Molecular epidemiology of hepatitis B in the Netherlands
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Summary

This thesis describes how molecular epidemiology is used to track the spread of hepatitis B virus (HBV) in the community. Molecular epidemiology was not only used to come to a better understanding of the HBV incidence and circulating genotypes among risk groups, but it was also used to evaluate the vaccination programme targeted at behavioural risk groups in the Netherlands.

Molecular epidemiology of HBV in the Netherlands
To obtain more insight into transmission networks and risk groups in the Netherlands, sera and the accompanying demographic information and data on risk behaviour on risk behaviour of acute HBV cases were collected. Only sera and data from acutely infected patients were collected, since they give insight into the direction HBV transmission is evolving. Chapter 2 demonstrates that sexual transmission, especially between men, is the most important transmission route for HBV in the Netherlands. Injecting drug use plays a minor role in transmission. Genotypes A and D are predominant in the Netherlands. The majority of men having sex with men (MSM) acutely infected with HBV were infected with an identical genotype A strain. The majority of people infected with genotype D could be linked, directly or indirectly, to the Mediterranean area. Unlike the genotype A strain, there appeared to be no ongoing transmission of genotype D strains. In addition to the imported strains, there seems to be a pool of related but non-identical strains circulating among chronic carriers in the migrant population from which new patients are occasionally infected, primarily through heterosexual transmission.

HBV among risk groups
Chapter 3 describes the molecular epidemiology of HBV among MSM and drug users participating in the Amsterdam Cohort Studies. The first part of chapter 3 shows that an identical genotype A strain has been circulating among MSM in Amsterdam for the past two decades and possibly much longer, and is probably circulating in other western countries as well. The HBV incidence among this group declined dramatically in the first years after the start of the cohort in 1984 and then remained stable throughout the rest of the study period. Although HBV is generally considered to be more infectious than HIV, the HBV and HIV incidences among MSM were similar in trend and magnitude.
In general, little is known about HBV incidence among drug users, especially among non-injecting drug users. Therefore, changes in HBV incidence, risk factors, and circulating genotypes were determined among drug users in Amsterdam over time (1985-2002). This resulted in chapter 3.2 describing a decline in HBV incidence among drug users in Amsterdam after 1993, probably caused by a decrease in injecting. Injecting and non-injecting drug users were infected with the same strain, indicating that drug users infect one another regardless of their risk behaviour. After 2000, no injecting drug users with an acute HBV infection were reported to the Public Health Service Amsterdam and the specific
genotype D strain had disappeared. Altogether, this suggests that drug users are no longer a high-risk group for HBV infection. However, trends in drug use need to be monitored, because when injecting regains popularity in the Netherlands, drug users will become a high-risk group again.

Impact of a vaccination programme targeted at behavioural risk groups
The Netherlands is a low-endemic country with an estimated HBsAg prevalence of 0.3-0.5%, with HBV transmission mainly restricted to risk groups. The reported HBV incidence in the Netherlands is also low, between 1.4 and 2.0 per 100,000 inhabitants. Consequently, the Netherlands has not adopted a universal HBV vaccination programme, but a programme targeted at behavioural risk groups (since November 2002). Between 1998 and 2000, a pilot of the targeted vaccination programme was conducted in several regions of which Amsterdam was one. In chapter 4.1, two consecutive time periods were compared, the 6 years prior to vaccination and the 6 years during which the targeted vaccination programme was carried out. In the second time period, the genotype D strain specific for injecting drug users and their heterosexual partners disappeared. This result could probably not be ascribed to the vaccination programme, but was a result of the decrease in injecting behaviour and the decrease in the injecting drug user population. Furthermore, both studies in this chapter showed that although a considerable number have been reached by the current vaccination programme, its coverage is too low to have had a large impact on the HBV incidence among the various risk groups. The median age of participants in the targeted programme was relatively high. Clearly, in the current vaccination approach, people have already been involved in risk behaviour for several years before they are vaccinated. Furthermore, it is debatable whether the programme reaches the core group of MSM, since the anti-HBc prevalence found among MSM participating in this programme was relatively low.

As the current programme continues and more effort is being put into vaccinating more susceptibles and younger people in the risk groups, the coverage will somewhat increase, but this will not be sufficient to substantially reduce the incidence of HBV in the Netherlands. Therefore, low endemic countries such as the Netherlands should introduce universal vaccination against HBV.

Molecular data versus case registration
Chapter 5 demonstrates that, besides conventional case registration, molecular sequence data provide a powerful additional monitoring instrument. The study in this chapter showed that the molecular data showed a significant decrease in genetic diversity. This decrease could have been a marker for a decrease in HBV incidence, which had not been picked up in the case registration. However, the introduction of a pilot of the targeted vaccination programme could not have led to the observed decrease, since the decrease in genetic diversity occurred immediately after its introduction. Alternative explanations for the decrease in genetic diversity are the increase in sexual risk behaviour among MSM in the same time period, a decrease in generation time, or confounding due to imported strains.
This study again demonstrates that combining molecular and epidemiological data is far more powerful than analyzing the different data sources separately.

**General discussion**
Molecular epidemiology has proven to be an effective tool, not only in studying the transmission of HBV in the Netherlands, but also in evaluating the current vaccination programme. More insight into HBV transmission is necessary to obtain even more insight into prevention measures taken in the past, but also to formulate better prevention strategies in future. Even if universal vaccination is introduced in future, the Netherlands has to continue with the vaccination programme targeted at behavioural risk groups for at least another decade. Optimizing this current programme is therefore very important. The combination of molecular epidemiology and mathematical modelling will be a helpful tool in reaching this goal.
Finally, as the spread of HBV is a global issue, looking beyond our borders and realizing that a successful prevention strategy does not end with universal vaccination in our country is essential when facing the challenge of optimizing HBV prevention.