Discussion

This thesis brings together studies in primary and secondary infectious disease prevention, using analytic epidemiology to identify risk groups and risk factors for disease in the slowly evolving context of public vaccination programmes, and in sudden-onset outbreaks. The research in this thesis develops the evidence base for, and practically supports, infectious disease control at regional and national level in the Netherlands.

Section 1. Immunisation

In the first section, we examined the epidemiology of vaccine preventable diseases, hepatitis B and hepatitis A, to define current risk groups. We make recommendations for targeted vaccination and improved disease prevention. Historically, the incidence of both diseases is higher in Amsterdam than the national average. Amsterdam is one of the most ethnically diverse cities in the world and more than 35% of the population are non-Western immigrants (compared to 8.5% nationally). It is projected that the total non-western population in Amsterdam will increase by 50,000 people between 2011 and 2030, of whom an estimated 60% will be new first generation migrants. In addition, it is estimated that 10% of the adult male population in Amsterdam are MSM (7–8% nationally) and the city is also known internationally for its sexual and social diversity, tolerance of prostitution and some drug use. Recognising the increased risk of related infectious disease transmission, PHS Amsterdam regularly conducts local research and has enhanced surveillance systems in place since the early 1980s, collecting detailed data on contacts of notified cases in addition to routine requirements. As such it has helped to shape and inform local and national public health policy and programme development.

Incidence of hepatitis B in ethnic groups (Chapter 2)

What was already known on this topic

Studies conducted nationally and in Amsterdam suggest that the prevalence of HBV in first and second generation migrants from countries where HBV is endemic (FGM and SGM, respectively) including Morocco, Turkey and Suriname, is higher than in the Dutch population. In recent years, as evidence of the cost-effectiveness of screening FGM at risk of chronic HBV infection has accumulated, the development of a national policy on migrant screening is now seen as a priority. In addition, vaccination programmes targeting children born to hepatitis B infected mothers (since 1989) and children of whom either parent was born in a middle- or high-endemic country for hepatitis B (since 2003) have been shown to be effective in preventing both acute and chronic infections. In 2012, vaccination coverage in both groups was 96.1% and 94.3% respectively, and vaccination of the latter cohort of children has largely eliminated...
infection in this group. In the Netherlands in 2011, 1732 cases of hepatitis B virus (HBV) infection were notified, of which 89% were chronic infections and 9% were acute infections. In terms of acute infection, this represents the lowest incidence since records began, and most of this decline is attributed to a drop in the number of notifications among MSM. The majority of acute infections were of unknown origin (25%) or were heterosexually transmitted (32%) and there are indications that adult migrants may be overrepresented in these figures.

What this study adds

The incidence of acute HBV infection in FGM in Amsterdam was 4.1/100,000 showing little fluctuation over calendar year from 1992 to 2009. Since 1999 the incidence in Dutch-born cases in Amsterdam has increased by 13% annually from 0.2/100,000 in 1999 to 2.1/100,000 in 2009. Although data regarding ethnic background of Dutch-born cases was only available from 2004, there are indications that some of this increase in incidence could be accounted for by SGM, as it also mirrors a doubling of the SGM population over the study period. The proportion of cases where the route of transmission was unknown in our study (23%) was similar to that reported nationally. Overall, between 2004 and 2009, the incidence was 4.3/100,000 in FGM, 3.7/100,000 in Dutch-born SGM, and 1.6/100,000 in native Dutch. This study confirms that new, potentially preventable infections are occurring in adult FGM and SGM who are resident in Amsterdam.

Recommendations arising from this study

Our findings support the proposal that migrants from HBV endemic countries should be offered screening for HBV infection, but also highlights the risk of new infections among FGM already resident and SGM born prior to 2003. Further research will be required to determine if a screening and catch-up vaccination programme would be acceptable, feasible and cost-effective, and to better understand the routes of transmission among migrants where it is recorded as ‘unknown’.

Incidence of hepatitis B in MSM: Targeted vaccination proves successful (Chapter 3)

What is already known on this topic

Between 1997 and 2002, the incidence of acute hepatitis B in Amsterdam was estimated at 2.2–3.7/100,000 population compared to 1.4–1.8/100,000 nationally. Given this elevated risk in the Amsterdam population, screening and vaccination of behavioural risk groups including MSM, commercial sex workers and drug users was commenced (initially on a pilot basis) in 1998 and rolled out nationally in 2002. The effectiveness of these programmes has been evaluated continuously since 2002. Despite observed falls in the number of notifications of acute HBV in MSM in recent years, marked fluctuations in numbers reported over time, limited programme reach (an estimated 6–12% vaccination coverage in the risk group) combined
with a lack of demonstrable programme effect until 2006, led to concerns about the ability of these programmes to eliminate HBV disease in these groups. On this premise, supported by dynamic transmission models tailored to the Dutch context, universal vaccination of infants was introduced in 2011. As no “catch-up” campaign for young teenagers would be offered (due to a perceived lack of support for adolescent vaccination), it was proposed that the targeted programmes already in situ would continue as necessary for 20 to 30 years to come.

What this study adds
This study showed that the incidence of HBV infection in MSM in Amsterdam decreased by 78% between 2004 and 2012. Despite ongoing high-risk sexual behaviour and vaccination coverage below the 40% target, the Amsterdam HBV programme appears to have been successful in reducing HBV transmission among Amsterdam MSM. A mathematical model in this study demonstrated that the decline in incidence is best explained by the scenario in which high-risk MSM are vaccinated. The study also showed that MSM born between 1960 and 1970 have been at highest risk in the past 20 years.

Recommendations arising from this study
HBV vaccination programmes targeting MSM do not require full coverage in order to be effective. Incidence can be substantially reduced if those who engage most in high-risk sex, and those who contribute most to transmission are reached. Policy decisions should therefore focus on identified MSM networks responsible for continued HBV transmission.

Immunogenicity of the hepatitis B component of hexavalent vaccine (Chapter 4)
What is already known on this topic
Children in the Netherlands have been vaccinated against infectious diseases under the National Immunisation Programme (NIP) since 1957. As vaccines against an increasing number of infectious agents have been introduced into the schedule, combination vaccines containing multiple components in a single injection are being administered simultaneously with newer vaccines against meningococcus C (since 2001) or pneumococcus (since 2006). This is thought to be easier for the vaccine recipient, more acceptable to parents and more convenient, cost-effective and efficient for health care workers. However, co-administration of multi-component vaccines with other mono- or multi-valent vaccines has lead to concerns about a suboptimal induced immune response. Reduced clinical efficacy was shown in the UK when the Hemophilus influenzae type b (Hib) component was given in a combined, acellular pertussis containing vaccine (DTaP-Hib). More latterly in 2005, authorization of a hexavalent vaccine, Hexavac™ (Sanofi Pasteur, MSD), was suspended by the European Medicines Agency (EMEA)
due to concerns about long-term immunogenicity of the hepatitis B component when co-administered with meningococcal or pneumococcal vaccines.\textsuperscript{24}

**What this study adds**
Since June 2006, the hexavalent vaccine, Infanrix hexa\textsuperscript{TM} (DTaP–IPV–Hib–HBV) has been offered concomitantly with pneumococcal vaccine (Prevenar\textsuperscript{TM}), to children at increased risk of hepatitis B infection. We assessed the immunogenicity of the HBV component of Infanrix hexa\textsuperscript{TM} co-administered with Prevenar\textsuperscript{TM}, and also compared pertussis and Hib components in Infanrix hexa\textsuperscript{TM} with the standard Infanrix–IPV + Hib vaccine offered to all children. Target thresholds for immune responses were achieved for all antigens studied and over 99\% of children vaccinated with Infanrix hexa\textsuperscript{TM} achieved an adequate immune response (≥10 mIU/ml) to the HBV component. The geometric mean concentration of the HBV component in Infanrix hexa\textsuperscript{TM} when co-administered with pneumococcal vaccine was somewhat lower than expected when compared to other studies conducted internationally where Infanrix hexa was administered alone, though this is unlikely to be of any clinical significance.

**Recommendations arising from this study**
The findings of this study are generally encouraging. Protection against hepatitis B will be required for decades in people vaccinated in infancy and long-term immunogenicity of this vaccine administered in combination with Prevenar\textsuperscript{TM} should continue to be monitored. Long term monitoring will continue to be a priority as more components are added to vaccines and as more vaccinations are added to the childhood schedule.

Incidence of hepatitis A in migrants (Chapter 5)

**What is already known on this topic**
For decades, Amsterdam and other major urban centres in the Netherlands have seen a surge in hepatitis A virus (HAV) notifications in early Autumn each year.\textsuperscript{25} The majority occur in SGM children who contracted the infection while on summer holiday in the country of birth of their parents (predominantly Turkey or Morocco). The initial surge in notifications was followed one incubation period later, in November–December, by an increase in HAV infections among children and adults who did not travel, but instead acquired their infection in the Netherlands.\textsuperscript{26} In response, the PHS has organized annually since 1998, large vaccination campaigns prior to the summer targeted at SGM children of Turkish and Moroccan backgrounds and those of other North African countries. Nationally, in 2012, the number of HAV infections was the lowest recorded since this disease became notifiable in 1999.\textsuperscript{27} In Amsterdam, whether or not the ethnic make-up of cases had been influenced by the vaccination campaigns was unknown, although there were earlier indications that they were indeed effective in reducing infections.\textsuperscript{28}
A formal evaluation of vaccine uptake and the effectiveness of the vaccination campaigns was not possible as the absolute number of migrant children who travel to their parent's country of origin is unknown, and less than half of vaccinations are administered at the PHS (instead by the family doctor, or elsewhere).

What this study adds
This research confirmed a dramatic decrease in the incidence of acute HAV infections since 1996 in Amsterdam. In more recent years, since 2005, 56% of cases were imported. The incidence in Moroccan SGM was 4 times higher than in ethnic Dutch children. In Turkish children, the incidence was similar to that of the ethnic Dutch. Although it is likely the programme has had some effect, a second important finding was that the ethnic background of cases was more mixed than previously with cases coming from many different non-Western backgrounds. Targeting the vaccine appropriately in the vaccination campaigns as currently organised is therefore difficult.

Recommendations arising from this study
Although the number of infections occurring annually has decreased substantially, infections are still occurring and the majority are imported (since this research was conducted, 11/14 cases notified in Amsterdam in 2012 were imported). In July 2012, WHO recommended that single-dose inactivated HAV vaccine could be considered in national immunization schedules where appropriate. To achieve better and more consistent coverage than the current ad-hoc programmes (pending cost-effectiveness), children who are of non-western background could be offered a single dose of HAV vaccine at the same time as the MMR vaccine, which is currently given within the national immunisation programme at 14 months of age. The cost-effectiveness, acceptability, and feasibility of this approach would require further investigation.

Evaluation of hepatitis A vaccine in post-exposure prophylaxis (Chapter 6)
What is already known on this topic
When a patient presents with acute hepatitis A infection, persons who have had contact with them are offered post-exposure prophylaxis (PEP) in an attempt to prevent or attenuate secondary infection and limit tertiary spread. Historically, contacts of cases were offered immunoglobulin (IG, a human derived blood product) within the incubation period (15–50 days). Amid safety concerns about IG, public health authorities in many European countries and Canada have been recommending the vaccine to some extent for almost a decade, though guidelines differ, particularly in relation to upper age-limits for post-exposure vaccination. Evidence of vaccine effectiveness used routinely in PEP is also limited.
What this study adds

Our study was the first formal evaluation of hepatitis A vaccine in routine post-exposure prophylaxis to our knowledge. Of contacts identified between 2004 and 2012, hepatitis A vaccine was offered according to protocol, to contacts who were healthy and at low risk of severe disease (aged <30, or, 30–50 years and vaccinated <8 days post-exposure, overall 89% of contacts). Immunoglobulin was offered to the remaining 13%, who were considered at risk of severe infection because of advanced age or an underlying health disorder. At follow-up testing 4–8 weeks later, 7% had developed a laboratory confirmed infection. All secondary infections occurred in vaccinated contacts and half were >40 years of age.

Recommendations arising from this study

Timely administration of HAV vaccine in PEP was feasible and the secondary attack rate was low in those <40 years. Pending larger studies, immunoglobulin should be considered the PEP of choice in people >40 years of age and those vulnerable to severe disease, irrespective of the number of days post-exposure that the vaccine is administered.

Section 2: Outbreak Investigation

In this section, we report investigations of outbreaks that were identified through routine surveillance. Specifically, these investigations were conducted to study risk factors for exposure, infection and morbidity among susceptible hosts for a known organism, to inform current and future prevention and control measures. Outbreak investigations present many challenges. If there is an ongoing exposure, finding the source is urgent and there is considerable time pressure, e.g. during food-borne outbreaks (Chapter 10). Delays lead to limited human or environmental samples for testing and difficulty confirming the source. In practice, studies may have limited statistical power and recall bias can impede objectivity, particularly during outbreaks with a high media profile (Chapter 8 and Chapter 9). Outbreaks teach us to expect the unexpected – even where populations are highly vaccinated against the agent in question (Chapter 7). In some outbreak situations, risk factors for infection are well described and the added value in conducting an outbreak investigation lies in testing new research methodologies (Chapter 10), or evaluating current preventive strategies with a view to improving efficiency and maximising staff and resource capacities (Chapter 11).

Risk factors for Mumps among vaccinated university students (Chapter 7)

What is already known on this topic

Mumps outbreaks among highly vaccinated populations have occurred in the Netherlands and internationally. From 2009 to 2012, a mumps outbreak affected more than 1500 people in the
Netherlands, the majority of whom were fully vaccinated (72% had at least two doses of MMR).38 The outbreak was first identified among university students in the cities of Leiden, Utrecht and Delft,39 and the G5 genotype was identical to the mumps virus isolated from outbreaks in the UK and USA between 2005 and 2009. Sero-epidemiological results from the PIENTER 2 study (2006/7) showed waning immunity after both the first and second MMR and a susceptible group in the low vaccine coverage areas.40

What this study adds
We conducted a retrospective cohort study among almost 1000 students from the three university cities most affected by the initial outbreak in 2009–2010: Delft, Utrecht and Leiden. The mumps attack rate (AR) was 13.2% (95% CI:11.1–15.5%) among respondents. Attendance at a large student party, being unvaccinated and living in student residences with more than 15 housemates were independently associated with clinical mumps infection. The adjusted vaccine effectiveness (VE) estimate for two doses of MMR was 68% (95% CI:41–82%). We concluded that despite high MMR vaccination coverage, the most likely cause of this outbreak was intense social mixing during the party and the dense communal living environment of the students.

Recommendations arising from this study
On the basis of this outbreak, young adults were advised to ensure they had received two doses of MMR vaccination (particularly to reduce the risk of complications if infected). They were also advised to consider postponing parties or large social gatherings when mumps was known to be circulating. Consideration was also given to offering a third MMR dose to the vaccination schedule. Given low mumps-related morbidity, low expected vaccine uptake and cost and logistical concerns, it was considered that a third dose could not be justified based on current available evidence.

Risk factors for Q fever exposure and infection (Chapter 8 and Chapter 9)
What is already known on this topic
From 2007 to 2009 an arguably unprecedented outbreak of Q fever caused by the bacterium Coxiella burnetii occurred in the Netherlands, resulting in the notification of more than 4000 patients.41 Q fever outbreaks have been described in other populations, often where sheep and goats have been implicated in human infection,42 but never on such a scale. There were many unknowns in this outbreak related to the pathogen, the transmission dynamics and risk factors for human disease.
What these studies add

In Chapter 8, we examined risk factors for infection during occupational exposure to Q fever. Workers involved in culling more than 50,000 sheep and goats were recruited into a prospective cohort study to examine *Coxiella burnetii* seroconversion and related morbidity while culling. Despite the fact that workers were given a presentation, advised to read the occupational health and hygiene regulations, and were provided with personal protective equipment (PPE) including FFP3 masks (‘Face Filtering Pieces’ thought to filter at least 99% of airborne particles), 17.5% seroconverted for antibodies to *Coxiella burnetii*. Working in close proximity to the animals inside the stable and prolonged contact (>100 hours per week) were risk factors for seroconversion. Anecdotally, culling workers reported removing PPE during coffee breaks and lunch breaks which may have contributed to the high proportion of seroconversions recorded. In Chapter 9, we examined recreational exposure as a risk factor for Q fever. Preliminary investigations into an outbreak of 350 people implicated a public ‘lamb-viewing day’ on a non-dairy sheep farm. In a matched case-control study, the association was confirmed, and other risk factors identified were being a smoker, having a past medical history and being aged >40 years.

Recommendations arising from these studies

In the context of inevitable exposure during animal culling, workers should be carefully instructed on PPE compliance in designated risk areas. Vaccination of culling workers could be considered in this context. Where exposure to infected animals could be avoided (i.e. visiting infected farms) the advice was to do so, and the farm involved in this investigation was closed to the public pending vaccination of the herd (the farm reopened in the spring of 2011).

Risk factors for infectious gastrointestinal disease (Chapter 10 and Chapter 11)

What is already known on this topic

Outbreaks of infectious gastrointestinal disease are common and risk factors are often well recognised, but each outbreak affords us new insights. In 2011, *Salmonella spp.* was estimated to cause around 37,000 cases of gastroenteritis. This cost in the region of 22–23 million euro in the Netherlands, 12 million of which was estimated to be related to foodborne infections. Raw or rare contaminated meat products have been implicated in previous outbreaks. *Shigella*, an organism that is closely related to *Salmonella*, is also spread through the faecal-oral route. In the Netherlands, 75% of infections are imported. Nationally, 300–600 cases of bacillary dysentery attributed to *Shigella* are reported each year, yielding an approximate annual incidence of 3.2/100,000 population. Secondary infections are common and related socioeconomic costs can be high.
What these studies add
During some outbreaks, the added value in conducting an outbreak investigation lies in testing new research methodologies, or evaluating current practice with a view to improving efficiency and maximising staff and resource capacities. In 2009, an outbreak of a previously unreported Salmonella Typhimurium (Dutch) phage type 132 affected 23 people in the Netherlands. It was attributed to contaminated raw or undercooked beef products. A novel approach to the traditional case–control study was attempted using the food consumption component of responses to a routine quarterly population-based survey as a control group. In Chapter 11, also to ensure efficient use of staff and resources, we examined the incidence of secondary Shigella infection (SSI) in households. SSI occurred in 7.4% of household contacts. This was lower than expected, probably due to improved hygiene standards in households in the Netherlands and abroad. Diarrhoea in a contact was an indicator of SSI, and independently, being a contact of a case where the case was aged less than 6 years, was a predictor of SSI.

Recommendations arising from these studies
Use of the food consumption component of a routine quarterly population-based survey was timely and could be employed in other food-borne outbreaks. This approach reduced the surge in manpower required to conduct a case–control study after an outbreak, and proved effective and timely as controls returned questionnaires throughout the outbreak period reflecting food intake in the previous week. The control-survey should be reviewed as necessary to take account of newly recognised or seasonal links to food and behaviours that might place individuals at risk of food-borne infection. Children and elderly could be oversampled to achieve a better representation of groups known to be vulnerable to Salmonella and other infections. During outbreaks, contact tracing and screening also increase manpower requirements and cost. For contacts of Shigella cases, faecal screening should be targeted at all household contacts of preschool cases (0–3 years) and cases attending junior class in primary school (4–5 years) and any household contact with diarrhoea. We did not find evidence to support the exclusion of all asymptomatic contacts <6 years old (irrespective of the age of the case) from school or day-care pending microbiological clearance, as is currently recommended.48

Conclusion and future research
Nationally, and regionally in the Amsterdam Public Health Service, the Netherlands has a longstanding reputation for high-quality infectious disease surveillance, epidemiological research and public health programme evaluation. Descriptive and analytic epidemiological studies as described in this thesis help to interrupt chains of infectious disease transmission by identifying risk groups and risk factors for exposure as they change and evolve over time.
They practically inform primary and secondary preventive strategies for infectious disease control, which prevent disease at an individual level and are responsive to changes in disease epidemiology in the population over time.

The Netherlands will become increasingly ethnically diverse in the coming years, and minority ethnic groups are over-represented in infectious disease surveillance figures. Emerging infectious diseases, hepatitis C for example, rarely prevalent in the Netherlands previously, are likely to become more common as the population migrating from disease-endemic countries grows. Internationally, there is no consensus on the definition of ethnicity. It is variously defined by the country of birth of the individual, their nationality, self-declared racial/ethnic background, race, country of birth of the individual and his/her parents, or any combination of these. In the Netherlands, country of birth of both the individual and his or her parents are recorded. This allows for differences between first generation migrants and their Dutch-born descendants to be examined and is a particular strength of Dutch infectious disease surveillance. Also, as everyone in the Netherlands must register in the municipality in which they reside, population incidence rates can then be estimated by ethnic group and generation at the regional and national level. This facilitates future estimates of multi-generational differences in disease, targeted intervention through screening and/or vaccination, and evaluation of policy changes at a population level. For diseases that are of low endemicity in the Netherlands (such as hepatitis B and A), 10 year epidemiological evaluations are probably sufficient.

In MSM in Amsterdam, an early evaluation of the targeted hepatitis B vaccination programme was not encouraging due to low uptake and limited observed programme impact. Fourteen years after its introduction however, we demonstrated a decreasing incidence attributable to the programme, and showed that low coverage (<40%) did not impede its success. This has important policy implications. Rather than targeting all MSM, we recommend that future vaccination efforts should be concentrated among those to engage most in high-risk sexual contact. For hepatitis A disease, we showed that acute infections are at the lowest level ever recorded in Amsterdam, and that among cases occurring, the ethnic background is more diverse than previously. The current annual vaccination campaign targeting migrant children of Turkish and North African origin in Amsterdam may not be reaching those most at risk and should be reconsidered. Use of enhanced surveillance data, as collected by PHS Amsterdam, has helped to highlight evolving health inequalities in minority groups that might otherwise go unrecognised. It also allows evaluation, not just of individual cases, but of risk for contacts and secondary transmission. This in turn has direct implications for disease control guidelines as demonstrated with hepatitis A PEP and shigellosis contact screening. These examples show how preventive programmes must be adaptable. Where changes in vaccination guidelines are
proposed, ethical issues, acceptability, feasibility and cost-effectiveness of new programmes must be investigated. Criteria and strategies for reduction or discontinuation of vaccination programmes, where relevant, also need to be established.

Surveillance data has its limitations: cases who are asymptomatic or with mild disease may not seek health care and cases may be underreported or misclassified. For conditions that are still culturally sensitive or stigmatised, risk behaviour may go unreported: in 23% of acute HBV cases notified in Amsterdam, no route of transmission was identified. Molecular epidemiology and typing combined with surveillance data will contribute to a better understanding of transmission routes. Also, where the population denominator is uncertain (e.g. in behavioural risk groups such as MSM), molecular methods and behavioural surveillance help to evaluate programme effectiveness.

New and unexpected infectious disease events continue to occur, most recently, an outbreak of Q fever in the Netherlands, and the novel coronavirus (MERS) and SARS internationally. Even where successful vaccination programmes with high vaccination coverage have been implemented, diseases are re-emerging. This is illustrated here by the mumps outbreak in highly vaccinated students and probable waning mumps immunity as the first generation to be vaccinated reach adulthood. Waning protection post-vaccination has been observed in relation to other pathogens, and adaptation of the pathogen to vaccination is also occurring (pertussis, for example). Where such outbreaks occur, research to better understand transmission dynamics, the role of cellular immunity and viral evolution will be required. Intermittent sero-epidemiological studies (such as PIENTER in the Netherlands) help to identify waning immunity when it occurs and are required as population susceptibility changes post-vaccination. They help us to anticipate outbreaks (the current measles epidemic in an under-vaccinated group in the Netherlands, for example	extsuperscript{4}), and support planning and placement of a research infrastructure prior to or early in an outbreak, as the timing of outbreaks are unpredictable. In combination with case surveillance, sero-epidemiological studies will continue to be a priority as more components are added to vaccines and as more vaccinations are added to the childhood schedule. Finally, in some outbreak situations, risk factors for infection are well described, and the added value of conducting an outbreak investigation may lie in testing new research methodologies, evaluating current practice and applying the findings to improve day-to-day infectious disease prevention and control. The final link in the chain.
“I often say that when you can measure what you are speaking about, and express it in numbers, you know something about it; but when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind; it may be the beginning of knowledge, but you have scarcely, in your thoughts, advanced to the stage of science....”

William Thompson, Lord Kelvin.

Lecture on “Electrical Units of Measurement”, Popular Lectures, 1883.
References


