

Optimizing infectious disease control

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Valorisation

Besides its scientific relevance this thesis also has implications for society as we identified and addressed hidden infections and evaluated current infectious disease prevention, surveillance and control. Based upon this thesis and recent literature we have several recommendations on how to improve current practice and policy. Overall, better insight into hidden infections allows for more targeted and effective testing practices in order to eventually protect the most vulnerable groups at risk. Several methodologies can be used to detect hidden infections. This thesis showed the value of the surveillance pyramid as a tool to determine the different levels in infectious disease control and factors influencing its accuracy. Epidemiological and geographical analyses compliment each other in identifying risk groups and estimating the prevalence of infectious diseases including hidden infections. However, there is no one-size-fits-all approach which can be applied to every infectious disease. Furthermore, this thesis demonstrates the importance of examining models and estimates in a real-life setting.

Hidden pertussis infections

We were able to give more insight into the factors that hamper the identification of hidden pertussis infections. These findings function as an important input for the discussion on how to reduce the workload of Public Health Service (PHS) and the debate on how to reduce the overall delay until notification to improve pertussis control. Overall, it is likely that the identified misdiagnosis, under-notification and overall delay in surveillance data are not unique for this area of the Netherlands and are generalizable to the rest of Europe. These countries are likely to encounter varying guidelines, difficulties in pertussis diagnostics and unexplained local differences in notification data too. Ideally, the accuracy of surveillance would be improved by focusing on the factors identified here. This contributes to optimisation of the surveillance system and more importantly, to improved pertussis control by preventing young infants from being infected with pertussis and avoiding morbidity and mortality in this young group.

First, to reduce misdiagnosis and the variation in pertussis diagnostics, we recommend laboratories and healthcare providers (HCPs) to improve adherence to national guidelines concerning timing and choice of test. For laboratories, a national uniform and standardised guideline on cut-off values in serology and the use of IgA and/or IgG is desirable. Testing all patients presenting with cough is not feasible, as only 3% of adult patients presenting with acute cough in primary care had evidence of an acute pertussis infection in Europe. Moreover, testing for pertussis follows to an extent the general healthcare seeking behaviour for common respiratory infections, whereas the current pertussis incidence is largely the result of testing. Increased testing would thus not necessarily improve pertussis control. Therefore, HCPs should focus pertussis testing on family members surrounding incompletely vaccinated infants <1 year of age, women >34 weeks pregnant and children with severe comorbidities such as heart or lung failure. In addition, they are advised to check whether patients with symptoms

suggestive of whooping cough have vulnerable groups at risk in their household. As such, general practitioners (GPs) could play a more prominent role in contact tracing (now carried out by the PHS in the Netherlands) in order to minimise the disease burden in infants. We informed the GPs and laboratories in our region about our study results to remind them of the pertussis testing guidelines and to advise on possible preventive measures.

Second, to reduce under-notification, medical microbiology laboratories and HCPs could benefit from introducing automated notification systems. In an endemic situation with severe underreporting, the obligatory notification of pertussis is not effective for the protection of unvaccinated children. On the other hand, the notification of pertussis infections is of great value to national policy on pertussis surveillance and control although we showed the limitations of pertussis surveillance. Pertussis has to remain a notifiable disease as it is necessary to prohibit a pertussis-positive patient to go to work when he/she works with vulnerable young infants. In this thesis, we showed that the detection of pertussis outbreaks using space-time cluster detection is feasible and could help to facilitate an early and appropriate public health response. However, this approach has to be adjusted for the strong dependency to testing and is probably most efficient when using test-positivity as indicator.

Third, as public health is almost always too late to intervene, delays need to be reduced and we need earlier preventive measures by healthcare providers. Patient delays due to late presentation to healthcare may be unavoidable, however delays in reporting once a patient presents can be reduced. GPs, midwives and day nursery employees could play a major role here. Creating awareness among these professionals as well as patients themselves about taking timely preventive measures could lead to lower individual disease burden and to a higher cost-effectiveness of pertussis care.

At last, we also need additional preventive measures for the most vulnerable and susceptible group of unvaccinated infants, as the Dutch national vaccination program starts at the age of two months. In the first few months, young infants are unprotected as vaccination is only effective after at least three doses. The efficacy of pertussis vaccines has been debated because of waning immunity, incomplete protection of infants below 5 months, genetic changes in *Bordetella pertussis* and limited duration of protection. Currently, maternal immunisation provides good protection against infant disease, whilst no important side effects were observed, and has been recommended by the World Health Organisation and the European Centre for Disease Prevention and Control. The Dutch health council advised the introduction of maternal vaccination to the national vaccination program (December 2015) and pertussis vaccinations for healthcare workers (June 2017). Maternal vaccination will be executed at the child healthcare centres and introduced to the national vaccination program in 2019.

Hidden hepatitis infections

Lessons learned from our evidence-based practice to detect hidden hepatitis infections can be applied to future testing strategies and policy. The success factors of our high test uptake were the combina-

tion of a personal invitation letter accompanied by reminder letters, the birth cohort testing, the hot-spot approach and the cooperation between public health care and primary care.

At first, as no active hepatitis C virus (HCV) infections were found in the identified hotspots, the hotspot strategy would probably not work in other areas of the Netherlands as well as other countries with low HCV prevalence. Our findings partly informed the Dutch Health Council in their advice against screening of the general Dutch population for HCV and HBV (November 2016). This advice is part of the national hepatitis elimination plan, developed by specialists, doctors of the public health service and GPs, aimed at the prevention of transmission and reduction of hepatitis related disease burden and deaths. The committee recommends case finding by GPs for people in risk groups and by institutions who are responsible for delivering care to people in risk groups or for accommodating these people. The GP guidelines in the UK and the Netherlands advice to focus more on targeted HBV testing, especially among non-western migrants as they account for the largest proportion of HBV and HCV infections. This is in line with the recommendation of the Dutch Health Council on regional HBV screening programmes in areas with relatively large groups of first-generation migrants from high-endemic countries ($\geq 2\%$ chronic HBV infection). In the Netherlands, people who inject drugs (PWID) and HIV-positive men who have sex with men are tested for HBV and/or HCV as part of comprehensive health care programs (i.e., HIV treatment, HBV vaccination, and harm reduction programs for PWID). However, for migrants there are no structural screening programs. This may partly be caused by the heterogeneity of this population, in terms of ethnic origin, risk for infection and awareness of infection status. Some screening interventions in the Netherlands have targeted different migrant groups. These interventions, however, were limited in geographical coverage, and uptake was often low/moderate depending on the screening model. Structural screening programs for (subgroups of) migrants are needed to substantially reduce chronic viral hepatitis related morbidity and mortality among migrants, and the sustainability, linkage to care and access to treatment has to be ensured.

Additionally, our testing strategy could be applied to detecting HCV and HBV in high-endemic countries, to other infectious diseases and high-endemic settings. Higher positivity rates have been found in studies of countries with higher prevalence and in settings other than the general population with higher prevalence, such as the emergency department. An American study showed that HCV-infected individuals are more likely to use the emergency department (ED) for care than any other health care setting. Testing in this setting reveals hidden infections as this testing could reach those who do not respond to screening projects, do not feel at risk or avoid health care in general. Furthermore, test-uptake in this setting may be very high as tests can be offered and performed within routine diagnostic work-up. Several studies in the UK and US support routine testing on HCV in the ED setting with high test-uptakes and anti-HCV prevalence. In the context of applicability, it is shown that routinely offering HCV testing to patients who are undergoing laboratory testing had no effect on length of stay at the emergency department.

Consciousness of health care providers, for example to prompt viral hepatitis testing when people present with abnormal liver function, is needed to identify those infected who do not belong to one of

the risk groups. Automated screening alerts for ALAT elevation (diagnostic liver enzyme) at the GP clinic can be a tool to detect hidden HCV infections, although this is a challenging process. The risk of HCV infection is substantially elevated in Dutch primary care patients with an ALAT elevation between 50 IU/l and 100 IU/l, whereas the risk of HBV infection is not. Therefore, diagnostic follow-up for HCV is recommended in all these patients, particularly in those for whom no clear explanation for the ALAT elevation is found. Among HBV patients without an indication for referral, ALAT should be checked, both the GP and the patient should be reminded for these check-ups.

Future projects aimed at detecting chronic HBV and HCV infections hidden to care in the Netherlands should focus on retrieval projects. This includes retracing and evaluating patients previously diagnosed with HBV or HCV who are eligible for treatment. In the Netherlands, there is evidence for patients diagnosed with HBV or HCV who are eligible for treatment still remain untreated. These patients were lost to follow-up as they stopped treatment because of the side effects, were not able to start treatment because of contra-indications, or did not attend their follow-up appointments. The Health Council of the Netherlands recommend retracing people who have been diagnosed with HBV or HCV in the past but are no longer receiving care. This retracing should focus on giving patients the opportunity to make use of the new treatment options. Once they have been retraced, they must promptly be given appropriate care. Studies on detection of chronic hepatitis B and C patients who were lost to follow up, enables evaluation of the indication for current treatment options.

Currently, a national registry of all HBV and HCV infected patients is in development and will include patients characteristics and treatment data. HBV infections and recent HCV infections are notifiable diseases. Until now, chronic HCV infections are not notifiable. Therefore, there is no national surveillance system nor a database for chronic HCV infections. The surveillance of HCV could be improved by introducing chronic HCV infections into the notification policy. This would also make the current HBV and HCV estimated prevalence more precise.

We have provided scientific and societal relevance in the work presented. We identified and addressed hidden infections and evaluated current infectious disease prevention, surveillance and control. Based upon this work and recent literature we suggested on improvements of current practice and policy in hepatitis and pertussis control. Overall, better insight into hidden infections allows for more targeted and effective testing practices in order to eventually protect the most vulnerable groups at risk. Although, there is no one-size-fits-all approach we showed several methodologies that can be applied to the assessment of hidden infections in infectious diseases.