, especially when vaccinated during the incubation period or being immunocompromised [38]. Furthermore, we assumed that once people choose HAV vaccination, compliance with follow up vaccines would be similar to that of the HBV programme (84% complied with second and 71% with the third vaccination [29]). In contrast to hepatitis B, previous studies have

indicated that a single hepatitis A dose is sufficient to establish long-lasting immune memory response [39].

5. Conclusion

Based on (i) the recent HAV outbreaks among MSM in Europe [19–22,27], (ii) the fact that MSM usually become infected at later ages when the disease is more likely to become clinically evident [1,6], (iii) a low proportion of individuals immune for HAV was observed among MSM visitors of the STI clinic in Amsterdam in this study, and (iv) a dramatic reduction in HAV vaccination uptake occurring when payment was required, we strongly recommend that MSM in the Netherlands have access to free hepatitis A vaccination. A combined HAV/HBV vaccination --as part of the ongoing HBV vaccination programme-- would be a highly preferred strategy, allowing the largest public health impact with the lowest cost.

Ethics, consent and permissions

Because routinely collected anonymous data was used for this study and HAV was tested on anonymised serum samples, no ethical clearance was sought.

Consent to publish

Not applicable, there are no patient identifying data.

Availability of data and materials

We welcome proposals for collaborative projects and requests for data sharing.

Competing interests

All other authors declare that they have no competing financial or other interests.

Authors' contributions

GS and AH conceived the idea and arranged funding; data collection was executed by ES, TH and SB; samples were tested in the laboratory under supervision of SB; sample selection and data management was done by MR, AB, and CA; statistical advise was provided by AB; statistical analysis was performed by CA; data interpretation was done by all authors; CA drafted manuscript and subsequent versions of the manuscript; all authors participated in review of the manuscript, and saw and approved the last version.

Funding

Funding was kindly provided by a Research and Development grant from GGD Amsterdam (number 75722495).

Acknowledgements

We are most grateful to the participants of this study. We would like to thank the team of research nurses and laboratory technicians that allowed us to collect and analyse samples necessary for analyses.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.03.048.

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