

On the Diagnosis and Management of Viral Respiratory Infections

AKADEMISK AVHANDLING

som för avläggande av medicine doktorexamen vid Sahlgrenska Akademin vid Göteborgs Universitet kommer att offentligen försvaras i föreläsningssalen, Infektionskliniken, Sahlgrenska Universitetssjukhuset/Östra

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av

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Avhandlingen baseras på följande arbeten:

- I. Brittain-Long R, Nord S, Olofsson S, Westin J, Andersson L-M, Lindh M. **Multiplex real-time PCR for detection of respiratory tract infections.** *Journal of Clinical Virology* 41 (2008) 53–56
- II. Brittain-Long R, Westin J, Olofsson S, Lindh M, Andersson L-M. **Prospective evaluation of a novel multiplex real-time PCR assay for detection of fifteen respiratory pathogens – Duration of symptoms significantly affects detection rate.** *Journal of Clinical Virology* 47 (2010) 263–267.
- III. Brittain-Long R, Westin J, Olofsson S, Lindh M, Andersson L-M. **The use of a multiplex real time-PCR method targeting thirteen viruses – impact on antibiotic prescription rate in a prospective study.** In manuscript
- IV. Brittain-Long R, Andersson L-M, Lindh M, Westin J. **Seasonal variations influence diagnostic yield of a multiplex PCR assay targeting 13 respiratory viruses.** In manuscript.



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Abstract

Acute respiratory tract infections (ARTIs), are the most common infections in man, and represent a major global health burden. Viruses, most often causing a mild and self-limiting disease, yet with substantial morbidity and high costs for society, mainly cause upper respiratory tract infections. 70% of all infections in primary care in Sweden are due to ARTIs. Lower respiratory infections on the other hand constitute the third leading cause of death worldwide, mainly in children <5 years of age in resource poor settings. Distinguishing virus from bacteria can be difficult, and often lead to an over-prescription of antibiotics. Modern molecular based diagnostic methods have increased the possibility of an etiologic diagnosis of ARTIs significantly. This thesis aims to evaluate the use of a multiplex real time PCR assay targeting 13 respiratory viruses and two bacteria, from a clinical perspective.

In paper I, a retrospective study of 954 nasopharyngeal samples, the PCR assay, which is based on automated specimen extraction and multiplex amplification, is described. Detection rate was 48%. Streamlined testing and cost limitation (€ 33 per sample) along with high accuracy and prompt result delivery, is key to successful implementation of broad molecular testing.

Paper II evaluates in a prospective study of 209 adults with ARTI in primary care, and 100 asymptomatic controls, the impact duration of symptoms have on detection rate. Overall positive yield was 43% in patients and 2% in controls, with a significantly higher detection rate in patients with < 6 days duration of symptoms (51%) compared to ≥ 7 days (30%, $p < 0.01$).

Having access to the PCR assay reduced antibiotic prescription rates by 50%, in a prospective study (paper III) of 426 adults with ARTI. Patients receiving a result within 48 hours were prescribed antibiotics in 6,8% ($n=14$) compared to 15.1% ($n=33$, $p < 0.01$) in the delayed result group.

The diagnostic yield in paper IV, a retrospective study of 8753 patients of all ages during 36 consecutive months, was significantly higher during winter (54.7%) than in summer (31.1%, $p < 0.001$), and in children (61.5%) compared with adults (30.5%, $p < 0.001$). Rhinovirus was the most frequently found virus (32.5%), independent of season, and displayed a high genetic variability across seasons.

The findings of this thesis support the implementation of similar methods in routine clinical care.

Keywords: Respiratory virus, Respiratory tract infection, Real-time PCR, Multiplex PCR, Antibiotic use.

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