Breaking the chain of transmission: Immunisation and outbreak investigation
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Introduction
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‘1.3 grams of mercurous chloride, followed by 3 grams of pulverized cornachin.... The same doses followed for four days and nights.’

The dose of mercury was considered sufficient to cause drooling and diarrhoea, and perhaps even to make a patient’s teeth fall out. Combined with cornachin, ‘a retch-inducing mixture of antimony and cream of tartar’, and ‘where necessary, some blood [to] gently purge the humors’, the cocktail was lauded in the 1750s as part of an elaborate preparation to prevent smallpox. At first, in a process known as variolation, a small amount of live smallpox virus from the pustule of an infected patient was scratched into a person’s skin with a needle or knife. This was followed by three weeks of daily vomiting, bleeding, purging, and fevers. Finally, if well enough to go home, the patients and their clothes were hosed down with sulphur.

By today’s standards, it’s difficult to conceive that healthy individuals would volunteer themselves and their children for such a punishing preventive routine, with limited guarantee of its safety or effect. By 1800, Edward Jenner (who himself had been subjected to this miserable experience as a boy), had developed a safer and more reliable cow-pox derived vaccine, credited by a contemporary as ‘one of the greatest improvements that has ever been made in medicine’. It would be another 100 years before the association between microbial agents, infection, disease, and immunity would be elucidated and allied control measures effectively evolved: sanitation, disinfection, antibiotics and vaccination.

Despite extraordinary recent advances in cellular immunology, vaccinology, communications, epidemiology, mathematics and related fields, effective infectious disease control remains elusive. New threats are emerging or re-emerging as a combination of drivers result in dynamic changes in the distribution of disease over geographic areas and through populations. These include socio-demographic factors such as unprecedented population growth, changing human demography and behaviour; environmental and globalisation factors such as climate change, urbanisation, changes in food production, migration and international travel; and public health capacity factors including health care provision, animal health and food safety. Meanwhile microbes are constantly adapting beyond our technology.
1. The transmission chain and principles of infectious disease control

A contemporary model of infection is the transmission chain (figure 1). The chain comprises essential elements or links which, occurring in a sequential process, lead to infection. These elements include: an etiologic or causative agent (virus, bacterium, protozoan, fungus or the like), a reservoir or habitat where the agent pools and propagates (this may be human, animal or environmental), a source (contaminated foodstuff in a supermarket, infectious patient), a mode of transmission (direct contact with contaminated material, or indirect contact via a vector such as a mosquito), an entry portal into the host (respiratory tract, alimentary canal for example), and a susceptible host who because of genetic, immune, or other factors may be predisposed to infection. The elements are diverse and once the susceptible host has been exposed, progression to disease, cure or death is non-linear. Not all susceptible hosts exposed to an infectious agent will become infected, and agent properties and host outcomes differ: Some hosts will be infected but never develop symptoms, some will become ill but will recover, and some may die; Some agents will be eliminated from the host, and some will leave a life-long legacy as the host develops temporary or lifelong immunity in the form of antibodies and other immune markers, or becomes a carrier of the agent and can go on to infect other susceptible hosts, thus perpetuating the cycle. As chains of transmission occur in a population over time, the risk factors for exposure and disease progression, and rates of transition between states in the infectious process, undergo dynamic change. Change may occur rapidly, as in sudden unexpected disease outbreaks, or evolve slowly over time. Underpinning effective action is good surveillance, and focused epidemiological studies which inform public health action as problems evolve. Breaking the chain of transmission is complex, requiring timely intervention at some or every step in the transmission chain. Management of the within-host infectious process and disease progression lies within the medical realm, while controlling disease transmission through prevention of exposure and infection is traditionally a public health function. This is an interdisciplinary process involving human, environmental and animal health sectors, local and national government bodies and policy makers within countries and sometimes internationally.

2. Preventing exposure and infection: primary and secondary prevention

Protecting the susceptible host from exposure to an infectious agent is known as primary prevention. Primary prevention may involve elimination of the infectious agent at the environmental level, through reservoir destruction, pest control, water treatment etc. (figure), or may be targeted at the host (promoting healthy behaviour for example). Second to clean water, the single most effective primary public health intervention is vaccination. Vaccination
**Figure.** The transmission chain and intervention points for infection control.
programmes may be universal (offered to whole populations), or targeted at particular high-risk groups and individuals. In the event that exposure has already occurred, protecting the host from infection or disease is known as secondary prevention. Secondary prevention (so called post-exposure prophylaxis) may involve use of antimicrobials and antiviral agents or vaccination, and its purpose is to prevent infection, to attenuate disease morbidity and sometimes, to limit further spread of the infectious agent.

2.1 Primary prevention through vaccination
An egalitarian system of vaccination, not only to protect individual health, but also for the common good was recognised as early as the 18th century in relation to smallpox:

‘... if the inoculation be general, no subjects liable to infection would remain’

The Netherlands has been a world leader in delivering public vaccination programmes, with a vaccination uptake among infants that consistently exceeds the World Health Organisation recommendations. Every child registered in the Netherlands is offered state-subsidised vaccination that is free at the point of access within the National Childhood Vaccination Programme (RVP) beginning at 2 months of age. Vaccines targeting infectious agents Corynebacterium diphtheriae (D), Clostridium tetani (T) and Bordetella pertussis (aP), were introduced in the RVP in 1953, polio in 1957 (oral polio vaccine, OPV, and later inactivated polio vaccine, IPV), rubella (R) in 1974, measles (M) in 1976, mumps (M) in 1987, Haemophilus influenza type B (Hib) in 1993, Neisseria meningitidis type C (Men C) in 2002, Streptococcus pneumoniae (Pneu) in 2006 and most recently hepatitis B (HepB) in August 2011. To boost programme efficiency and cost-effectiveness, to improve parental acceptance, and to relieve the burden of multiple injections for infants, multi-component vaccines against several infectious agents are now offered in a single shot. The maximum number of injections administered to infants at any one time is thus currently limited to two. Despite many advantages, as the composition of combination vaccines has become increasingly complex, their widespread use is not without controversy. Based on experiences in the Netherlands and elsewhere, concerns have been expressed that co-administration of multicomponent and mono- or multivalent vaccines may lead to a suboptimal induced immune response. The RVP closely monitors new vaccines as they are introduced into the national immunization programme, as we will report in this thesis in relation to the new hexavalent DTaP-Hib-IPV-HBV childhood vaccine, Infanrix hexa.

Universal vaccination & herd immunity
The effectiveness of universal vaccination, as offered by the RVP, is increased by a form of immunity known as herd immunity i.e. if a sufficient proportion of the population are immune to
a disease, the probability that a susceptible individual will come into contact with an infectious individual is reduced, and the chain of transmission is interrupted. The herd immunity threshold is the proportion of immune individuals in a population above which a disease can no longer propagate. This threshold depends on a number of variables: the virulence of the disease, the efficacy of the vaccine, and the contact parameter for the population. The herd immunity threshold for measles, for example, is reported to be 92-94% of the population, and for rubella is 80-85%. Since the inception of the RVP in the Netherlands, average national vaccination coverage has been consistently high, and for babies, it exceeded 95% in 2012, although among school children, MMR coverage is somewhat lower, at 93%. Despite high vaccination coverage, outbreaks have continued to occur. Firstly, there are pockets of susceptible children who are unvaccinated either due to conscientious or religious objection on behalf of their parents (particularly in the so-called ‘Bible-belt’ region of the Netherlands), or because they are too young to respond optimally to vaccination. This has resulted in intermittent outbreaks: In June 2013, more than 160 unvaccinated children, largely within the Bible-belt region of low vaccination coverage, developed measles; In 2012, there was a national pertussis epidemic with a large increase in the number of cases in unvaccinated infants aged 0-2 months of age. Secondly, even where children are vaccinated according to protocol, the vaccine may fail (primary failure), or the effectiveness of the vaccine may wane as the child get older (secondary failure) leading to a radical change in the epidemiology of the disease. During the pertussis epidemic for example, a peak in cases was seen in children 8-years and over, probably due to decreasing vaccine effectiveness from this age; also, between 2009 and 2012, a large outbreak of mumps affecting college students occurred despite the fact that a large majority were vaccinated. Why secondary vaccine failure occurs is poorly understood and the changing epidemiology of what were traditionally childhood diseases poses a particular challenge for effective intervention.

Criteria for including new vaccines in public programmes are stringent and are based on the ethical principles that the best possible protection should be afforded to the population as a whole, and that the benefit should be fairly distributed across population groups with protection provided on the basis of need. The criteria are hierarchal and each must be met before considering the next: The seriousness of the disease for the individual and the extent of the disease burden in the population must be weighed against the safety of the vaccine and its effectiveness in reducing the disease burden; The vaccine must be acceptable to the recipient and not cause undue discomfort or inconvenience; The vaccination must be efficient, i.e. the ratio between the cost of vaccination and the associated health benefit should compare favourably to that associated with other means of reducing the disease burden; Finally, the provision of the vaccination should be a priority, and serve an urgent public health need relative to other vaccines. These principles may best be met by offering universal vaccination to the entire
population for some vaccines. For others, targeted vaccination, offered to at-risk population subgroups is considered more appropriate. For others still, protection offered on an individual basis is thought to be optimal. The ratio between the costs, benefits and positive / negative health implications can change over time and so too can the criteria for inclusion in a public programme. Such a decision is highlighted by the example of the hepatitis B vaccine which was introduced into the childhood vaccination schedule for all children in the Netherlands in 2011.

**Hepatitis B in the Netherlands: from targeted to universal vaccination**

Hepatitis B – ‘serum hepatitis’ as it was known before the causative virus was identified in 1970 is transmitted through body fluids, predominantly blood. People most at risk are babies of infected mothers (particularly in developing countries), intravenous drug addicts and men who have sex with men (MSM). Hepatitis B infection is associated with a spectrum of morbidity ranging from seemingly innocuous mild acute infections, to chronic infections that can lead many years later, to liver cirrhosis, cancer and fulminant hepatic failure. A safe effective vaccine came on the market in the 1986, and shortly thereafter the World Health Organisation (WHO) called for all countries to add hepatitis B vaccine to their childhood immunisation programmes. The Netherlands, and other similarly low–endemic countries in Europe, initially targeted the vaccine at high risk groups only. Antenatal screening was introduced in 1989, and neonates and household contacts of hepatitis B positive mothers were immediately vaccinated and/or given immunoprophylaxis in the form of immunoglobulin. In 2003, the neonatal vaccination programme was extended and hepatitis B vaccine was offered to children whose parent(s) comes from an intermediate- or high-endemic HBV country (approximately 18% of the total birth cohort). Screening and vaccination of high-incidence groups including commercial sex workers, drug users, MSM and heterosexuals with a high rate of partner change was introduced in 2002 (though the latter was discontinued in 2007). Initial evaluations of the programme targeting MSM were not encouraging and ultimately, the potential of the existing programmes to further reduce the incidence of HBV was considered to have peaked. Universal vaccination was deemed cost-effective and the vaccine was finally introduced into the childhood schedule for all children in 2011. This is not the whole story. Acute and chronic HBV infections are still being notified, particularly among migrants from mid- and high-endemic countries. Evidence supporting the cost-effectiveness of systematic screening of migrants for chronic HBV infection, suggests that a single screening could reduce mortality from liver-related diseases by 10%. Development of a national policy on this subject is therefore considered a priority. Depending on feasibility and cost-effectiveness, second generation migrants who may also at higher risk of infection, could also be considered for screening and vaccination.
2.2 Secondary prevention: contact tracing and post-exposure prophylaxis

Vaccination pre-exposure to a pathogen is not always feasible, effective or cost-effective. In the event that an individual has been exposed to a vaccine preventable disease, but where (s)he is unvaccinated, incompletely vaccinated or the duration of protection of a vaccine has expired, (s)he may be offered post-exposure vaccination under certain conditions. This is called post-exposure prophylaxis (PEP). The premise is that sufficiently early intervention post-exposure may prevent infection or attenuate disease in the exposed individual, and for some organisms (hepatitis A, for example), it may limit further spread of the pathogen thus breaking the chain of transmission and protecting public health. PEP has involved passive immunisation since the late 1940s. Passive immunisation is the direct administration of concentrated antibody preparations (typically harvested from human or animal blood), called immunoglobulin (IG). Human normal IG preparations are used for hepatitis A, measles, polio and rubella and specific IG preparations for hepatitis B, rabies and varicella zoster.\(^26\) IG confers immediate protection, is highly effective, and is often the PEP of choice in an exposed individual who is at high risk of developing severe disease or serious complications. There are some disadvantages however. Recently, healthcare professionals and the public have become concerned about the safety of human-derived blood products, particularly in connection with Creutzfeld Jakob Disease. IG may also be prohibitively expensive, availability is sometimes limited, and protection is short-lived. Depending on the agent and the nature of the exposure, active vaccination is increasingly offered as an alternative to IG. Active vaccination as for the RVP vaccines referred to above, involves stimulation of the recipient’s immune system to produce antibodies and / or cellular immune memory. Immunity is generally assumed to arise 2-4 weeks later and protection is long-lived, and in some cases may be life-long. In recent years, as new-generation vaccines that are safe and effective become more readily available, they are being used in PEP. For hepatitis A for example, evidence of the short-term effectiveness of vaccination alone is sometimes lacking. Vaccines are offered in preference to IG if the risk of transmission is low, or if the individual is considered to be at low risk of severe disease.\(^27\)

3. Information for action

3.1 Surveillance and epidemiological research

Effective intervention is founded on good information conveyed in a timely fashion to policy makers and programme managers. Public health surveillance has been defined as ‘the ongoing systematic collection, analysis, and interpretation of health-related data essential to the planning, implementation, and evaluation of public health practice, closely integrated with the timely dissemination of these data to those who need to know. The final link in the surveillance chain is the application of the data to prevention and control’.\(^28\)
In the Netherlands, mandatory surveillance of infectious diseases that threaten public health has been enshrined in law since 1865. Latterly, in response to the revised International Health Regulations of 2005, three acts governing infectious disease reporting and control were repealed (the Collective Prevention in Public Health Act of 1990 ‘Wet collectieve preventie volksgezondheid’, the Infectious Disease Act of 1998 ‘de Infectieziektenwet’ and the Quarantine Act of 1960 ‘de Quarantainewet’) and replaced with a single act, ‘the Public Health Act’ in 2008. Building on the earlier acts, legal requirements for infectious disease notification are extended to include 42 infectious diseases, and any unexpected or unusual public health event of known or unknown origin that may constitute a public health emergency of international concern. Notifications are made to the local Public Health Service (PHS) where the executive function of the act resides. This function is operationalised on a per disease basis in the national infectious disease control guidelines, published centrally by the Centre for Infectious Disease Control at the National Institute for Public Health and the Environment (RIVM-CIh). In addition to responding to cases notified under the Act, surveillance data collected by the PHS is aggregated over many years and serves multiple functions: to quantify the magnitude of a health problem at a population level; to document the distribution of disease over time and identify those at risk; and to target and evaluate public health actions and the use of resource. Surveillance data can therefore be used to facilitate epidemiologic, laboratory and behavioural research, and to generate and test hypotheses through monitoring changes in the nature and distribution of disease, infectious agents or health behaviour and practice. Finally, surveillance data allows us to establish baseline rates of disease in the local population. When unexpected events such as disease outbreaks or the emergence of new infectious diseases occur, surveillance data can provide an ‘early warning signal’ to public health officials.

3.2. Outbreak investigation
An outbreak occurs when more cases of an infectious disease than are expected arise in a particular population, in a specific geographical area over a specified period of time. Outbreaks present a particular challenge to public health authorities. They often require swift intervention with emergency control measures and place acute demands on staffing and manpower for undefined periods of time. Outbreak investigations help to inform measures to stop the outbreak, to prevent new episodes occurring, to establish a new surveillance system and to evaluate an existing system. They are also unique opportunities to study risk factors for exposure, infection, morbidity and mortality among susceptible hosts for a known organism, and can lead to the identification of, or further the understanding of, new and emerging infectious agents. Outbreaks that are fuelled by person-to-person transmission are known as propagated outbreaks, and those attributable to a common source (e.g. contaminated foodstuff) are known as point-source outbreaks if limited to a single place and time, or ongoing exposure outbreaks, if exposure
Outbreak investigations generally require a high degree of collaboration between stakeholders.

4. Infectious Disease Control in the Netherlands

4.1 Public Health Service, Amsterdam
The Public Health Service of Amsterdam (GGD Amsterdam) has a catchment population of approximately 900,000 people. The city of Amsterdam has a unique profile: it is one of the most ethnically diverse cities in the world, welcoming 178 nationalities in 2013. More than 35% of the population are non-Western immigrants, often from countries where infectious diseases rarely seen in the Netherlands, are endemic. Amsterdam is also known internationally for its tolerance of sexual and social diversity. It is estimated that 10% of the adult male population in Amsterdam are men who have sex with men (MSM) and is widely known as the ‘Gay Capital’ of Europe. The city is also tolerant of prostitution (which is legal and regulated since 2000) and drug use (principally marijuana, ‘hard’ drug use is illegal), and the attendant risk of sex- and drug-related infectious disease transmission. It is also a popular destination for sex and drug tourism. In this context, PHS Amsterdam has enhanced local surveillance systems in place since the early 1980s. In addition to routine data collection, the PHS collects details of contacts of notified cases, conducts intermittent cross-sectional studies in at-risk population groups, and longitudinal cohort studies among MSM and drug users. It has a longstanding reputation for providing evidence to support and shape local and national public health policy and programme development.

4.2 RIVM Centre for Infectious Disease Control, RIVM-CIb
Local and regional notifications are aggregated within the Centre for Infectious Disease Control (Centrum Infectieziektebestrijding, CIb), a division of the National Institute for Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu, RIVM), which was established in 2005. In addition to its role in national surveillance, RIVM-CIb offers support and advice to regional PHS during complex or unusual disease events, coordinates collaboration between relevant partners during cross-regional or international disease outbreaks (including local PHS departments, local and national government bodies and policy makers), and communicates directly with international partners (ECDC, WHO) and the public. Its primary aims are to assure the effectiveness of the National Immunisation Programme, reduce the burden of healthcare-related infections and antimicrobial resistance, sexually transmitted disease, and zoonoses, and working with the PHS and other network partners, to provide relevant sectors with advice that is based on early detection and research. Data is directly applied to infectious disease prevention and control through support of policy initiatives - the final link in the chain.
5. Aims and outline of this thesis

The aim of this thesis is to demonstrate the application of epidemiological studies in informing primary and secondary preventive strategies for infectious disease control in the Netherlands. This is achieved through recognition of current risk groups for known agents, identification of risk factors for new agents 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 infectious diseases and unexpected disease events are reported.

Section 1: Immunisation

Here, we focus on the epidemiology of hepatitis B virus (HBV) and hepatitis A virus (HAV) infections in current population groups at risk in the Netherlands.

In Chapter 2, we hypothesize that a recent observed increase in HBV infections through heterosexual contact may be associated with the ethnic background of the case. We describe trends in the incidence of acute HBV among heterosexual adults in ethnic groups in Amsterdam identifying ethnic sub-groups at risk of acute HBV infection, and discuss the implications for future control policy.

In Chapter 3, we focus on another population group, men who sleep with men (MSM), who are at risk of HBV infection, describing trends in the incidence of acute HBV in the MSM population in Amsterdam. We evaluate the impact of the HBV vaccination programme targeting MSM that began in 1998, and make recommendations about how the vaccination programme could be most effectively targeted in the future.

In Chapter 4, as the Netherlands prepared to introduce universal vaccination of infants against HBV, we assessed whether the immune response to the HBV component in a new hexavalent combination vaccine was sufficient according to WHO standards, and whether the immunogenicity of the other vaccine components was similar to that of the standard vaccine, which did not include the HBV component. This study was conducted in children who, because of their ethnic background, were vaccinated within the RVP under the targeted hepatitis B vaccination programme before universal vaccination was introduced.

In Chapter 5, we follow up on study conducted in 2006, which reported a downward trend in the number of imported HAV cases in Turkish and Moroccan children in Amsterdam in recent
years. HAV is predominantly an imported infection in the Netherlands, and our aim was to describe recent trends in HAV infection in ethnic groups in Amsterdam, to identify current risk groups and to recommend targeted prevention through vaccination.

In **Chapter 6**, we evaluate the routine use of hepatitis A vaccine as an alternative to immunoglobulin in prevention of secondary HAV infection in contacts that have been exposed to HAV. Historically post-exposure, contacts of cases were offered immunoglobulin (IG, a human derived blood product) as an immunoprophylactic but the vaccine is increasingly recommended though its routine use in post-exposure prophylaxis has never been evaluated.

**Section II: Outbreak investigation**

In the second section, outbreaks identified through routine surveillance are investigated and analytic studies are conducted to identify risk factors for exposure, infection and morbidity among those exposed.

In **Chapter 7**, we investigate risk factors for mumps in a population of highly vaccinated university students and identify factors associated with mumps vaccine failure among those who were vaccinated. This study was conducted in response to a large nationwide outbreak of mumps in the Netherlands from 2009-2011, which occurred in students, most of whom had been vaccinated in childhood.

In **Chapter 8**, we determine risk factors for infection associated with occupational exposure to *Coxiella burnetii* in culling workers who were involved in the mass slaughter of sheep and goats during the Q fever outbreak of 2007-2009 in the Netherlands.

In **Chapter 9**, we examine whether visiting a particular farm was a risk factor for the development of Q fever in local residents, and we identify other risk factors for acquiring Q fever (or a *C. burnetii* infection) in people who visited the farm.

In **Chapter 10**, we test our hypothesis that consumption of raw or undercooked meat was associated with infection with *S. Typhimurium* ft132 during an outbreak in 2009. We also identify other risk factors for infection, and attempt a novel approach to the traditional case-control study for investigation of a food-borne outbreak.

In **Chapter 11**, we examine risk factors for secondary transmission of Shigella infection within households. We consider the implications for current prevention policy and make recommendations on the basis of our findings.
In **Chapter 12**, the findings of the thesis are summarised, giving an overview of what was already known in each area, what the research reported here adds to the evidence base, the recommendations arising from these studies, and implications for future research.

**References**

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