Göteborg, 2019

Acute febrile illness in preschool children in Zanzibar-

Infectious aetiologies, diagnosis and treatment

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Arvid Carlsson salen, Medicinaregatan 3, Göteborg, den 4 oktober 2019, klockan 13.00.

av Kristina Elfving

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Avhandlingen baseras på följande delarbeten

I. Shakely D, Elfving K, Aydin-Schmidt B, Msellem MI, Morris U et al. *The usefulness of rapid diagnostic tests in the new context of low malaria transmission in Zanzibar*. PLoS One. 2013.

II. Elfving K, Shakely D, Andersson M, Baltzell K, Ali AS et al. *Acute Uncomplicated Febrile Illness in Children Aged 2-59 months in Zanzibar - Aetiologies, Antibiotic Treatment and Outcome.* PLoS One. 2016.

III. Elfving K, Andersson M, Msellem MI, Welinder-Olsson C, Petzold M et al. *Real-time PCR threshold cycle cutoffs help to identify agents causing acute childhood diarrhea in Zanzibar.* Journal of clinical microbiology. 2014.

IV. Elfving K, Shakely D, Andersson M, Baltzell K, Msellem MI et al. *Pathogen Clearance and New Respiratory Tract Infections Among Febrile Children in Zanzibar Investigated With Multitargeting Real-Time Polymerase Chain Reaction on Paired Nasopharyngeal Swab Samples.* Pediatr Infect Dis J. 2018

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Background: A majority of the three million children in Africa that do not survive their fifth birthday die from infections that often start as a seemingly uncomplicated febrile illness. Primary health care workers frequently encounter febrile children with a negative malaria rapid diagnostic test (mRDT), in particular in places like Zanzibar with a considerable decline in malaria prevalence. In recent years, accurate and sensitive molecular techniques like the polymerase chain reaction (PCR) have revealed increased detection of pathogens not only in ill patients but also in asymptomatic subjects. These factors underline the importance of re-evaluating the infectious disease aetiology and pathogen dynamics in febrile children and to assess whether existing diagnostic tools like mRDT and fever management guidelines like the IMCI (Integrated Management for childhood illness) remain useful and safe. **Methods and Findings:** The thesis is based on two field studies, both conducted on patients with acute uncomplicated febrile illness (by history or axillary temperature) in primary health care facilities April-July 2010 and 2011 in Zanzibar, Tanzania. In **study 1** (*paper I*), 3890 febrile patients ≥2 months were included. Malaria prevalence by mRDT was 3.1%, with the highest prevalence, 6.1% in children aged 5-14 years old. Malaria microscopy and PCR were conducted on all mRDT positive and a randomly selected 20% of the mRDT negative patients. The sensitivities of mRDT versus malaria microscopy and PCR were below 80%, respectively. **Study 2** (*paper II-IV*) included 677 febrile children aged 2-59 months of age that depending on the clinical picture were subjected to point-of-care tests, PCR analyses (on inclusion and day 14), urine culture and radiological analyses. For comparison, 167 geographically- and age-matched asymptomatic controls from the surrounding communities were recruited for selected PCR analyses. More than one pathogen was detected by PCR in 98% of patients and 93% of healthy controls. After application of study specific diagnostic criteria using clinical characteristics and laboratory results, including a comparison with detection in healthy controls, a cause of fever was assigned to 86%. The most common were respiratory syncytial virus (RSV), influenza A or B, rhinoviruses, enteroviruses, and *S. pyogenes* (Group A Streptococcus) (*paper II and III*). C-reactive Protein (CRP) was the only variable significantly associated with radiological pneumonia. Antibiotics were prescribed to 74% of patients whereas 22% had an infection that required antibiotics (*paper II*). On follow-up after two weeks >80% of the infections were cleared, but almost half of the sampled patients had a new infection on day 14 (*paper IV*). **Conclusion:** The sensitivity of the malaria RDT was relatively low. Thus, more sensitive tools than histidine-rich protein 2 (HRP-2) based mRDTs are warranted. Most of the uncomplicated febrile illness in children in Zanzibar was caused by a viral respiratory tract infection. Comparison of pathogen detection in febrile and healthy children was crucial for identifying cause of disease. The accuracy of the IMCI guidelines to guide antibiotic prescription was suboptimal with both over- as well as underprescription of antibiotics. However, the study did not find any diagnostic tool to help in guiding antibiotic prescription although C-reactive Protein might be a promising biomarker for future intervention studies. Respiratory infections usually cleared within two weeks. However, many children had acquired a new viral infection, suggesting that prolonged symptoms often are due to acquisition of new infections rather than to persistence.

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