Catching the common cold
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Citation for published version (APA):
Bruning, A. H. L. (2017). Catching the common cold: Rapid detection and epidemiology of respiratory viruses

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Chapter 10

Summary
Acute respiratory tract infections are one of the most frequent reasons for health care consultations and hospitalizations, and a leading cause of morbidity and mortality worldwide. Respiratory tract infections can be caused by many different pathogens. Although bacteria were historically considered the main pathogens causing severe infections, the role of viruses is increasingly recognized. Rapid and accurate etiological diagnosis of respiratory tract infections is important for clinical patient management, public health surveillance, and infection prevention. In recent years, the diagnostic opportunities for the detection of respiratory viruses have advanced rapidly. There is a clear trend towards faster diagnostics. Increasing numbers of rapid tests designed for use at the point-of-care have been developed. The aim of this thesis was 1) to evaluate the use and diagnostic accuracy of rapid tests for respiratory viruses in the hospital setting and in primary health care; 2) to increase our insight in the epidemiology and clinical relevance of respiratory viruses.

PART 1: RAPID DETECTION OF RESPIRATORY VIRUSES

In chapter 2 we provided a systematic literature overview of the rapid tests that are currently available for the detection of respiratory viruses. Following our strict inclusion criteria, in which a rapid test was defined as any commercially available quick (up to two hours) and easy-to-use test requiring little or no additional equipment or technological skills, we included 125 articles evaluating 50 different rapid tests in our systematic review. Although our search strategy contained search terms for all common respiratory viruses, most rapid tests were capable of detecting only one virus, either influenza virus, or Respiratory Syncytial Virus (RSV). Overall, pooled sensitivity and specificity for detection of influenza was 61.1% (95% confidence interval [CI], 53.3 to 68.3) and 98.9% (95% CI, 98.4 to 99.3), respectively. Performance for RSV was higher in general, with a pooled sensitivity of 75.3% (95% CI, 72.6 to 77.8), and a pooled specificity of 98.7% (95% CI, 97.3 to 99.4). Even though all rapid tests studied in this review were designed to be performed by non-laboratory trained personnel at the point-of-care, many studies were not evaluated at the point-of-care. Quality assessment of included studies revealed that because of the frequently incomplete reporting of study characteristics, risk of bias for included studies was often unclear. Although the newer tests seem to be more sensitive, there is a lack of high quality evaluations of these tests.

According to our systematic review, one of the rapid tests with the best diagnostic performance characteristics was Quidel’s Sofia Fluorescent Immunoassay. In chapter 3 we evaluated the clinical use of the Sofia FIA for the detection of influenza and RSV in our own hospital, the Academic Medical Center (AMC) in Amsterdam, in a pediatric hospitalized population at the
point-of-care. Using our in-house multiplex PCR as reference test, Sofia had a sensitivity of 75\% (95\% CI, 57.7-92.3) and a specificity of 97.5\% (95\% CI, 92.7-100) for RSV. For influenza A, sensitivity was 66.7\% (95\% CI, 35.9-97.5) and specificity 96.6\% (95\% CI, 92.0-100) and for influenza B sensitivity was 40\% (95\% CI, 9.6-70.4) and specificity 89.7\% (95\% CI, 81.8-97.5). Diagnostic performance of the test was lower than expected, but the availability of a rapid test at the point-of-care was appreciated by pediatric residents.

As described in Chapter 2 many of the available point-of-care tests for respiratory viruses can detect only one single virus, i.e. influenza virus or RSV. In the past decade, new respiratory viruses have been discovered, such as human bocavirus 1 in 2005 and several new coronaviruses. Causative associations between infection with these respiratory viruses and severe disease, e.g. unexplained severe lower respiratory tract infections or encephalitis, have recently been described. It is therefore important to rapidly identify acute, clinically relevant infections caused by these viruses. The mariPOC\textsuperscript{®} test system (ArcDia International Oy Ltd., Turku, Finland) might be a suitable option for rapid detection of acute infections. MariPOC\textsuperscript{®} is an automated and point-of-care compatible test for rapid and simultaneous detection of antigens of eight respiratory viruses (influenza A and B, RSV, adenovirus, human metapneumovirus, and parainfluenza type 1, 2, and 3 viruses) and Streptococcus pneumoniae from a single nasopharyngeal sample. In chapter 4 and chapter 5, we described the addition of two new targets, human bocavirus 1 and coronavirus, on the mariPOC assay. We demonstrated that the new tests correctly identified and enabled monitoring of respectively human bocavirus and coronavirus infections. It should be noted that both studies were proof-of-principle studies. The exact performance characteristics of the new targets need to be evaluated in larger validation studies.

As previously described in the introduction of this thesis not only laboratory validation studies are needed to evaluate the diagnostic accuracy and use of rapid tests. In chapter 6 we therefore evaluated not only the diagnostic performance, but also the clinical feasibility of a rapid test. In patients with respiratory tract infection symptoms presenting to a family practice during the 2015-2016 winter season, we determined the sensitivity and specificity of the mariPOC\textsuperscript{®} respi test relative to PCR testing performed in our laboratory. The clinical feasibility of the rapid test was evaluated by interviewing study participants and general practitioners. One or more respiratory viruses were detected in 54.9\% of the included patients with respiratory tract infection symptoms (n=204). Rhinovirus and influenza A virus were the most frequently detected viruses. Overall, the mariPOC\textsuperscript{®} had a sensitivity of 47.1\% (95\% CI, 35.2-59.4), a specificity of 99.7\% (95\% CI, 99.2-99.9), a positive predictive value of 84.6\% (95\% CI, 68.8-93.6), and a negative predictive value of 97.9\% (95\% CI, 97.1-98.5) for the panel of 9 viruses that it
tests for. For influenza A virus, sensitivity of the mariPOC was 54.2% (95% CI, 33.2-73.8); for influenza B virus, sensitivity was 72.2% (95% CI, 46.4-89.3) and for RSV, sensitivity was 50.0% (95% CI, 22.3-77.7). Specificity was high, ranging from 98.9% to 100.0%. In samples with higher viral load, i.e. Ct-value below 30, sensitivity was 85.7% for influenza A virus, 78.6% for influenza B virus and 85.7% for RSV. The availability of a diagnostic test for respiratory viruses was appreciated by both patients and general practitioners with more than two-third of the patients considering it to be a valuable or very valuable addition for primary care. Patients reported being more confident about the self-limiting aspect of the disease and general practitioners considered the rapid test helpful as they now had a tool to convince patients about the viral diagnosis.

**PART 2: EPIDEMIOLOGY OF RESPIRATORY VIRUSES**

Part 2 of this thesis focused on the epidemiology and clinical relevance of respiratory viruses, in particular rhinoviruses. Rhinoviruses are the most frequently detected respiratory viruses in humans and the predominant cause of the common cold. Although most of the time responsible for relatively mild respiratory illness, rhinoviruses can also cause severe lower respiratory tract infections. Rhinoviruses, members of the family *Picornaviridae* and the genus *Enterovirus*, can be classified into three species, RV-A, RV-B, and RV-C, and more than 150 types. It is unclear whether pathogenicity and clinical significance differ between the three rhinovirus species, let alone between the individual rhinovirus types.

In chapter 7, we investigated the prevalence of rhinovirus types in the patient population of the AMC by genotyping all rhinovirus-positive samples submitted for respiratory viral diagnostics from 2007 to 2012. In total, 52.4% of the samples (n=637) belonged to RV-A, 11.3% to RV-B, and 36.2% to RV-C. The majority of the currently classified rhinovirus types could be detected in our population. Some types were more frequently present than others, such as RV-A12, RV-A78, and RV-C2. Furthermore, we detected eight previously described provisionally assigned types, i.e. virus strains predicted to be new rhinovirus types. Rhinoviruses circulated the whole year around, with a slightly higher frequency in autumn, and a decline in summer. Some rhinovirus types could be detected intermittently during the whole study period, while others were detected mainly in winter and early spring. A limitation of this study was that we could not investigate associations between the clinical symptoms of patients and the different rhinovirus types.
Because of the limitation described above, we set up a study linking different characteristics of rhinovirus infections to clinical outcome. In chapter 8 we describe the results of this study which compared the clinical, virological and epidemiological characteristics of rhinovirus infections in young children with mild or asymptomatic infection to young children admitted to the hospital because of their respiratory illness. RV-A was the most frequently detected rhinovirus species in both study populations, followed closely by RV-C. The distribution of the rhinovirus species was comparable in non-hospitalised and hospitalised children. A subgroup analysis was performed to investigate the circulation of rhinovirus species and types in children with more severe respiratory disease, i.e. children admitted to the ICU due to respiratory distress. Also, in this latter group, distribution of rhinovirus species did not significantly differ, which is in contrast with previous studies suggesting that infection with RV-C is associated with more severe respiratory tract disease. No predominant rhinovirus type could be found in severely ill children. We therefore conclude from our study that clinical outcome is not related to rhinovirus species or types alone, but may more likely be influenced by multiple (host-specific) factors, such as age, chronic underlying illness, viral load and the presence of a bacterial co-infection.

Rhinoviruses are the most frequently detected respiratory viruses in hospitalized patients with respiratory tract infection symptoms, but for primary health care patients this is uncertain as diagnostic testing of respiratory tract infections is not routinely performed in primary health care. The contribution of different respiratory viruses is unclear. The purpose of chapter 9 was to describe the epidemiology of viral RTIs in primary health care and to evaluate the accuracy of the GP’s clinical diagnosis of influenza virus infection. This study was part of the study described in chapter 6, in which we prospectively recruited patients who presented with RTI symptoms to a primary health care facility in Amsterdam, the Netherlands, in the 2015-2016 winter season. We used the results of our multiplex PCR assay to determine the presence of a respiratory virus. We compared the clinical characteristics of patients in whom no virus was detected, patients diagnosed with an influenza virus infection, and patients with respiratory virus infections other than influenza. At least one virus was present in 42.5% of the patients with RTI symptoms. Rhinovirus was the most frequently detected virus, followed by coronavirus, and influenza A virus. Although influenza viruses were among the most frequently detected viruses, we showed that it is difficult to clinically distinguish influenza virus infection from other respiratory viruses as sensitivity of GP’s clinical diagnosis for influenza was only 52.6% (95% CI, 36.0 – 68.7) and specificity 78.3% (95% CI, 70.9 – 84.2).
In conclusion, the aim of this thesis was 1) to evaluate the use and diagnostic accuracy of rapid tests for respiratory viruses; 2) to increase our insight in the epidemiology and clinical relevance of respiratory viruses, in particular rhinoviruses. There is a growing need for rapid and accurate diagnostics for respiratory tract infections. Rapid tests have the potential to fulfil this need. However, sensitivity of rapid tests needs improvement and the development of new rapid tests, preferably tests that can detect viruses and bacteria in combination with host response markers, should be encouraged. Before implementation in the clinic, high quality evaluation studies on the impact of these tests on clinical patient management should be performed.