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Chapter 8

Summary

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Down syndrome is one of the most common chromosomal disorders among children, with an estimated prevalence of 16 per 10,000 live births in the Netherlands. Aside from mental retardation, congenital malformations of the heart and gastro-intestinal system, children with Down syndrome are also susceptible to respiratory tract infections. In this thesis we try to elucidate some of the alterations in their innate and adaptive immune system that may contribute to this enhanced vulnerability.

Chapter 1 contains a general introduction.

Chapter 2 presents a review of all types of immunological alterations in children with DS, possibly related to their increased frequency of respiratory tract infections. Patients with Down syndrome show multiple abnormalities in both the innate and adaptive immunity. These immunologic abnormalities combined, whether or not directly interacting with each other, strongly suggest diminished viral and bacterial clearance in Down syndrome.

The next two chapters describe alterations in the innate immunity of 61 children with Down syndrome, as compared to 57 of their age-matched, healthy siblings. **Chapter 3** outlines an ex-vivo experiment of whole blood stimulation with heat-killed *S. pneumonia* and lipopolysaccharide in children with Down syndrome. Children with Down syndrome show an increased IL-10 production in response to ex-vivo stimulation with *S. pneumoniae*. This may result in a more severe course of pneumococcal disease in children with Down syndrome.

Chapter 4 follows this up with an ex-vivo experiment of whole blood stimulation with live influenza A virus in the same group of children with Down syndrome. Children with Down syndrome have a production of increased levels of pro-inflammatory cytokines, which may explain the more severe clinical course of viral infections they undergo.

Chapter 5 examines alterations in the adaptive immunity as related to the frequency of lower respiratory tract infections in this group. Children with Down syndrome have reduced levels of IgG2 and reduced numbers of lymphocytes, CD4+ T cells, CD4+ iNKT cells and T regs, as compared with their healthy siblings. This can contribute to an increased frequency of lower respiratory tract infections and related hospitalization.

Chapter 6 describes the frequency of otitis media, ear, nose and throat surgery and hearing loss in a group of 204 children with Down syndrome. In total, 57% of these children had one

or more episodes of otitis media and 59% of them underwent ear, nose and throat surgery, of which 74% were operated more than once. In total, 96 of the 204 children (47%) had undergone placement of ventilation tubes, with a high frequency of subsequent otorrhea (45%). Hearing loss was reported in 23%.

Chapter 7 concludes this thesis. Children with Down syndrome suffer more frequently and more severely from respiratory tract infections than other children. These respiratory tract infections are mainly caused by a virus, such as respiratory syncytial virus and influenza A virus. Several therapeutic strategies may prevent these respiratory tract infections: the use of trimethoprim/sulfamethoxazole (daily prophylactic use), palivizumab (passive immunization against the RS virus, especially for young children) and influenza A vaccination. Future studies must be performed to evaluate these therapeutic interventions in this group of children.