Breaking the chain of transmission: Immunisation and outbreak investigation
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Summary

The transmission of infections through populations is a complex and dynamic process. The chain of transmission can be thought of as the process and events that lead from exposure to a pathogen, to transmission to others in the community. As chains of transmission occur through a population over time, the risk factors for exposure and disease progression also undergo dynamic change. Depending on the pathogen, change may occur rapidly resulting in sudden-onset disease outbreaks or it may evolve more slowly over time. Population susceptibility and disease prevalence may be altered, for example, due to vaccination programmes and changing population dynamics over many years. To control disease effectively and influence the epidemiology of disease in a population, timely surveillance and focused epidemiological studies are required, which inform public health action as problems evolve. This is the responsibility regionally of the Amsterdam Public Health Service, and nationally of the Centre for Infectious Disease Control at the National Institute for Public Health and the Environment (RIVM) in the Netherlands. Control measures may be primary (i.e. before exposure to a pathogen has occurred, such as targeted and mass population vaccination programmes), or secondary (i.e. post-exposure prophylaxis (PEP), or other specific interventions in response to unusual or unexpected events and outbreak investigations).

The aim of this thesis is to demonstrate the application of epidemiological studies to inform primary and secondary preventive strategies for infectious disease control. This is achieved through recognition of current risk groups for known pathogens, identification of risk factors for emerging pathogens and unexpected disease events, and the application of this knowledge to inform infectious disease control guidelines. The thesis is divided in two parts: In the first part (Chapter 2 – Chapter 6), studies examining current risk groups for vaccine preventable diseases are described; In the second part (Chapter 7 – Chapter 11) studies identifying risk factors for emerging diseases and unexpected disease events are reported.

Chapter 1 provides a general introduction, describing elements of the transmission chain and the principles of primary and secondary prevention in infectious disease control. The rationale behind primary preventive programmes, such as universal and targeted vaccination, is explained, and an overview of current programmes in the Netherlands is given. Secondary prevention is discussed in relation to contact tracing and post-exposure prophylaxis. The concepts of disease surveillance and outbreak investigation are introduced and an overview of the contents of each chapter is provided.
Part I: Immunisation

In Chapter 2, we describe trends in the incidence of acute Hepatitis B virus (HBV) infection among heterosexual adults in ethnic groups, from 1992 to 2009 in Amsterdam. Routinely collected surveillance data was used to estimate the incidence of HBV in the largest ethnic groups in Amsterdam, classified as Dutch, Surinamese, Turkish, Moroccan, Ghanaian, other Western or non-Western. We found that the incidence among first generation migrants (FGM) was on average three times higher, and among their children (second generation migrants; SGM, themselves born in the Netherlands), two times higher than in the native Dutch population. The incidence in Dutch-born cases has increased by 13% annually since 1992. This may in part be explained by a doubling of the population of Dutch-born SGM whose parents originate from mid and high-endemic HBV countries. The non-Western population in Amsterdam is set to increase by approximately 50,000 people between 2011 and 2030, and 60% will be FGM. We recommend that consideration should be given to offering HBV screening and vaccination to prevent new infections in FGM and SGM born prior to 2003 (who are not currently targeted in any vaccination programme).

In Chapter 3, we focus on another population group who are at risk of HBV infection, men who sleep with men (MSM), describing trends in the incidence of acute HBV in MSM in Amsterdam. We evaluated the effectiveness of the HBV screening and vaccination programme targeted at high-risk behavioural groups using mathematical modelling. The models accounted for vaccination data and trends in sexual risk behaviour among MSM. It is estimated that 10% of the Amsterdam population are MSM. Since the late 1990s, an active HBV screening and vaccination programme has been offered to MSM. Between 1998 and 2012, over 12,000 participated in the programme in Amsterdam. By the end of 2011, we estimated that 41% of MSM had come in contact with the programme, mainly via the Sexually Transmitted Infection outpatient clinic (STI-OPD) of the Public Health Service of Amsterdam and other recruitment sites such as saunas and gay bars. Eighty-two percent of programme participants were susceptible to HBV infection at the outset, of whom 71% went on to complete the 3-vaccination series. Since 2004, the incidence of acute HBV in MSM has dropped by 78%. According to model predictions, HBV vaccination programmes targeting MSM do not require full coverage in order to be effective, and the incidence can be substantially reduced if those who engage most in high-risk sex (estimated at 20% of the MSM population) and who contribute most to transmission are reached. Policy decisions should therefore focus on identified MSM networks responsible for continued HBV transmission.
Within the National Childhood Vaccination programme (RVP), children born to a parent from a country that is mid- or high-endemic for HBV have been offered HBV vaccination since 2003. In recent years, the HBV component has been integrated in a 'hexavalent' vaccine i.e. one that contains components against 6 infectious diseases in a single shot: diphtheria, tetanus, pertussis, polio, Haemophilus influenzae type b (Hib) and hepatitis B. Other children were offered a similar shot, but without the HBV component. Following an evaluation of HBV vaccination by the Health Council of the Netherlands, a decision was made to move to universal vaccination of all infants born in the Netherlands. This was implemented in 2011. Worldwide, combination vaccines are becoming increasingly complex as more components are added. In the Netherlands and elsewhere, concern had been expressed that combination vaccines containing multiple components may lead to a suboptimal immune response in the child.

In Chapter 4, we assessed whether the immune response to the hepatitis B component in the hexavalent vaccine was sufficient according to WHO standards, and whether the immune response to the other vaccine components was similar to that of the standard vaccine offered to all other children. Target thresholds for immune responses were achieved for all antigens studied. Over 99% of children vaccinated with the hexavalent vaccine achieved an adequate immune response to the HBV component (≥10 mIU/ml), although the peak level achieved (known as the geometric mean concentration; GMC) was somewhat lower than might have been expected.

In Chapter 5, the focus was again on health of minority ethnic groups in Amsterdam. Here, we examined trends within ethnic groups, in the number of cases of acute hepatitis A virus (HAV) infection notified in Amsterdam between 1996 and 2011. Every year there is a surge in HAV notifications after the summer holiday period, typically affecting SGM children of Turkish or Moroccan background who have returned from holiday after visiting their parents’ homeland, where HAV is endemic. Four to six weeks later (one incubation period of HAV), this is followed by a secondary wave of infections in children and adults in the Netherlands who have not travelled. Since 1998, PHS Amsterdam has run annual pre-summer hepatitis A vaccination campaigns targeted at children of Turkish and North African background planning to visit their parent’s country of origin. In a study conducted in 2006, there were suggestions that this programme was effective in reducing infections. In accordance with this study, we found that acute HAV notifications in 2011 were at the lowest level recorded to date in Amsterdam. The incidence in children of Moroccan and other non-Western backgrounds returning form holiday is still higher than in the native Dutch population however. As long as HAV is endemic in the countries visited, we suggest that it is necessary to continue with the vaccination campaigns as currently offered. An alternative would be to offer hepatitis A vaccine within the national immunisation schedule.
at the same time as the MMR vaccine (at 14 months of age), to children known to be at risk of HAV infection.

When a case of acute HAV is notified, it is the duty of the PHS to identify contacts and offer post-exposure prophylaxis (PEP) in the form of immunisation to prevent or attenuate secondary infection and to prevent further spread of the virus. Two agents are currently offered: human immunoglobulin (IG), which is derived from human blood products and provides very effective, but short-lived protection; and hepatitis A vaccine, a newer agent which is known to be safe and to stimulate long lasting immunity, but evidence of its effectiveness in PEP is limited. The vaccine is increasingly being offered in preference to IG because of safety concerns about the latter.

In Chapter 6, we evaluated the routine use of hepatitis A vaccine as an alternative to IG in the prevention of secondary HAV infection in contacts that have been exposed to HAV. According to guidelines, 87% of contacts were offered the vaccine, and 13% IG. Overall, 7% developed a secondary laboratory-confirmed infection: all occurred in those who had received the vaccine and half were over 40 years of age. Among those vaccinated according to protocol, the risk of a secondary HAV infection was 12 times higher in those ≥40 years, compared to those ≤15 years. We concluded the vaccine was effective in younger people, where the secondary attack rate was low and consistent with international norms. We recommend that, pending larger studies, IG should remain the PEP of choice in contacts over 40 years of age, and in those otherwise vulnerable to severe disease.

Part II: Outbreak Investigation

The Netherlands is a world leader in delivering public vaccination programmes, with a vaccination uptake among infants that consistently exceeds World Health Organisation recommendations. Despite this, from 2009 to 2012, a mumps outbreak affected more than 1500 people in the Netherlands. The majority were students who were fully vaccinated.

In Chapter 7, we investigated risk factors for mumps in this population of highly vaccinated students (72% had at least two doses of MMR) and identified factors associated with mumps vaccine failure. The mumps attack rate (AR) was 13.2% (95% CI 11.1–15.5%) among study respondents. Being unvaccinated, attending a large student party, 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. On the basis of this outbreak, young adults were advised to ensure that they were fully vaccinated, and 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, but it was considered that a third dose could not be justified based on current evidence.

Under the international health regulations of 2005, any unexpected or unusual public health event (of known or unknown origin), which may constitute a public health emergency of international concern is notifiable. In 2007, two patients with severe pneumonia who had not responded to antibiotic treatment were reported to the local Brabant Public Health Service by a medical microbiologist. An unusually high number of cases of pneumonia and severe flu-like symptoms were simultaneously notified in the province of Noord-Brabant. Testing implicated a hitherto relatively rare human pathogen in the Netherlands, *Coxiella burnetii*, the causative bacterium of Q fever. The outbreak that ensued between 2007 and 2010 was of an unprecedented scale, ultimately resulting in more than 4000 notified patients. Q fever outbreaks in humans, often implicating sheep and goats as the source, have been described in other regions. Despite this, there were many unknown factors in this outbreak related to the pathogen, the transmission dynamics and risk factors for human disease. In Chapter 8 and Chapter 9 we examined risk factors associated with occupational and recreational exposure to *Coxiella burnetii*.

In **Chapter 8**, over 500 workers who were involved in culling more than 50,000 sheep and goats during the epidemic took part in the study. Among those who showed no signs of exposure to *Coxiella burnetii* prior to the culling, 17.5% later seroconverted for antibodies to *Coxiella burnetii*. To avoid infection, workers had been provided with personal protective equipment (PPE) including gloves, overalls and FFP3 masks (“Face Filtering Pieces” thought to filter at least 99% of airborne particles). Despite this, prolonged time working in close proximity to the animals was a risk factor for infection. Anecdotally, culling workers removed some of their PPE during coffee breaks and lunch breaks. This may have contributed to the high proportion of seroconversions recorded, though we couldn’t directly test this. We recommended that, should similar culling be required again, vaccination of workers could be considered, and long-term follow-up of infected workers will be required.

In **Chapter 9**, we examined whether visiting a particular farm was a risk factor for the development of Q fever in local residents. Of the cases affected in this outbreak, 62% (162/248) took part in a case-control study and 433 address-matched controls were recruited in the area. As there were other farms in the area that were infected with *Coxiella burnetii*, we couldn’t
prove a causal association between visiting the farm and developing Q fever, but we found that the adjusted odds ratio for having visited the farm in question was 43.3 in cases compared to controls. Other risk factors for infection were being a smoker, having a history of other medical problems and being aged >40 years. The farm was closed to the public in the spring of 2010. After all animals were vaccinated, the farm reopened to the public in spring, 2011.

In some outbreak situations, risk factors for infection are well described and the added value in conducting an outbreak investigation may lie in testing new research methodologies, or evaluating current practice with a view to improving efficiency and maximising staff and resource capacities.

In Chapter 10, we describe a Salmonella Typhimurium outbreak that occurred in 2011 and was linked to consumption of raw or undercooked beef. An unusual aspect of this outbreak was that it was caused by a unique strain of S. Typhimurium (Dutch) phage type 132. We also used this opportunity to test a novel approach to a case–control study. Traditionally, such studies are time consuming, requiring a surge in manpower to source and interview controls during or after an outbreak. Controls are often questioned about their food intake weeks to months earlier leading to recall bias. We used responses from a routine food consumption survey, which is conducted quarterly. This proved effective and timely, as controls returned questionnaires throughout the outbreak period reflecting food intake in the previous week. We recommend that this approach could be used in future food-borne outbreaks, incorporating questions related to newly recognised or seasonal links to food and behaviours as appropriate, which 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.

In Chapter 11, we examined risk factors for secondary transmission of Shigella infection within households. Under current guidelines, household contacts who are attending pre-school or junior classes in primary school (aged ≤6 years) are excluded from school, irrespective of whether or not they have symptoms, pending microbiological clearance. In our study, we found a secondary infection rate of 7.4% in household contacts. We determined that cases aged 6 years or under were most likely to transmit secondary infections; however, the risk for the contact did not depend on the age of the contact, but on whether or not they were symptomatic. We did not find evidence to support the exclusion of asymptomatic contacts <6 years old from school or day-care while awaiting microbiological clearance, as is currently recommended.

Finally, in Chapter 12, the findings of this thesis are synthesized into a brief overview of what was already known in each area, what the research reported here adds to the evidence base,
and what recommendations arise from the research. This is followed by a brief discussion of the contribution of epidemiological research to infectious disease control and suggestions for further areas of research in the coming years. The studies in this thesis were carried out with the Amsterdam Public Health Service (PHS), and the National Institute of Public Health and the Environment (RIVM) in the Netherlands.