Surveillance studies on Infectious diseases: Evidence for action
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Discussion
General Discussion

In the Netherlands, on a local level, the actual control and prevention of infectious diseases in the general population is a responsibility of the regional public health services with specialised public health doctors and nurses, who are guided by the recommendations in the national practice guidelines (the LCI-Richtlijnen). The LCI guidelines give guidance to the daily practice of case ascertainment, active surveillance, source-and contact tracing, preventive interventions, health education, and outbreak management. In addition, the department of infectious diseases of the PHS carries out public health programmes such as vaccination programmes for behavioural risk groups, as described in LCI-Draaiboeken. Many recommendations in the national guidelines are based on evidence, clear and instructive, yet most recommendations are still expert opinions based on practice-or knowledge, and not equally supported by evidence, or lack detailed information, e.g. on risk groups.

The population-based surveillance studies presented in this thesis used locally acquired data. As the city of Amsterdam holds higher proportions of risk groups for several infectious diseases than the rest of the Netherlands, these studies offer extra value for the evaluation of current recommendations, or intervention programmes, targeting these risk groups. The studies presented in this thesis were intended to answer specific research questions generated from the actual day-to-day practice of infectious disease control by the PHS of Amsterdam. The outcomes are intended to serve as evidence for the national practice guidelines on the control of infectious diseases, and to support the implementation of its recommendations.

Seroprevalence of varicella-zoster virus, parvovirus B19, and cytomegalovirus

In the first part (chapter 2, 3 and 4) data from the Amsterdam Health Monitor (AHM) in 2004 are used. The AHM is a cross-sectional health survey carried out by the PHS of Amsterdam regularly to obtain insight into the health situation of the general Amsterdam population. By using a weighting method in the statistical analysis, the results are considered representative for the whole population, including the large immigrant communities originating from Morocco, Surinam, and Turkey. Besides the survey questionnaire, blood samples were collected from the same individuals, from which a serum repository was established. In chapter 4 only
women of childbearing age (16 to 44 years) were included. Besides data of the AHM, data on child day care personnel were obtained through a cross-sectional survey among female employees of Amsterdam day care centres carried out by the PHS of Amsterdam in 2007.

Chapter 2: Varicella-zoster virus

This study describes the seroprevalence of IgG antibodies against varicella-zoster-virus (VZV) among various ethnic groups in the Amsterdam adult population. Our findings show a rather low overall VZV seroprevalence in the adult population of Amsterdam (94%; 95%CI 92-96%), compared to the near-total VZV seropositivity (97-100%) in the national general population. This outcome is probably representative for a highly urbanized area, and may be explained by the ethnic diversity present in Amsterdam. VZV seroprevalence rates among first-generation immigrants (Moroccan immigrants 90%, Surinamese or Antillean immigrants 91%, and Turkish 92%) were significantly lower than among those born in the Netherlands. On average, first-generation immigrants had a 2 times higher risk of being VZV seronegative. In addition, the age of immigration was a positive predictor for VZV seronegativity. Those immigrants who migrated after the age of 11 years, were more likely to be VZV seronegative compared to those arriving at an earlier age or those born in the Netherlands. This is understandable as most persons born in the Netherlands acquire VZV immunity during childhood.

These findings have several implications. The results of this study imply that about 4-8% of the general adult Amsterdam population is still susceptible to infection with VZV, and that first-generation immigrants are a specific risk group for VZV seronegativity. When assessing the risk of infection after VZV exposure alertness is needed for vulnerable persons like pregnant women, patients with haematological malignancies or organ transplants in particular among first-generation immigrants. There is scarce and anecdotic evidence that non-immune adult immigrants experience VZV infection after settling in the Netherlands, and other countries have described outbreaks of chickenpox among newly arrived immigrants. Adults and adolescents with a primary VZV have an increased risk of complications, and hospitalisation. As in the Netherlands chickenpox is not a notifiable disease, little is known on the incidence of primary VZV infection or its complications in adults, and the current overall burden of VZV infection in the adult population cannot be estimated, but is
considered low, because most infections occur in pre-school children aged 1–5 years.\textsuperscript{8,9}

At the moment, a vaccination programme in the Netherlands is not yet recommended. One of the issues relates to cost-effectiveness and the uncertainty of the burden of disease of VZV in children, yet in adults near-total seropositivity is assumed. This assumption is based on the national population-based VZV seroprevalence study executed in 1995–1996. Yet, that study included relatively few residents of non-Dutch origin.\textsuperscript{8} Mathematical models predict that in the long run, a universal childhood programme may induce a shift in the age of primary VZV infection from childhood to adolescents and adults.\textsuperscript{9-13} In terms of health policies and the cost-effectiveness of the introduction of a universal VZV vaccination programme, the prevalence of specific risk groups for VZV seronegativity among adults, like first-generation immigrants should be taken into account. Besides improved surveillance on VZV complications in children and adults, more comprehensive research on VZV seronegativity in the general population, including the immigrant populations, is recommended.

\textbf{Chapter 3 Parvovirus B19}

This study describes the seroprevalence of IgG antibodies against parvovirus B19 among various ethnic groups in the Amsterdam adult population. The outcomes show an overall seroprevalence of 61\%, which is comparable to the estimates found in neighbouring countries.\textsuperscript{14-17} Knowing that immunity may depend on the country of birth, it was anticipated to find differences in seroprevalence between people born in the Netherlands and immigrants. Yet, no independent association of parvovirus B19 seropositivity with country of birth, or age at immigration (or the number of years living in the Netherlands) was found. In contrast to other research, parvovirus B19 seropositivity was not associated with having children,\textsuperscript{16-18} but as over a quarter (27.4\%) of the data on ‘having children’ was missing, these results were inconclusive. However, among those reporting having children, parvovirus B19 seropositivity was associated with the number of children.

As almost 40\% of the adult Amsterdam population is still susceptible to infection, vigilance is needed among doctors when suspecting a child of having erythema infectiosum, or when outbreaks occur at schools or at child day care centres. Those at risk for complications, mainly pregnant women, need swift identification to assess the risk of infection. The LCI-guideline “Erythema infectiosum” recommends, after confirmed exposure to parvovirus B19, testing for
(non)immunity to parvovirus B19 in pregnant women in the first half of their pregnancy, in order to ease women’s anxiety. Yet, parvovirus B19 seronegative women have a long worrying follow-up period, and require more blood tests at 3 and 8 weeks to exclude infection. If infection occurs, the overall risk of an abnormal outcome is approximately 5 to 10%, and the follow-up extends as they need close monitoring during the whole pregnancy.\textsuperscript{19}

As our study sample is limited to adults only, age-specific parvovirus B19 seroprevalence for children and adolescents could not be calculated. It is known that the age-specific risk for parvovirus B19 is the highest in school-aged children (7-9 years), and most people (60%) acquire antibodies against parvovirus B19 before they are 15 years old. Other studies show that new infections may occur throughout life in all age groups, resulting in a continuing increase of seroprevalence up to more than 80% in the elderly population (>70 years).\textsuperscript{14-17,20,21} Yet, our study could not demonstrate an increasing prevalence with increasing age, nor significant differences between age groups.

The epidemiological evidence of parvovirus B19 in the Netherlands is scarce. Representative data of its seroprevalence in the general Dutch population are lacking, and existing estimates are based on samples of convenience. Little is known about the incidence or the disease burden in the population. Accurate estimates on the age specific risks of infection, the force of infection, and the incidence during epidemic and during non-epidemic years in the Netherlands is needed. Therefore national population-based research on parvovirus B19 seroprevalence with more emphasis on children is recommended with equal emphasis on immigrant populations. As infection with parvovirus B19 may go unnoticed, high-risk groups for exposure need to be identified, especially those in occupational settings.

\textbf{Chapter 4 Occupational risk of VZV, Parvovirus B19, and Cytomegalovirus in child day care}

In this chapter the association between occupation and infection in women working in child day care was assessed, by comparing the seroprevalence of IgG-class antibodies against CMV, VZV and parvovirus B19 in female day care workers with women not working in day care. Our findings demonstrated obvious higher CMV, parvovirus B19 and VZV seroprevalence in women working in Amsterdam day care centres, compared to those who are not. As pregnant (susceptible) employees of day care centres are repeatedly exposed to these childhood infections, they are
considered a risk group for congenital infection of their newborn. Although the occupational risk of infection in child care is not new and has been described since the 1990s, in the Netherlands this knowledge has not contributed to the implementation of effective preventive policies for this particular risk group.22-29

Parvovirus B19 infection may cause a mild, usually non-febrile illness with a systemic maculopapular rash (erythema infectiosum), especially among children, or may be asymptomatic. This is an important finding as exposure to parvovirus B19 may go unnoticed. In this study, working in day care was independently associated with parvovirus B19 infection, as women working in day care had a significantly higher seroprevalence (73%) compared to women not working in day care (60%). Although worldwide geographic differences in B19V seroprevalence (with lower parvovirus B19 seroprevalence in tropical regions) are described, seroprevalence rates did not differ between ethnic groups.20 In 2007 the Netherlands Society of Occupational Medicine (NVAB) published the practice guideline ‘Pregnancy, Postpartum Period and Work’, in which recommendations on pregnancy and the occupational risk of infection in day care centres are made.30 For parvovirus B19, the NVAB guideline recommends primary health education, and screening of female employees of childbearing age when they start working in a day care centre. In addition, those who are seronegative or have an unknown immune status, and are wishing to become pregnant, should be offered repeated blood tests.30 In practice however, most of the exposed pregnant women presenting at the PHS are unaware of their immune status.

Infection with cytomegalovirus (CMV) is the most common congenital infection, occurring in 0.3% to 1.0% of all live births worldwide. In most patients, infection does not give clinical symptoms.31 It is well known that CMV seroprevalence varies worldwide, and is related to geographic, ethnic and social factors.32,33 In our study, CMV seroprevalence differed strongly between European women (57%) and non-European women (96%). Although the association between CMV seropositivity and occupation could not be demonstrated for non-European women (because of their high background seropositivity), it is likely they have a similar occupational risk of (re-)infection as their European colleagues.

The NVAB guideline recommends that pregnant employees should receive health education on following standard hygienic procedures. If a CMV infection in the workplace is demonstrated by a clinician and/or by laboratory tests pregnant
employees must avoid all contact with saliva (hugging) and urine. Pre-conception screening of employees for IgG antibodies is not advised.\textsuperscript{30} The development of a vaccine against CMV is in progress.\textsuperscript{28,34} Once it becomes available, female child day care workers should be considered a risk group eligible for vaccination. Until that time, other preventive strategies are necessary, such as behavioural interventions and awareness campaigns among child day care workers, child day care management, and the occupational health specialists. Indeed, several studies have described a lack of knowledge, not only among risk groups, but also among occupational specialists about the effects of CMV during pregnancy.\textsuperscript{35,36} Primary CMV infection results in life-long latent infection, and although congenital infection after reactivation and re-infection with a different CMV strain may occur (mostly unnoticed), the risk of congenital infection is highest for seronegative women.\textsuperscript{37,38} Pre-conception screening should be considered as a recommendation, as knowledge of one’s serostatus might enhance the effect of behavioural interventions and adherence to hygiene measures such as hand washing after diaper changing.

The association between working in day care and VZV seroprevalence could not be shown, because it was statistically not possible to control for likely confounders, e.g. age or ethnic background as all child day care workers were VZV seropositive compared to 94% of the women not working in child care. This total VZV seropositivity suggests that some susceptible women may have contracted VZV after they started working in child care, yet, the incidence of chickenpox in child day care workers is not known. For VZV, a safe and effective vaccine is available and although the CBO guideline (like some other countries) have adopted guidelines to screen and vaccinate risk groups (like health care workers) this is not applicable to women working in child day care.\textsuperscript{39,40} The NVAB guideline does recommend screening of female employees of childbearing age (with a negative history) when they start working in a day care centre, and vaccination in those planning to become pregnant.\textsuperscript{30} In public health practice in Amsterdam, many pregnant day care workers exposed to chickenpox still need rapid testing, and post-exposure prophylaxis with human varicella-human immunoglobulin within 72 hours when seronegative (or when test results cannot be required in time). Therefore it would be recommended that female child day care workers, similar to the CBO guideline for health care workers, be screened and if seronegative, be vaccinated beforehand.
Our findings show that 27% percent of the women working in day care are still susceptible to infection with parvovirus B19 or CMV. As both infections may go unnoticed, the employer, the occupational specialist, and the pregnant employee who is susceptible to CMV or parvovirus B19 infections could agree on alternative work during at least part of the pregnancy, and those still susceptible for VZV should be vaccinated.

Although the NVAB recommends screening of employees for parvovirus B19 and VZV, adherence to these recommendations is apparently low. None of the 285 participants (from 38 Amsterdam child day care centres) of the cross-sectional survey were previously screened for parvovirus B19, or for VZV, nor were aware of their parvovirus B19 (or CMV) serostatus, nor had knowledge of the effects of these infections during pregnancy. Further research on reasons why the NVAB recommendations are not implemented are recommended.

**Travel related diseases**

**Chapter 5 Malaria**

In this chapter a comprehensive overview of trends in imported malaria in the Netherlands in the period from 2000 through 2007 is described, for which the national surveillance data of all laboratory-confirmed infections of malaria notified was used. To put the time lines of reported patients into its current context: increased global travel and the availability of new malaria chemoprophylactic drugs, travel statistics and data from Dutch pharmacies regarding annual prescriptions for different kinds of malaria chemoprophylaxis were used. Despite increasing travel to malaria-endemic countries, the estimated incidence of imported *P. falciparum* infections per 10,000 travellers declined from 10.0 in 2000 to 3.4 in 2007. The causes for this decrease are likely multi-factorial, and not readily explained by more (or better use) of malaria chemoprophylaxis alone. Although the number of prescriptions for chemoprophylaxis collected from Dutch pharmacies increased, this increase did not match the growth in travel. In this study the estimated proportion of travellers to malaria endemic countries not using chemoprophylaxis rose slightly from 47% to 52% of all travellers. Remarkably, the incidence of imported *P. falciparum* in this group did not rise, but fell from 21.5 to 6.6 infections per 10,000 unprotected travellers, indicating that other factors must have caused the decrease of import malaria. Increased use of personal protective measures (such as impregnated bed nets and mosquito repellents), and a decreased risk of infection in malaria-endemic countries due to a reduction in local
malaria transmission or a combination of these factors may be the cause of the decline.\textsuperscript{41} The drop in incidence of imported \textit{P. falciparum} infections is greatest in travellers returning from Middle and West Africa, even though travel to this sub-region has doubled. Most malaria infections in the Netherlands are acquired in that region, and occur in immigrants (immigrants from endemic countries returning to their country of origin to visit friends and relatives, so-called VFR) originating from Ghana and Nigeria. The import of malaria by VFR from this region decreased from 138 infections in 2000 to 69 infections in 2007, making a large contribution to the observed decline in incidence. Also among tourist travellers, the number of infections from this region (mainly from Ghana and the Gambia) decreased from 65 infections in 2000 to 25 infections in 2007. These VFR may have improved their accommodations when visiting, e.g. by investing in better local housing, often in cities and urban areas, and having better access to protective measures like indoor spraying and insecticide-treated bed nets. Other western countries describe a similar declining incidence of malaria imported from West Africa, which may be explained by a decreased risk of infection in their destination country.\textsuperscript{41-43} Some African countries have achieved a high coverage of measures to control malaria, including extended use of bed nets treated with insecticide and improved access to malaria treatment, resulting in a reduction in local malaria transmission, especially in urban areas. Yet, most parts of Africa are still considered areas of high endemicity.\textsuperscript{43-47}

As import of \textit{P. falciparum} infection mainly occurred in travellers not using malaria chemoprophylaxis, one may conclude that the recommendations in the LCR-guideline for malaria are adequate. However, the number of travellers not seeking travel health advice remains a great concern, and needs close monitoring and more public attention.\textsuperscript{48,49} VFR from West-Africa remain the highest risk group for acquiring import malaria as many West Africans (in particular non-Ghanaians, illegal immigrants, and immigrants leaving at short notice) are not consulting pre-travel preventive health services.\textsuperscript{50} Holidaymakers on a cheap package tour to West-Africa appear to be a new risk group.\textsuperscript{51} Further research on the social and cultural aspects of health seeking behaviour for, and/or compliance to malaria chemoprophylaxis is needed, enabling subsequent recommendations for targeted risk-group interventions. Also, the evidence for decreased malaria endemicity in some continents needs close monitoring. For some destinations, such as the Indian subcontinent, and Middle and South America, the force of infection is
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declining so fast, that less strict guidelines on malaria prophylaxis in the near future may be plausible.52,53
Lastly, a limitation of this study was the absence of clinical data in the national surveillance data base, which could contribute to a better understanding of the burden of disease in returning travellers with malaria, and e.g. the reasons for not taking malaria chemoprophylaxis. At the moment clinical data on imported malaria are collected separately by several medical centres. In order to improve the quality of future surveillance studies it is recommended to create a combined national database with epidemiological and clinical data.

Chapter 6 Acute hepatitis B in travellers
In 1996, the LCR developed a practice guideline for the prevention of acute hepatitis B (HBV) in travellers targeting a limited number of travellers with a clear increased risk while travelling for HBV vaccination.54 In order to evaluate these recommendations in the LCR-guideline (valid in 2008) all notified acute HBV cases in Amsterdam between 1992 and 2003 were analyzed.
The findings show a much lower risk of infection than was expected from the estimated potential risk of infection from behavioural studies, and the increasing number of travellers in the past decades. In this twelve-year period 27 people (9% of all acute HBV patients in Amsterdam) of the estimated 600,000 residents from Amsterdam who visited a HBV-endemic country were likely to have acquired acute HBV while being abroad, making an overall incidence of 4.5/100,000 travellers. Only 10 out of the 27 patients would have been eligible for HBV vaccination according to the indications of the 2008 LCR-guideline, of whom only two sought pre-travel health advice, but were inadequately (partly) vaccinated) The majority of patients (18/27 or 67%) were immigrants from HBV-endemic countries returning to their country of origin to visit friends and relatives (VFR), Most (14/18) of this VFR group was not targeted by the 2008 guideline. The increased risk of infection is irrespective of the duration of travel, and in contrast to the infected Dutch short-term travellers (3 in total), immigrants were not infected by sexual transmission alone, but also by horizontal transmission, and by receiving medical care in their home country.54 Based on these findings, the working group of the Dutch National Coordination Centre for Travellers Health (LCR) decided to change the guideline and recommended that all susceptible immigrants from HBV-endemic countries were eligible for HBV vaccination, irrespective of the duration of travel. Also, the risk of infection in Dutch short-term travellers is low, and probably similar to the low
risk of infection in Dutch-born persons in the Netherlands, it was decided not to target all travellers for hepatitis B vaccination.

In contrast, immigrants from HBV-endemic also have an increased risk of infection irrespective of travel.\textsuperscript{55,56} Since 2003, all newborns with at least one parent from a HBV-endemic country are vaccinated, and in August 2011 a nationwide infant vaccination programme was initiated, yet no catch-up campaign for older children and adolescents nor adults will be implemented.\textsuperscript{57} As a consequence, first and second generation migrants continue to be a risk group for acquiring HBV for at least another 20-30 years (and probably longer, as the number of new immigrants will continue to rise over the next decades). At the moment this knowledge has resulted in an undesirable sprawl of local screening and vaccination practices among diverse ethnic groups in the Netherlands. The introduction of a nationwide and uniform screening and vaccination programme for all (new) immigrants born prior 2003 in the Netherlands should therefore urgently be considered.

**Sexually transmitted diseases in men having sex with men**

**Chapter 7 Trends in hepatitis A, B, and shigellosis compared with gonorrhoea and syphilis in men who have sex with men in Amsterdam, 1992-2006**

In this chapter, data of all Amsterdam notifications of hepatitis A (HAV, acute hepatitis B (HBV), and shigellosis from 1992, to 2007, are compared with data from all patients newly diagnosed with gonorrhoea and infectious syphilis at the STI outpatient department of the PHS in Amsterdam.

The findings in this study confirm the rising incidence of gonorrhoea and infectious syphilis infections in Amsterdam MSM since the late 1990s.\textsuperscript{58} Syphilis mainly increased in older MSM (35 years and older). A similar trend was seen for gonorrhoea in all age groups. Both infections are regarded as re-emerging epidemics among MSM. These trends are not followed by STI in the heterosexual population, nor by less conventional STI caused by the HAV and HBV or shigella in the MSM population. Whereas the rising trends in gonorrhoea and infectious syphilis are easily explained by the increased high-risk sexual behaviour, the trends in HAV, and probably in shigellosis too, seem not to be effected by this.
HAV infection among Amsterdam MSM occurs in year-round micro-epidemics following occasional introduction of HAV strains from homosexual communities outside the Netherlands. Molecular epidemiological studies have shown that HAV is endemic among MSM all over Europe. 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, as well as the trend observed in this study. 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. Although MSM are identified as a risk group for HAV infection, no national efforts have been made to vaccinate all MSM against HAV. In Amsterdam, combined hepatitis B/hepatitis A vaccination is offered to MSM since the start of the targeted HBV vaccination campaign in 1998.

The incidence rates of shigellosis in MSM show large fluctuations, with two distinct peaks in 1995 and in 2001 and the number of 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 peaky pattern of shigellosis in MSM indicate clustered outbreaks, probably in specific social groups, Other factors, such as a co-infection with HIV seem to play a more important role. Outbreaks of shigellosis usually occur after the introduction of a shigella species by a traveller returning from an endemic country. It could also be possible that some shigella species 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 *Shigella flexneri* or *Shigella sonnei* species. At the moment molecular cluster analysis on all shigella infections in Amsterdam is attempted, to gain insight into these possible transmission networks.

Until 2006, the incidence of HBV among MSM appears to be unaffected by the increased high-risk sexual behaviour. Yet in the past the association between sexual risk behaviour and HBV incidence is clearly evident. Although before 1985 information on the source or mode of transmission are lacking, the course of the HBV epidemic among MSM probable mirrors the epidemic curve of acute HBV in
male residents in the Netherlands. Since 1970 the number of acute HBV in men rapidly increased from <100 to a peak of almost 600 cases per year in 1981. From 1981 onwards the number of male cases dropped rapidly. In 1984-1987 incidence in Amsterdam male residents decreased from 23 to 8 per 100,000 men. Contact tracing showed that in many of these cases the HBV infections were acquired homosexually. This decrease was largely explained by the decreased high-risk sexual behaviour in the MSM population, due to the fear for HIV/AIDS, and as a consequence the incidence of HIV infection in Amsterdam MSM decreased as well at that time. Since the introduction of combination antiretroviral therapy (cART) for HIV infected patients in the mid-1990s, high-risk sexual behaviour among MSM increased again. It is plausible that the negative effects of this increased risky sexual behaviour among MSM counterbalanced the positive effects of the targeted vaccination campaign launched in 1998. The apparently absent effect of the increase of high-risk sexual behaviour on the incidence of HBV needs a more profound evaluation to understand the positive, negative, and counterbalancing effects of this intervention programme.

Chapter 8 Evaluation of the Amsterdam HBV vaccination programme targeting MSM

The HBV epidemic in MSM in Amsterdam is decreasing. From 2004 to 2012, the incidence rate of infection in MSM decreased by 78% (from 75 to 17/100,000), indicating that transmission among MSM has decreased. Our findings show that, despite ongoing high-risk sexual behaviour, and a vaccination coverage below 40%, the targeted Amsterdam HBV vaccination programme has been successful in diminishing HBV transmission among Amsterdam MSM. This is a remarkable finding, as it is this is the first time that a targeted HBV vaccination programme has been proven to be effective. Comprehensive analysis of the Amsterdam participants of the HBV vaccination programme showed that over two-third of the participants were MSM who engage most in high-risk sex. These were MSM recruited at STI-OPD (51%), and outreach locations such as saunas and gay bars (16%). These participants were significantly more often immune by infection (anti-HBc+: 19-21%), and 78% of all HBsAg seropositive (infectious) MSM were recruited at these locations. The mathematical model in our study demonstrates that the current decline in incidence is best explained by the scenario in which high-risk MSM (about 20% of the MSM population) are vaccinated. In 2008, a mathematical model by Xiridou et al. predicted already a greater benefit if MSM engaging most in high-risk sex could be reached.
Analysis of acute HBV infection in MSM showed that those born between 1960 and 1970 have been at highest risk for the disease in the past 20 years. The vaccination programme included almost 4000 MSM born between 1960 and 1970, and the estimated programme coverage was highest (62%) within this group. This aging cohort has contributed heavily to transmission of HBV in the last two decades and therefore can be considered a high-risk core group. If we assume that this core group has become immune either by infection or vaccination, we have a potential explanation for the declining HBV incidence, despite ongoing sexual high-risk sexual behaviour. Whether this is because this cohort really has more high-risk sexual than others is unknown, but it may well be that in their social network, more and acute/chronic HBV, thus more infectious partners were present. This finding is not easily understood, and needs further exploration.

Our results are in line with the results from several molecular epidemiological studies on HBV genotypes that circulate in Dutch MSM. For the past two decades, an identical HBV genotype A strain has been circulating among Amsterdam MSM. In 2009, the analysis of molecular DNA sequences revealed a significant decrease in genetic diversity of the HBV genotype A viral sequences collected from the Amsterdam MSM population (1992-2006), indicating a lower transmission rate of the virus.

Our findings have important implications for programme policy decisions. In the past HBV vaccination programme focused to include as many MSM as possible. Yet this study shows that full coverage is not required, as long as those MSM who engage most in high-risk sex (MSM attending STI-OPD or outreach locations such as saunas and sex clubs) are reached. Since 2005, as the average age of recruitment was 39 years and similar to the average age of infection, the Dutch Expert Group on Prevention of Hepatitis B recommended, to increase the impact of the programme, to target young MSM. Since then much effort was been made to reach this group. However, our findings indicate that the epidemic is mostly driven by an aging cohort. At the moment, young (non-immune) MSM have no particular increased risk of infection.

In August 2011, a nationwide infant HBV vaccination programme was initiated. As no catch-up campaign will be implemented, the ‘high-risk group’ policy must be continued for at least another 20-30 years. Since the programme seems to be effective in Amsterdam, (and in the rest of the Netherlands) with the current coverage in high-risk MSM, policy makers should evaluate how much more effort and resources are needed to vaccinate the large group of ‘low-risk’ MSM.
findings of our study imply, that as long as MSM (networks) in which the virus circulates, are identified and reached, the programme will be effective.

**Conclusion**

The research in this thesis relates to a variety of national practice guidelines used in the Netherlands for the control and prevention of infectious diseases. Most of the research used routinely collected and/or locally acquired data, yet the evidence acquired from these studies has proven to be more than ‘local’ evidence alone, and has induced several direct ‘actions’, such as the amendment in the national LCI-guidelines on HBV vaccination for travellers (chapter 6). Other findings may have raised the discussion to do so. In chapter 4, improvements of current NVAB recommendations for child day care workers are proposed, but more important: it revealed that the current practice guideline is not put into practice, which needs further investigation. Other outcome has generated new specific research questions, or led to new research (i.e. shigellosis in chapter 7). The VZV seroprevalence study revealed that risk groups for VZV seronegativity are present, a finding not previously described in the Netherlands (chapter 2). In addition the parvovirus B19 seroprevalence study is the first study testing parvovirus B19 in a random sample of the Dutch adult population (chapter 3). Local serosurveillance studies that contain large groups of immigrants provide additional evidence to national serosurveillance studies in which immigrant groups are under-represented. Both studies emphasise the need for improved disease surveillance, and up-to-date national seroprevalence studies with more prominence on immigrant populations.

Lastly, the evaluation of the Amsterdam HBV vaccination programme targeting MSM (chapter 8) proves the additional value of local evaluation of national prevention programmes. As the estimated proportion of the targeted population is more accurate and higher than the rest of the Netherlands, and additional data on sexual risk behaviour was available, the effectiveness of this risk group vaccination programme could be studied in detail. The findings of this study are likely to shape future national (and international) policy developments.
References


