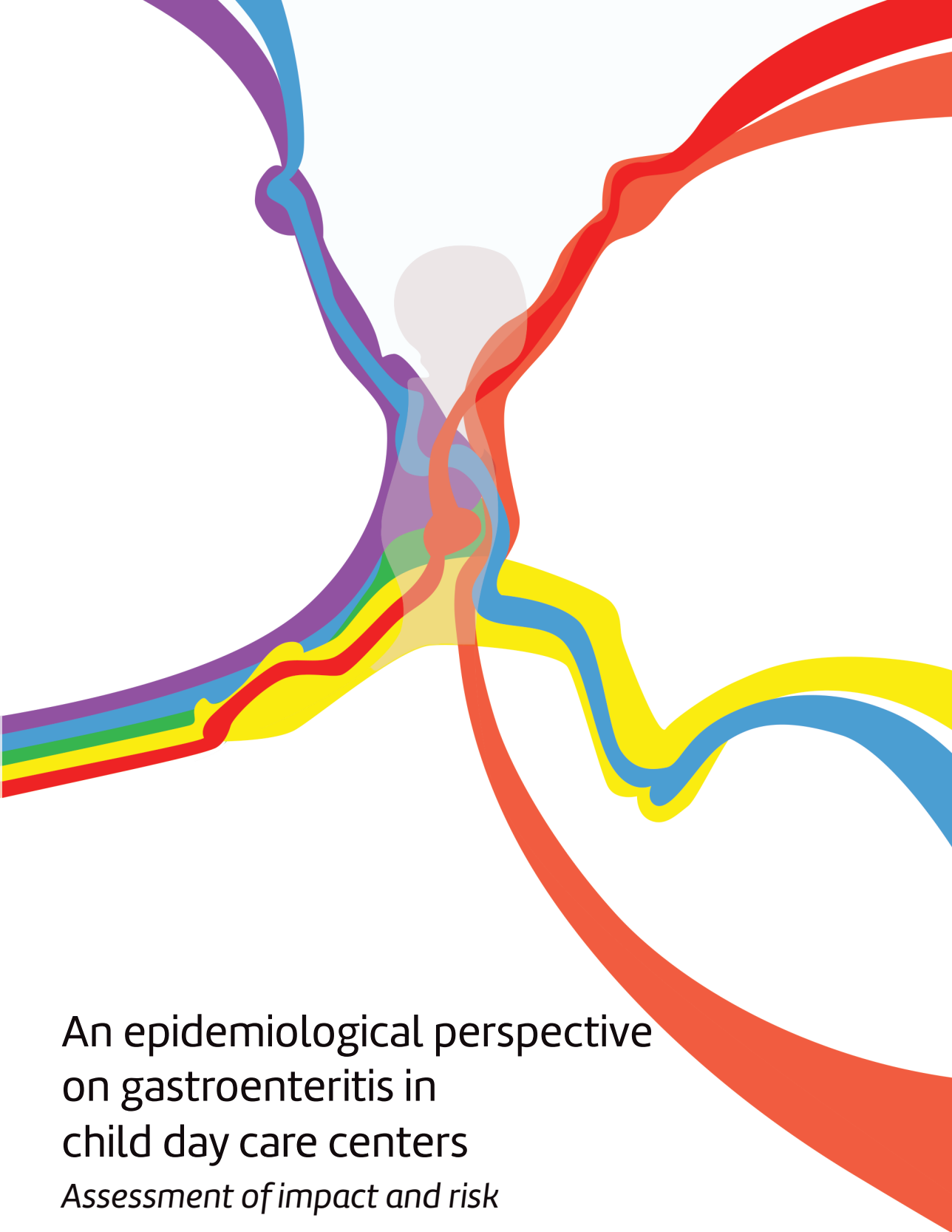




An epidemiological perspective
on gastroenteritis in
child day care centers

Assessment of impact and risk

Remko Enserink

**An epidemiological perspective on gastroenteritis
in child day care centers**

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An epidemiological perspective on gastroenteritis in child day care centers; Assessment of impact and risk

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**An epidemiological perspective on gastroenteritis
in child day care centers**

Assessment of impact and risk

**Een epidemiologisch perspectief op gastroenteritis
in kinderdagverblijven**

Evaluatie van impact en risico
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector
magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in
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'People often confuse an explanation of causes with a justification or acceptance of results. However, understanding 'why?' is a question separate from the explanation itself'.

Guns, Germs and Steel, Jared Diamond, 1997

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Chapter 1

General introduction



General introduction

Introduction

Child Day Care Centres (DCCs) have been amongst us since 1840¹ and have become an increasingly prominent feature of modern child rearing in the industrialized world, including the Netherlands. Quintupled since 1989², half of the Dutch preschool population (350,000 children) currently spends an average of 2.5 days in one of the 6,000 DCCs active in the Netherlands, ranking our country second only to Denmark in the utilization of child day care services in Europe.³ Although the number of DCC facilities in the Netherlands has stabilized over the last years, it is unlikely that the Netherlands will stop relying on their services any time soon. The DCC is in fact an institution here to stay, and its presence poses unique challenges regarding infectious disease control.

'[...] Ever since our children started attending day care, my wife and I, as well as my children, have been constantly ill. I developed polyposis nasi, my son multiple episodes of otitis, my daughter chronic blefaritis and my wife required multiple antibiotic treatments for persisting nasopharyngitis. These disease episodes have had a tremendous impact on our family. It cannot be normal to be sick so much, can it [...]?'

Email from a concerned parent, 2013

Actually, it can. In fact, the syndrome the concerned parent describes has a name: Daycaritis.⁴ Daycaritis refers to the phenomenon that healthy infants and toddlers in DCCs are at an increased risk for developing common and, generally, mild childhood illnesses. Daycaritis includes a broad spectrum of syndromes affecting the respiratory and gastrointestinal tract ('colds', bronchiolitis, otitis media, conjunctivitis, pharyngitis, gastroenteritis, etc.) as well as exanthematous syndromes (dermatitis, pustulosis, etc.). Although DCCs have been around for more than 170 years and the intention has always been to support children's (healthy) growth and the society as a whole,

the epidemiology and control of daycaritis have received relatively little attention by the scientific community. As a result, the majority of recommendations in current international DCC-guidelines for infection control are expert- rather than evidence-based.^{5,6}

The Netherlands would benefit from a scientific assessment that aims at improving our understanding of the epidemiology of daycaritis. This thesis contributes to that assessment. However, it is beyond the scope of this thesis to study the epidemiology of all major childhood diseases belonging to the daycaritis phenomena. This thesis, therefore, focusses on one of its

major clinical manifestations: gastroenteritis, as the microorganisms (or enteropathogens) underlying gastroenteritis are transmitted via the faecal-oral route. Strategies to prevent faecal contamination of the DCC environment may therefore, in principle, help to reduce the gastroenteritis burden. For respiratory infections, modifiable characteristics with intervention potential are much more difficult to identify.^{7, 8} Similarly, although there are two major types of formal out-of-home care facilities related to the Netherlands - the DCC (size: 5 up to a few hundred children) and the day care home⁹ (size: 1 to 6 children) -, this thesis focuses mainly on the DCC. We will provide answers to two core questions of DCC-related gastroenteritis: (1) 'what is the impact of gastroenteritis related to child day care centers' and (2) which risk factors are associated with gastroenteritis in child day care centers?'

The large remainder of this introductory chapter is dedicated to discussing the gastroenteritis syndrome, the characteristics that predispose a DCC towards transmission of enteropathogens that cause gastroenteritis, and the potential and feasibility of day care control strategies that may reduce enteropathogen transmission. As these aspects are considered, several questions arise for which the Netherlands currently lacks evidence-based answers. These questions are operationalized in seven research questions that this thesis will attempt to answer using a variety of data sources.

Gastroenteritis and the day care center environment

Gastroenteritis; increased risk in child day care centers

In this thesis, we refer to gastroenteritis as an inflammation of the gastrointestinal tract. Gastroenteritis has infectious and non-infectious causes. It is defined by its clinical picture, which may include a myriad of symptoms including vomiting, diarrhoea, nausea, fever and abdominal pain. Gastroenteritis causes mortality, accounting for 4% (or 2.2 million) of annual deaths worldwide.¹⁰ Most deaths occur in developing countries among children under five years of age. In developed countries such as the Netherlands, child mortality rates are low, primarily due to improved hygiene and sanitation standards, improved nutritional status and timely treatment when needed. In the Netherlands, gastroenteritis episodes are mainly mild and self-limiting, although episodes with a high burden do occur.¹¹ However, given the high incidence of generally mild gastroenteritis episodes, the overall morbidity remains high.¹¹⁻¹³ This holds especially true for children attending DCCs that, in the Netherlands, provide government-regulated, paid, non-custodial care for five and up to a few hundred children aged 0-4 years. Several studies have indicated that children attending DCCs are at increased risk of developing gastroenteritis compared to children cared for at home.¹⁴⁻¹⁶ The caring for and treatment of children with gastroenteritis is likely to result in substantial

societal costs. These costs arise from health care visits, medication usage and productivity losses due to parents' absence from work to care for their ill child.^{17, 18} Because children in out-of-home group settings experience more infections compared with children cared for only at home, they also receive more antibiotics to treat illness, including gastroenteritis.¹⁹⁻²¹ The higher antimicrobial consumption of children in day care raises concern for the potential societal role DCCs may play in the selection and transmission of microorganisms that are resistant for important antimicrobials, in particular Extended Spectrum beta-Lactamase-producing (ESBL) organisms.²²⁻²⁴

The DCC environment; a unique epidemiological setting facilitating pathogen transmission

A DCC has unique epidemiological characteristics that provide a setting conducive to the increased transmission of enteropathogens that, upon infection, may cause gastrointestinal illness.^{4, 15, 25} These characteristics relate to the child, and to the DCC's physical characteristics and disease control strategies (figure 1).²⁶

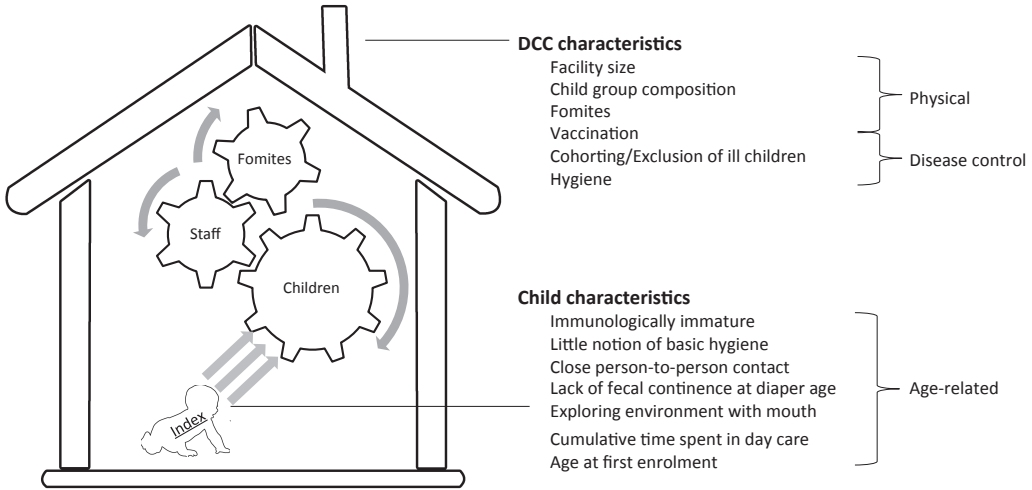


Figure 1: Characteristics of the DCC facility and its attending child-population that hypothetically facilitate the direct and indirect transmission of enteropathogens (arrows) from the index child to other children, staff and fomites.

Characteristics of the child

A child's age may contribute to increased transmission to enteropathogens because of age-specific personal hygiene and age-specific immunological factors.²⁷ Children attending day care lack faecal continence at diaper age, explore their environment with mouth and hands and appreciate interpersonal contact with other children and staff.²⁸ Furthermore, young children that start attending day care are often more immunologically naïve, and require frequent and substantial 'immunity boosts' before they produce adequate immunity.²⁹ Until that time, children are more prone to gastrointestinal infections. In addition, the cumulative time spent in day care, as well as the age at first enrolment might influence a child's exposure to gastrointestinal pathogens circulating in day care.

Characteristics of the DCC (physical characteristics and disease control strategies)

The microbial causes of gastroenteritis include a wide range of bacteria, viruses and parasites, and many of them circulate in DCCs. These include viruses such as rotavirus³⁰, norovirus⁵, astrovirus³¹, adenovirus³² and sapovirus³³; bacteria such as *Salmonella*³⁴, *Campylobacter*³⁵, *Clostridium*³⁶, *Yersinia*³⁷, *Shigella*³⁸ and *Escherichia coli*³⁹; and parasites including *Dientamoeba*⁴⁰, *Giardia*⁴¹ and *Cryptosporidium*.⁴² These enteropathogens transmit faecal-orally via food, water and animals; either directly via hand-mediated, person-to-person contact among children/staff members,⁴³ or indirectly via hand-to-mouth contact with environmental

contamination of inanimate objects (fomites) such as changing tables, toilet seats, doorknobs, toys and other classroom objects.⁴⁴⁻⁴⁶ Indirect transmission is facilitated as many of these enteropathogens can remain viable on surfaces for hours (rotavirus) or even days (*Giardia* cysts), contrary to enteropathogens such as *Campylobacter* that are more likely to transmit directly since they require specific environmental circumstances to survive.

In addition to fomites, other characteristics of the DCC might be associated with increased transmission to enteropathogens, such as the size of the facility. The probability that a child becomes infected with an enteropathogen seems directly related to the probability that such an enteropathogen is introduced in the child's environment.⁴⁷ Large DCCs therefore potentially provide more opportunities for enteropathogen introduction and exposure than small facilities. In addition, size and age-composition of child-groups appear to determine the likelihood of exposure: some studies observe that small, same-aged groups not mixed with other-age groups ensure lower rates of exposure, even in larger centers.⁴⁸

Finally, disease control strategies are part of a DCC's characteristics. A DCC has three main strategies to reduce the gastrointestinal disease burden: vaccination, cohorting/exclusion and hygiene.^{28, 49} These strategies together define the disease control program of the facility.²⁸ Although the first two strategies are important in reducing the spread of enteropathogens,

perhaps the most promising strategy a facility has to prevent gastroenteritis burden is by implementing an effective hygiene code.⁵⁰ There are several potential components to such a code, and it helps to analyse these components in terms of transmission routes.⁵¹ Hygienic components that could prove to be valuable in reducing the impact of gastroenteritis include: good hand hygiene by staff and children, optimal staff-child ratios, limited staff mixing between child-groups, appropriate cleaning and disinfecting of contaminated surfaces and separation of food preparation and diaper changing activities.^{49, 52-54}

The limited evidence-base of gastroenteritis control strategies in child day care centers

Efforts to reduce the gastroenteritis impact related to day care should focus on identifying the facility characteristics and disease control practices that confer the highest risk of illness. The potential impact of the ease with which enteropathogens circulate in DCCs, both for the child attending care as well as for society, raises the question whether the DCC control strategies mentioned above are currently optimal in reducing the spread of enteropathogens in the DCC environment. A deliberation on this subject requires answers to several questions on the impact of DCC-related gastroenteritis on the attending child and society, as well as on the DCC risk factors involved.

Impact-related questions

- What is the incidence of gastroenteritis related to children attending a DCC in the Netherlands and how does this incidence compare to other common childhood illnesses of respiratory and exanthematous nature among children attending day care, or to children solely cared for at home?
- Are the gastroenteritis episodes mild, short-term and limited to the early years of the child's life or does attending a DCC also have severe and long-term effects that are present regardless of the age of the attending child?
- Is there a developmental stage in a child's preschool years during which these effects are more prominent? Does the cumulated time spent in day care, or the type of child day care facility modify these effects?
- Finally, what are the societal costs associated with gastroenteritis among children in the Netherlands and do these costs differ between children that do and do not attend day care?

Risk factor-related questions

- What is the prevalence of enteropathogens of bacterial, viral or parasitic origin in the intestinal flora of children attending day care and how does the prevalence relate to the child's age and gastroenteritis status, as well as the season and the year?
- Which enteropathogens contribute most to gastroenteritis in day care?
- Which characteristics of the Dutch DCC environment are associated with an increased/decreased gastroenteritis risk?

Unfortunately, the evidence-base to address these questions is currently rather restricted, for two reasons. Firstly, the epidemiology of gastroenteritis in DCCs in the Netherlands has received limited scientific consideration since 1974, when the term 'child day care' was introduced in the Index Medicus; especially when comparing the Netherlands to countries such as the USA, Scandinavia and the UK. Less than 1% of the roughly 500 studies so far published internationally on major childhood diseases in child day care originate from the Netherlands (figure 2); none of these studies focused on gastroenteritis. We could try to extrapolate insights from the other 99% of international studies, but this warrants caution if studies do not originate from countries that have comparable socio-economic conditions, surveillance schemes, gastroenteritis aetiology, vaccination schemes, antibiotic regimes and facility licensing regulations/practices as

the Netherlands. We could also try to use data emanating from surveillance initiatives currently active in the Netherlands. However, these initiatives give limited consideration to the infectious disease dynamics of a DCC as these initiatives do not discriminate between children that do and do not attend day care in a standardized way. A second reason why the evidence-base to answer the questions raised above is restricted is because most studies conducted are primarily interested in factors related to the (households of) children attending DCCs, rather than factors related to the DCC setting itself, making it difficult to determine which DCC strategies are associated with a gastroenteritis disease and which are not.⁵⁵

Research rationale and research questions

The Netherlands could benefit from a scientific assessment that aims at improving our understanding of the epidemiology of daycaritis by answering the questions posed in the previous subchapter. This assessment could assist public health and day care professionals to determine the desirability and feasibility of intensified avocation of disease control measures in DCCs, and if desirable, to prioritize public health spending constrained by limited resources. Additionally, such improved knowledge may help to reassure ourselves as society that our DCCs have a strong program for gastroenteritis disease prevention and control.

As aforementioned, this thesis focuses on providing answers to two core questions:

- I What is the impact of gastroenteritis related to child day care centers?
- II Which risk factors are associated with gastroenteritis in child day care centers?

The focus on gastroenteritis impact is important. Ultimately, our effectiveness as society in controlling gastroenteritis depends on our recognition of its impact on the health of children and the society as a whole. To determine the impact of gastroenteritis means comparing the impact among children attending day care relative to those not attending day care. The focus on risk factors is also essential. Many enteropathogens underlying gastroenteritis are transmitted via the faecal-oral route. Direct (person-to-person) and indirect transmission (via contaminated surfaces) plays an important role in their spread; strategies preventing contamination of the DCC environment may therefore reduce the gastroenteritis burden. To determine the risks of gastroenteritis requires us to consider the DCC as a complex setting in which the interplay of many factors influences the occurrence of gastroenteritis, rather than as one homogeneous risk factor for gastrointestinal infections.⁵⁶⁻⁵⁸

The questions posed in the subchapter on the limited evidence-base underlying gastroenteritis control strategies in DCCs have been operationalized into research questions.

These research questions, along with the data sources developed/used to answer these questions, are presented in table 1.

Thesis outline

This thesis aims at improving our knowledge on the epidemiology of gastroenteritis in DCCs. It provides a quantitative assessment on the impact of gastroenteritis in day care, both in the short- and long-run, in clinical and financial terms (section I, **chapter 3-5**) as well as on the associated enteropathogens and DCC risk factors (section II, **chapter 6-8**). As such, it aims to contribute to the evidence-base underlying prevention and control of gastroenteritis in child day care.

In order to address our aim, several registry- and novel web-based surveillance systems targeting the general population, the DCC and household were realized (table 1). However, the foundation of most of the research in this thesis is provided by our nationwide, three-year prospective DCC cohort study on the clinical and microbiological aspects of gastroenteritis (acronym: KIzSS). Its aim, design and potentialities are presented in **chapter 2**.

Section I: impact

The first section of this thesis focuses on the impact of gastroenteritis related to child day care. We start in **chapter 3**, where we use data generated by the DCC network to estimate the incidence of gastroenteritis

Table 1: Research questions, data sources* and gastroenteritis definitions** used to study the impact and risk factors related to gastroenteritis in Dutch day care.

Core question	Research question	Data source	Source description
Impact	What are the incidence rates for episodes of gastroenteritis among DCC-children? (chapter 3)	Dutch DCC sentinel surveillance network (KIZSS;	Description: National Dutch network of 100 DCCs that prospectively monitors syndromic and microbiological aspects of major childhood illnesses among its child-population
Risk	What are the prevalence rates of a range of enteropathogens among children in DCCs and how do these rates relate to age, clinical symptoms and season? (chapter 6)	Kinderdagverblijven Infectieziekten Surveillance System)	Data period: 2010-2012 (chapter 3), 2010-2013 (chapter 6,7,8) Gastroenteritis definition: An acute onset of ≥ 3 episodes of watery stools per day and/or an acute onset of ≥ 3 emetic (vomiting) episodes per day that result in absence of the child for one or more days during which the child was scheduled to attend day care
Risk	What are the relative contributions of these enteropathogens to the gastroenteritis incidence in DCCs? (chapter 7)		
Risk	Which DCC characteristics and practices are associated with a high/low gastroenteritis incidence in DCCs? (chapter 8)		
Impact	What are the DCC incidence rates for mild episodes of gastroenteritis requiring a visit to a general practitioner and how do these rates compare to children in the general population? (chapter 3)	The Netherlands Institute of Primary Health Care (NIVEL)	Description: National Dutch network of 45 general medical practitioners that provides weekly consultation data on gastroenteritis and influenza-like illness (ILI) among their cared population Data period: 2010-2012 Gastroenteritis definition: same as KIZSS
Impact	What are the transient and sustained effects of day care attendance on hospitalization of a child with gastroenteritis, and are these effects modified by the cumulated amount of time spent in day care, the age at which a child starts attending day care and the type of facility the child attends? (chapter 4)	Danish Childcare database	Description: National Danish registry-based database of 1.2 million children aged 0-12 years supplemented with child and family characteristics, day care characteristics and arrangements, elementary school arrangements and hospitalizations due to gastroenteritis Data period: 1994-2011 Gastroenteritis definition: Defined according to the International Classification of Diseases, 10th revision (ICD-10). Includes ICD-codes 000-009, 014, 054.01, 054.08
Impact	What are the societal costs for care and treatment of a child with gastroenteritis, and do these costs differ between children that do and do not attend a DCC? (chapter 5)	Family and Health (G&G; Gezin en Gezondheid)	Description: National Dutch cross-sectional survey conducted among households with children aged 0-48 months on the occurrence of gastroenteritis episodes and their costs Data period: 2012-2013 Gastroenteritis definition: an acute onset of ≥ 3 episodes of watery stools per day and/or an acute onset of ≥ 3 emetic (vomiting) episodes per day

* A more detailed description of each data source is given in the chapter indicated.

** There is no internationally accepted case definition for gastroenteritis. Comparison between countries is difficult and is possible only if case definitions are similar.

among Dutch day care attendees that result in a child's absence from day care or in a visit to the general practitioner. The DCC practitioner estimates were compared to national GP estimates (acronym: NIVEL) for children eligible for day care to crudely estimate the excess incidence of gastroenteritis attributable to Dutch day care attendance. In **chapter 4**, we shift our focus from episodes with a mild impact to episodes with a severe impact by examining whether children attending day care experience a higher short- and long-term risk of hospitalization for gastroenteritis compared to children that do not attend day care. We also assess whether the cumulated day care-time, type of day-care facility attended and the age at first enrolment modify these risks. As the follow-up time and sample size required for this study has no equivalent in the Netherlands, this study is conducted using Danish registry data (acronym: Childcare database). The impact of gastroenteritis, whether short- or long-term, is obviously not restricted to the clinical domain. Estimates on, and differences between, the societal costs for gastroenteritis episodes among children that do and do not attend day care would provide valuable additional information on the financial impact of day care related gastroenteritis and was the aim of **chapter 5**. As the DCC network did not allow for such a comparison, we developed and implemented a separate web-based survey among households with children aged 0-48 months (acronym: G&G).

Section II: risk factors

The second section of this thesis (**chapter 6-8**) is dedicated to unravelling the risk factors of gastroenteritis, both in terms of the enteropathogens involved in the gastroenteritis syndrome as well as characteristics of the DCC that facilitate their transmission. In **chapter 6**, we estimate the prevalence of a range of circulating enteropathogens in asymptomatic children and relate the prevalence to demographic, seasonal and clinical characteristics of the children themselves. In **chapter 7**, we estimate the proportion of gastroenteritis incidence in day care that can be attributed to the circulating enteropathogens. In an attempt to gain further knowledge towards reducing the burden of DCC-related gastroenteritis, **chapter 8** identifies DCC risk factors for the circulation of these enteropathogens and for the occurrence of the gastroenteritis at the DCC level.

The insights provided by **chapter 3-8** allow us to propose a number of feasible action points that might assist in increased control of gastroenteritis in the day care setting (**chapter 9**).

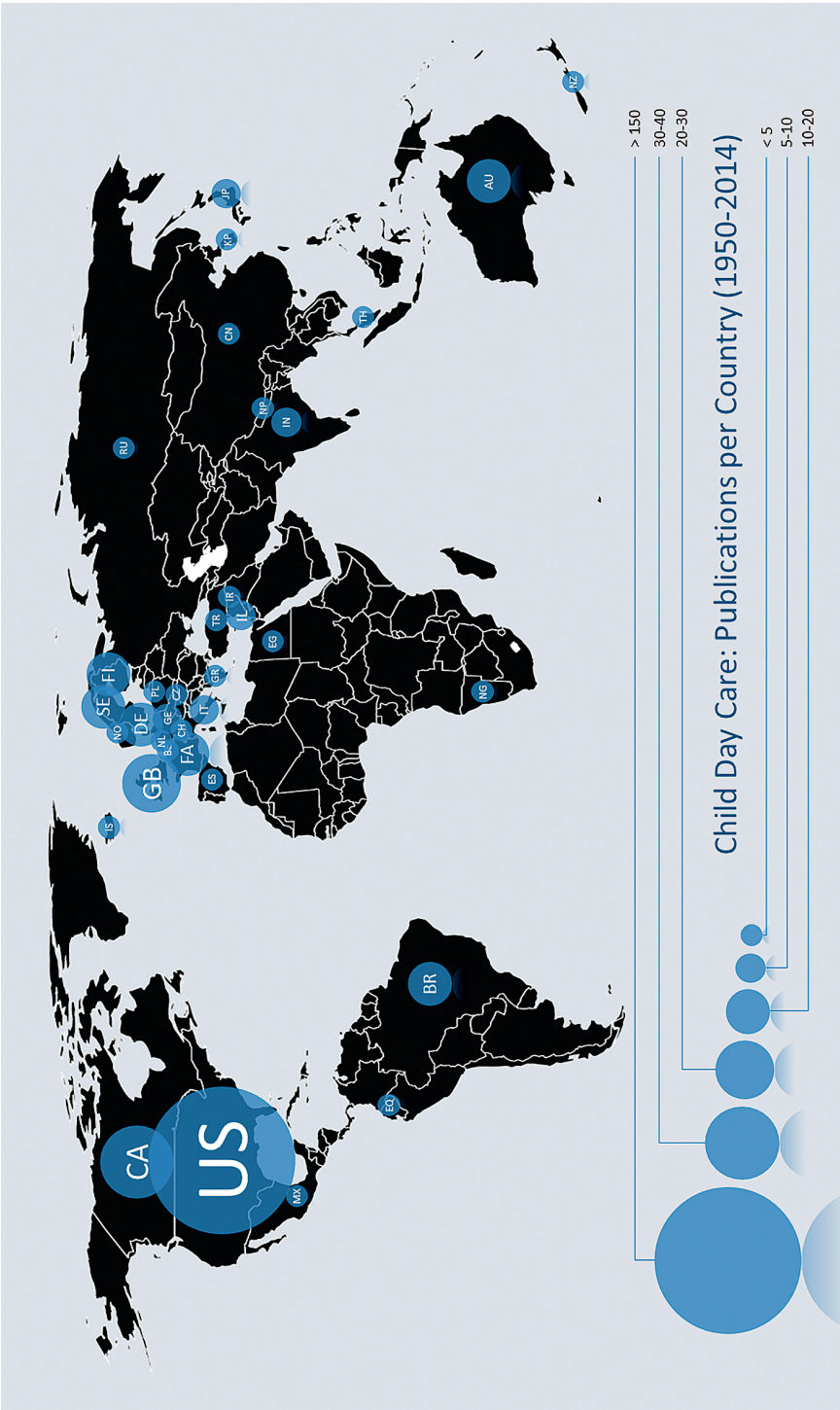


Figure 2: Number of international publications on major childhood diseases in child day care (source: PubMed, since 1950).



Chapter 9

General discussion



General discussion

This thesis aims to provide insight into epidemiology of gastroenteritis in child day care by providing a quantitative assessment of the impact and the risk factors of gastroenteritis in the DCC setting. It is the result of several studies conducted nationally and internationally, analysing data from registry- and novel web-based surveillance systems targeting the DCC-, general population-, and household-setting. This discussion chapter will address the two core questions - as posed in the introductory chapter - on the impact and risks related to gastroenteritis related to day care in light of our findings. Deliberating on our core questions will raise two additional questions: how could we, and why would we attempt to reduce the impact of gastroenteritis related to day care further? Addressing the 'how could we' question will result in the outline of several evidence-based recommendations on the physical characteristics and disease control strategies of the DCC, prioritizing those proven to be associated with illness and that are putatively modifiable by the DCC. Addressing the 'why would we' question is of a more philosophical nature, and thereby more difficult to answer. Yet it deserves consideration, as it will influence our appreciation towards future surveillance and research strategies in day care.

Impact of gastroenteritis related to child day care centers (the first core question)

We observed that gastroenteritis was the most common illness leading to a child's absence from day care in the Netherlands. With 387 episodes per 1000 child-years, the incidence rate for gastroenteritis absences even surpassed rates for respiratory illness (247 per 1000 child-years, chapter 3). When compared to home-cared children, day care-attending children experienced a 1.4 times higher incidence of gastroenteritis (chapter 5). Children attending day care did not only experience more episodes of gastroenteritis compared to children cared for at home, but the morbidity per episode also appeared to be higher. Children attending a

DCC consulted the GP approximately 1.7 times as often for gastroenteritis as reported by the Dutch Sentinel GP Network during the same period and for the same age group (chapter 3). Based on Danish data, DCC-attending children experienced an up to 1.7 times short-term increased probability of severe episodes of gastroenteritis requiring hospitalization compared to children that never attended day care facilities, regardless of their age. However, children who experienced a significant higher short-term risk for hospitalization due to gastroenteritis also had a significant 0.8 times lower long-term risk for such hospitalizations in the subsequent five years of preschool life; as long as they started attending day care before the age of one year and they remained attending child day care until elementary school (chapter

4). The impact of day care-related gastroenteritis is not restricted to the ill attending child, or to the clinical domain for that matter; it also generates substantial societal costs. The societal costs involved per episode of gastroenteritis for a child attending day care were estimated at €215.45, twice as high compared to these costs for home-cared children. Extrapolated to the Dutch society, the excess societal costs for DCC-related gastroenteritis would sum up to an estimated annual €25 million. The greater societal costs are predominantly attributable to differences in productivity losses experienced by households utilizing day care services, as these are more often composed of two working, better-earning partners than households not utilizing such services (chapter 5).

Concluding, the impact of gastroenteritis related to child day care appears substantial. Reducing the impact of gastroenteritis would hypothetically not only reduce the clinical impact of gastroenteritis, but also generate substantial cost savings from a societal point of view. Impact reduction from a DCC perspective starts with identifying the physical characteristics and disease control strategies in day care that confer the highest risks for gastroenteritis.

Risk factors for gastroenteritis in child day care centers (the second core question)

The clinical and economic impact of gastroenteritis related to the DCC setting needs to be supplemented by identifying the enteropathogens and their dynamics that putatively underlie the gastroenteritis burden in day care as well as study the DCC characteristics that are associated with their circulation.

We observed that a broad range of bacterial, parasitic and viral enteropathogens circulated in the intestinal flora of children attending day care. Bacterial enteropathogens were frequently detected (45% of samples) followed by parasitic enteropathogens (27%) and viral enteropathogens (22%). Ninety-five percent of children in which an enteropathogen was detected experienced no gastroenteritis symptoms (asymptomatic) at time of sampling. The role that asymptomatic children play in the risk of enteropathogen transmission was not studied and remains unclear. Children detected with rotavirus or norovirus (~10%) did, however, have a twice as high odds for gastroenteritis. The risk of infection with any viral enteropathogen decreased with increasing age of the sampled child, while the opposite was observed for all enteropathogenic parasites; no age associations were not found for enteropathogenic bacteria. Viral enteropathogens displayed seasonal patterns, with peak prevalence during the winter months, whereas the opposite held true for some bacterial enteropathogens. No parasitic,

and few bacterial enteropathogens showed notable seasonal trends (chapter 6). Viruses and parasites, rather than bacteria, conferred the highest risk for gastroenteritis in child day care. Together, rotavirus, norovirus, astrovirus, *Giardia lamblia* and *Cryptosporidium hominis* accounted for 39% of gastroenteritis cases observed in the DCC network during 2010-2013. We estimated that 52,000 children experience gastroenteritis in DCCs because of infection with these five enteropathogens in the Netherlands each year (chapter 7).

The circulation of these enteropathogens in day care, as well as the incidence of gastroenteritis, appears not only to be related to risk factors associated with the attending child such as age (chapter 6), but also with the physical characteristics and disease control strategies of the DCC. Large and densely populated DCCs were associated with an increased gastroenteritis risk. For each additional DCC child, the GE incidence increased by 0.1%. Similarly, for each percent increase in crowding of the DCC environment, GE incidence increased by 0.7%. Children attending animal-owning DCCs had a significantly increased risk of being exposed to enteropathogens with zoonotic potential such as *Giardia*, thus increasing the risk that such children develop gastroenteritis (chapter 7). Sandpits and paddling pools were associated with increased circulation of norovirus and *Giardia*. With respect to disease control strategies, regular cleaning with cloth to remove the bulk of the organic material and subsequent disinfecting with chlorine of objects and surfaces

that children and staff commonly interact with, was associated with a lower gastroenteritis burden in the DCC setting. Staff movements between different child groups formed a risk factor for increased circulation of rotavirus. Several outbreak-related control measures were identified as being associated with a lower risk of enteropathogen circulation in day care. These measures included exclusion of children and personnel with gastroenteritis from the DCC, no mixing of staff during a gastroenteritis outbreak, and providing children with gastroenteritis with their own toilet. Surprisingly, our study found no evidence for the protective effects of hand hygiene, small group sizes and same-age child-groups as observed in several other studies (chapter 8).^{8, 206}

Concluding, several characteristics of the child and DCC environment correlated with gastroenteritis and with the circulation of major enteropathogens associated with gastroenteritis among children, suggesting that part of the gastroenteritis impact can be prevented. As we will highlight next, some of these characteristics are more easily modifiable than others.

Putatively modifiable characteristics for gastroenteritis control in child day care centers (the ‘how could we’ question)

The first part of this discussion provided evidence that the impact of gastroenteritis related to day care is substantial, whereas the second part indicated that this impact might be partly preventable by focussing on those child and DCC characteristics and practices most associated with gastrointestinal illness. However, not all characteristics are (easily) modifiable. Modification of some would be undesirable from a societal point of view or too expensive or impractical to implement from a DCC point of view, yet modification of others seems promising. We will discuss the putatively modifiable characteristics according to figure 1, as presented in the general introduction of chapter 1.

Child characteristics

We can do little to modify a DCC-child’s immunological immaturity or behavioural characteristics (little notion of basic hygiene, intrinsic propensity for close person-to-person contact, lack of faecal continence at diaper age, exploring environment with mouth). However, two child characteristics that we could modify are the age at which the child comes into first contact with day care and the time a child spends in day care. Both have been associated with increased rates in this thesis and in other studies.

Age at first enrolment

Hypothetically, we could postpone the enrolment of children into day care until the age of one, as some argue that the DCC-related gastroenteritis burden is mostly confined to infants.^{35, 207, 208} For example, the Dutch government could increase the period of subsidized parental leave after childbirth from 6 months to 1 year of age, as is Danish policy.⁵⁷ Not taking into account the substantial parental productivity losses and funding required for such a change in policy, the results of the Danish study suggest that this might actually reduce the long-term benefits of attending day care. In fact, the excess gastroenteritis morbidity seems more related to the moment of first exposure to the DCC environment, than to the age of the attending child (chapter 4). Thus, our results do not support postponing the age at first DCC enrolment in the Netherlands.

Cumulative time spent in day care

In theory, decreasing the time a child spends in day care could lower the probability that such a child experiences severe episodes of gastroenteritis (chapter 4).¹³³ In practice, however, the time a child spends in day care is rather fixed. Childcare centers provide an essential service to Dutch households, enabling parents to work, thereby enhancing income. In addition, other considerations play a role in the time spent in day care, including potential benefits of out-of-home childcare services for society and the attending child. For society, the economic contributions of parents who can join the labour force because their children are

cared for at a DCC are great. Reducing the time spent in day care could result in productivity losses far greater than the productivity losses incurred by DCC-related illness (chapter 5). For the child, attending a DCC could confer long-term beneficial effects on gastroenteritis morbidity until the elementary school age (chapter 4), probably due to the repeated immune challenges posed by the higher levels of exposure to pathogens circulating in the day care environment (chapter 6). Such benefits are not limited to gastroenteritis; other studies have observed day care attendance to reduce the long-term risk of developing allergic disease⁸⁸⁻⁹² and mild respiratory infections^{29, 94, 95}, even after the child has left day care. If true, some argue that the societal costs might not be avoided altogether for home-cared children, but that these costs are only delayed until elementary school.^{57, 58, 95} This notion, however, is not supported by our results (chapter 4).

DCC characteristics

Physical characteristics

Similar to previous research, we demonstrated that some physical characteristics of the DCC environment are associated with gastroenteritis occurrence and/or the circulation of enteropathogens, including the size and crowding rates of a DCC. The exposure to enteropathogens circulating in small day care homes appears low enough to avoid causing the most severe manifestations of gastroenteritis when a child starts attending a day care home, but high enough to allow for

the (gradual) development of a child's immune response to protect from such manifestations in the long-term. This suggests that, rather than postponing the child's enrolment into day care, children (particularly those with underlying illness) might benefit from enrolment into the smaller day care homes (size: 1 to 6 children) in preference of the larger DCCs (size: 5 up to a few hundred children). DCCs probably provide more opportunities for inter-child transmission, both directly through person-to-person and indirectly through the easily contaminated day care environment. However, the decision to promote one type of day care setting over another is likely to depend on many additional considerations, including psychological development for the child.^{209, 210} Further research is required in these domains to facilitate rational decision-making.

Disease control strategies (vaccination, cohorting/exclusion, hygiene)

The previous paragraph on the physical characteristics of a DCC for gastroenteritis also suggests that if we could effectively target DCC characteristics causally related to gastroenteritis, we might reduce the short-term health disadvantages associated with DCC attendance without reducing the long-term health advantages associated with such attendance. Of all DCC characteristics, disease control strategies are perhaps most directly under the control of the DCC management.⁸ Although this thesis certainly does not immediately provide evidence-based recommendations for improved infectious

disease control in DCCs, it provides a scientific basis for additional clinical intervention studies that will be able to provide such recommendations and some preliminary recommendations can be made. Based on the data presented in this thesis, these intervention studies might recommend the following. Although rotavirus vaccination is currently not implemented in the Netherlands for preschool children given its limited cost-effectiveness²¹¹, targeting rotavirus vaccination specifically for DCC-attending children may substantially reduce the gastroenteritis burden associated with day care attendance. DCC policies for exclusion and cohorting could be effective in reducing the burden of gastroenteritis despite high asymptomatic infection rates among attendees. If so, they should be an integral part of every DCC's strategy for prevention and control, regardless of the considerable burden these policies put on parents and DCC alike, since both have to make alternative care arrangements.^{42, 108, 212, 213} Improving hygienic standards in DCCs are likely to reduce the transmission of these enteropathogens that generally spread from person to person via the faecal-oral route, via aerosols and via contaminated surfaces. In that case, all surfaces and fomites, particularly toys, should receive routine cleaning, even when gross contamination is not obvious. This would also mean that the use of non-washable toys in areas with young children or in centers providing care to sick children should be discouraged. In addition to toys, dedicated diaper-changing areas would need special hygienic attention, as these seem to form 'hubs' for transmission of

enteropathogens. Staff movements should be minimized as much as possible, particularly during suspected gastroenteritis outbreaks. Finally, the sand and water of sandpits and paddling pools should be regularly replaced, in addition to being covered when not in use.

Reducing the impact of gastroenteritis related to child day care centers (the 'why would we' question)

Why would we attempt to reduce the impact of gastroenteritis related to day care? After all, many of us consider the gastroenteritis episodes as an educational experience for our child's immune system.²¹⁴⁻²¹⁶ In fact, some parents believe that children should be exposed to 'dirt' early in life for them to be protected against disease later in life.⁹² This oversimplified version of reality is worrisome as it is easily misinterpreted. Undoubtedly, a certain amount of microbiological exposure is required to confer long-term immune priming, but there is a difference between 'dirt' and 'pathogens' and between 'cleanliness' and 'hygiene'. We currently do not know the nature of microbiological exposure in day care that benefits the attending child. Even if we would, hygiene measures do not distinguish between beneficial exposures to 'good' pathogens and harmful exposures to 'bad' pathogens. The latter group includes measles, *H. influenzae* type b, *S. pneumoniae*, cytomegalovirus, parvovirus, rotavirus and respiratory pathogens causing

otitis media. Measles is re-emerging in day care in the Netherlands and Belgium among highly vaccinated children.^{217, 218} Infection by H. influenzae type b and *S. pneumonia* in day care cause severe infections such as pneumonia and meningitis in unvaccinated children.²¹⁹⁻²²² Cytomegalovirus (CMV) and parvovirus infectious can have severe consequences for unborn children of pregnant DCC staff and for immunocompromised attendees.²²³⁻²²⁵ Otitis media, a frequent syndrome associated with day care attendance, is associated with hearing loss, impeded speech development and reduced school achievements later in life.²²⁶⁻²²⁹ Rotavirus is responsible for 20-60% of hospital admissions of children due to dehydration by diarrhoea.²³⁰ The DCC has been considered an independent factor for colonization by resistant bacteria²³¹, such as penicillin-resistant *S. pneumoniae*^{232, 233} and Extended Spectrum Beta-Lactamase-producing (ESBL) *E. coli*.^{22-24, 234}

Thus, relaxing a DCC's disease control strategies based on the notion that 'dirt is good for our children' would represent a very poor trade-off indeed. As public health professionals, we need to keep stressing the difference between 'dirt', 'germs', 'cleanliness' and 'hygiene' in the future. Not doing so could cause loss of confidence among parents and DCCs regarding appropriate DCC disease control standards.⁹² Moreover, there is currently little evidence-based justification to relax such standards.²³⁵ Finally, DCC-related illness does not only concern the attending child. Indeed, preliminary analysis of the family and health data (table 1, introduction)

showed that parents with children attending a DCC currently have an up to 5 times higher risk for developing episodes of gastrointestinal and respiratory illness, suggesting that reducing the impact DCC-related illness is of interest to the entire Dutch community.⁶⁶

Why many stakeholders would benefit from continued infectious disease surveillance in child day care centers

Reducing the burden of DCC-related gastroenteritis, or general DCC-related illnesses for that matter, is a concern not only of parents, physicians, and public health officials, but also to employers and perhaps health insurers who might find it worthwhile to subsidize the possibly increased cost in DCC settings designed to minimize illness rates. Given the many stakeholders involved, we recommend that surveillance efforts in day care are continued in the future. The value of such standardized surveillance systems has been demonstrated in the past in the setting of general practice¹¹⁶, nursing home⁶⁹ and hospital.²³⁶ The DCC surveillance underlying much of the work performed in this thesis, has paved the way for such a sustainable, but currently absent, system.

Ideally, local and provincial health authorities would be in charge of DCC surveillance as they coordinate regional disease control efforts in the Netherlands. Each authority could be responsible for the DCCs operating within

its municipality. These authorities could use our web-based monitoring system. The closer contact between the local health department and DCC (rather than our national institute) would benefit the DCC in case of disease control issues and would benefit the local health department because it facilitates timely public health outreach to DCCs and vice versa. In addition to the local health authorities, registration of day care-related illnesses could be included in the continuous morbidity registration of our GP sentinel surveillance network organized by the Netherlands Institute for Health Services Research (NIVEL).

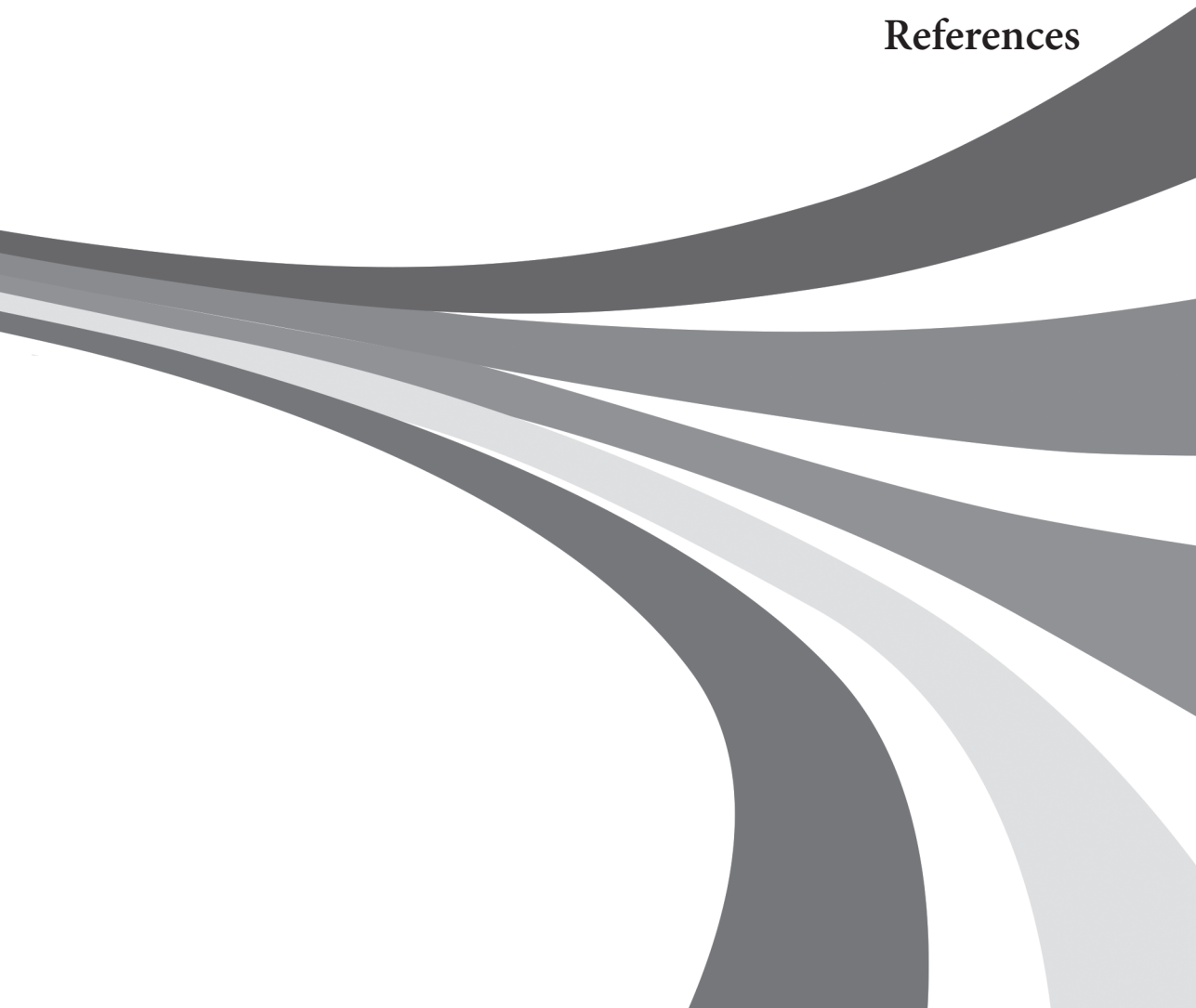
There are many benefits to implementing a DCC surveillance system. By linking regional or national general population, GP and hospital surveillance registries already in place, DCC surveillance data might assess whether infectious disease trends in child day care reflect or drive infectious disease patterns in the community at large. It could assist in rapid and comprehensive assessments of future impact of (shifts in) seasonal syndrome and/or microbiological trends of infectious diseases. It could monitor the effectiveness of day care targeted intervention strategies; for example, by monitoring the gastrointestinal disease burden in day care in pre- and post- rotavirus vaccination era should rotavirus vaccination of day care attendees become a national policy in the future.^{211, 237} Finally, data emanating from such a system could serve as input for a DCC certification label highlighting excellent hygiene practices, allowing DCCs to benchmark and

promote themselves against other DCCs active in the Netherlands. The feasibility of such a certificate is currently being considered by policy makers in the Netherlands.²³⁸

Concluding, the impact of gastroenteritis in day care is substantial. Many DCC characteristics related to gastroenteritis seem within control of the DCC management. Although this thesis does not demonstrate how these characteristics causally contribute to the actual transmission of enteropathogens underlying gastroenteritis *per sé*, it does provide scientific arguments on ‘how we could’, and ‘why we should’ aim at reducing the burden of day-care related gastroenteritis. Efforts are currently ongoing amongst stakeholders to determine whether increased control of DCC-related infectious diseases is desirable in the Netherlands. If desirable, important steps in future research would be to design intervention studies that unravel the critical elements of DCC-intervention programs for effective gastroenteritis control, including the costs of implementing and sustaining these programs.



Summary
Samenvatting
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Summary

This thesis aims to provide insight into the epidemiology of gastroenteritis related to child day care centers (DCCs) in the Netherlands. It is the result of several studies conducted nationally and internationally, analyzing data from registry- and novel web-based surveillance systems targeting the DCC-, general population-, and household-setting. It addressed two core questions on the impact and risks related to the DCC setting:

I What is the impact of gastroenteritis related to child day care centers?

The first core question is operationalized into three research questions addressed in **chapters 3-5**:

- I.1 What are the incidence rates for episodes of gastroenteritis among DCC-children and how do their general practitioner visits relate to children in the general population? (**chapter 3**)
- I.2 What are the transient and sustained effects of day care attendance on hospitalization of a child with gastroenteritis, and are these effects modified by the cumulated amount of time spent in day care, the age at which a child starts attending day care and the type of facility the child attends? (**chapter 4**)
- I.3 What are the societal costs for care and treatment of a child with gastroenteritis, and do these costs differ between children that do and do not attend a DCC? (**chapter 5**)

II Which risk factors are associated with gastroenteritis in child day care centers?

The second core question is operationalized into three research questions addressed in **chapters 6-8**:

- II.1 What are the prevalence rates of a range of enteropathogens among children in DCCs, and how do these rates relate to age, clinical symptoms and season? (**chapter 6**)
- II.2 What are the relative contributions of these enteropathogens to the gastroenteritis incidence in DCCs? (**chapter 7**)
- II.3 Which DCC characteristics and practices are associated with a high/low gastroenteritis incidence in DCCs? (**chapter 8**)

Our nationwide, day care-based surveillance network on the clinical and microbiological aspects of gastroenteritis (KIzSS) provided the foundation for answering many of the research questions in this thesis (research questions I.1, II.1, II.2 en II.3). **Chapter 2** elaborates upon the aim, design and potential of the KIzSS network. However, not all questions could be addressed using KIzSS data. Research question I.2 (**chapter 4**) required much longer periods of follow-up and a larger sample size than KIzSS could provide for and was therefore conducted using Danish data (Childcare database). Research question I.3 (**chapter 5**) required a household perspective, which meant developing and implementing a web-based survey among households with children aged 0-48 months (G&G).

What are the incidence rates for episodes of gastroenteritis among DCC-children and how do their general practitioner visits relate to children in the general population? (I.1)

In **chapter 3**, we observed that gastrointestinal illness (387 episodes per 1000 child-years), rather than influenza-like (247 per 1000 child-years) or exanthematous illness (59 per 1000 child-years) was the illness most commonly reported by DCCs. Gastroenteritis episodes occurred approximately twice as often among children aged 0-2 years compared to children aged 2-4 years (IRR 1.7 [95%CI: 1.5-1.9]). Children attending day care consulted their general practitioner almost twice as often for gastroenteritis episodes than expected based on national estimates (NIVEL) for 0-4 year old children (IRR: 1.7 [95%CI: 1.4-2.0]). Finally,

our DCC survey performed as part of this chapter indicated ample room for improvement in implementing simple measures for infectious disease prevention. For example, DCCs indicated that they not always washed the hands of children before eating (34%) or after a toilet visit (15%) and not always cleaned the toilet and kitchen areas (17%) on a daily basis.

What are the transient and sustained effects of day care attendance on hospitalization of a child with gastroenteritis, and are these effects modified by the cumulated amount of time spent in day care, the age at which a child starts attending day care and the type of facility the child attends? (I.2)

In **chapter 4**, we considered the transient and sustained effects of increased day care exposure for the most severe manifestations of gastroenteritis (those requiring hospitalization). Danish data allowed us to estimate the risk of being hospitalized for gastroenteritis using two large cohorts of preschool (<6 year-old) and elementary school-going (6-10 year-old) Danish children. Together, the two cohorts comprised 443,872 children, 21,038 hospitalizations and 1,742,284 child-years (1994-2011). We observed that from first day care attendance until 12 months of cumulated attendance, preschool children attending day care centers displayed an increased risk of hospitalization for gastroenteritis compared to children never attending registered day care (HR: 1.8 [95%CI: 1.5-2.0]). This increased risk was highest shortly after starting day care attendance and then gradually declined. After

12 months of attendance, attending day care was associated with a lower risk for hospitalization (HR: 0.8 [95%CI 0.7-0.9]). This decreased risk was confined to children that started attending day care before the age of one and extended throughout, not beyond, their preschool years.

What are the societal costs for care and treatment of a child with gastroenteritis, and do these costs differ between children that do and do not attend a DCC? (I.3)

In **chapter 5**, we provided estimates on, and differences between, the societal costs for gastroenteritis episodes among children that do and do not attend day care. We observed that particularly very young (<1 year) children attending a DCC experienced higher rates of gastroenteritis compared to children not attending a DCC (aIRR 1.6 [95%CI: 1.1-2.7]). However, the average societal costs for care and treatment of an episode of gastroenteritis experienced by a DCC-attending child were estimated at €215.45 ([95%CI: €115.69-€315.02]); twice as high as for a non-DCC-attending child. The greater societal costs were predominantly attributed to differences in productivity losses experienced by parents when having to care for their ill child. Households utilizing day care services more often had two working partners that together earned more. The DCC-attributable economic costs of gastroenteritis for the Netherlands were estimated at €25 million per year.

What are the prevalence rates of a range of enteropathogens among children in DCCs and how do these rates relate to age, clinical symptoms and season? (II.1)

In **chapter 6**, we estimated the prevalence of a range of enteropathogens present in the intestinal flora of children attending day care, and related the occurrence of these enteropathogens with characteristics of the sampled child and the sampling season. Enteropathogens were detected in 78.0% of 5197 faecal samples analyzed. The probability of detecting any viral or bacterial enteropathogen decreased with increasing age of the sampled child, while the opposite was observed for enteropathogenic parasites. Viral enteropathogens displayed yearly seasonal trends, but with peak prevalence's during the winter months, while bacterial enteropathogens were mainly detected during the summer months. The parasitic enteropathogens showed no notable seasonal trends. 95.4% of samples were obtained from children who had no gastroenteritis symptoms at time of sampling. The majority of gastro-intestinal infections among children attending DCCs appear to occur asymptotically.

What are the relative contributions of these enteropathogens to the gastroenteritis incidence in DCCs? (II.2)

Chapter 7 aimed to estimate the proportion of day care attendees experiencing gastroenteritis (chapter 3) that could be attributed to the overall circulation of enteropathogens among children attending DCCs (chapter 6). We demonstrated that rotavirus, norovirus, astrovirus, *Giardia*

and *Cryptosporidium* were the most significant contributors to gastroenteritis. Together, rotavirus (11%), norovirus (10%), astrovirus (7%), *Giardia* (8%) and *Cryptosporidium* (3%) accounted for 39% of the gastroenteritis incidence reported in the KIzSS network. We estimated that 52.000 day care-attending children experience gastroenteritis due to infection with these five enteropathogens in the Netherlands every year.

Which DCC characteristics and practices are associated with a high/low gastroenteritis incidence in DCCs? (II.3)

The weekly incidence of gastroenteritis events (chapter 3) and the weekly prevalence of the five major gastroenteritis-causing enteropathogens (chapter 7) enabled us to identify putative risk factors (general and/or pathogen-specific) for gastroenteritis at the level of the DCC in **chapter 8**. Factors associated with a high gastroenteritis incidence were: large capacity, crowding, having animals, sandpits, paddling pools, dedicated nappy changing areas, rotating staff among child-groups, and not cleaning bed linen or toys daily.

Factors associated with a low gastroenteritis incidence were: disinfecting fomites with chlorine, cleaning vomit with paper towels and cleaner, cohorting and excluding ill children and staff.

Conclusion

The clinical and economic impact of gastroenteritis related to Dutch DCCs is substantial, particularly among the very young attendees. Attending a DCC roughly doubles a child's probability of experiencing an episode of gastroenteritis that requires a visit to a general practitioner or hospital. A child might experience a lower risk of hospitalization for gastroenteritis after 12 months of attendance compared to a child that never attends day care, but only if the child starts attending day care before the age of one. In addition, this protective effect extends throughout, but not after the preschool years. The average societal costs for care and treatment of an episode of gastroenteritis experienced by a DCC-attending child are twice as high as for a non-DCC attending child. The impact of DCC-related gastroenteritis might be even more substantial if further research proves that asymptomatic day care-attendees contribute to the transmission of enteropathogens both within and beyond the borders of the DCC. The transmission potential of asymptomatic DCC children is currently under investigation. A significant proportion of gastroenteritis can be attributed to the circulation of five enteropathogens in the DCC. Improved implementation of existing DCC practices that are associated with circulation rates of these and other enteropathogens would theoretically not only reduce the disease burden of DCC-related gastroenteritis, but also generate substantial cost savings from a societal point of view. Therefore, future research might focus on

designing intervention studies that determine whether improved implementation of DCC risk factors as identified in this thesis is effective and feasible in reducing gastroenteritis in the Dutch DCC setting. Efforts are currently ongoing amongst stakeholders to determine whether increased control of DCC-related infectious diseases is desirable in the Netherlands.

Samenvatting

Dit proefschrift verschaft inzicht in de epidemiologie van gastro-enteritis met betrekking tot Nederlandse kinderdagverblijven. Het is het resultaat van verscheidene nationale en internationale studies waarin gegevens zijn verzameld en geanalyseerd uit nationale (huisarts)registraties en online surveillance systemen voor kinderdagverblijven, de algemene bevolking en jonge gezinnen. Het proefschrift richtte zich op twee kernvragen over de impact en risicofactoren van gastro-enteritis gerelateerd aan kinderdagverblijven:

I Wat is de impact van gastro-enteritis gerelateerd aan kinderdagverblijven?

De eerste kernvraag is uitgewerkt in drie onderzoeksvragen die behandeld worden in **hoofdstuk 3-5**:

- I.1 Wat is de incidentie van episodes van gastro-enteritis onder kinderen op het kinderdagverblijf, en hoe verhoudt hun huisartsenbezoek zich tot dat van kinderen in de algemene bevolking? (**hoofdstuk 3**)
- I.2 Wat zijn de directe en langdurende effecten van kinderdagverblijf opvang op ziekenhuisopname van een kind met gastro-enteritis, en zijn deze effecten afhankelijk van de hoeveelheid tijd die een kind in het kinderdagverblijf doorbrengt, de leeftijd waarop een kind voor het eerst naar de kinderopvang gaat, en het type verblijf dat het kind bezoekt? (**hoofdstuk 4**)
- I.3 Wat zijn de maatschappelijke kosten voor zorg en behandeling van een kind met gastro-enteritis, en verschillen deze kosten tussen kinderen die wel of niet naar het kinderdagverblijf gaan? (**hoofdstuk 5**)

II Welke risicofactoren zijn geassocieerd met gastro-enteritis op kinderdagverblijven?

De tweede kernvraag is uitgewerkt in drie onderzoeksvragen die behandeld worden in **hoofdstuk 6-8**:

- II.1 Wat zijn de prevalenties van, een reeks van, enteropathogenen onder kinderen op het kinderdagverblijf, en wat is het verband met leeftijd, het seizoen en klinische symptomen? (**hoofdstuk 6**)
- II.2 Wat zijn de relatieve bijdragen van deze enteropathogenen aan de gastro-enteritis incidentie op het kinderdagverblijf? (**hoofdstuk 7**)
- II.3 Welke kinderdagverblijfskenmerken en -werkwijzes zijn geassocieerd met een hoge/lage gastro-enteritis incidentie op het kinderdagverblijf? (**hoofdstuk 8**)

Een groot deel van de onderzoeksvragen in dit proefschrift (onderzoeksvragen I.1, II.1, II.2 en II.3) konden beantwoord worden met gegevens die werden verzameld in ons landelijke netwerk van kinderdagverblijven (KIzSS). Het doel, ontwerpen van een surveillancenetwerk voor het in kaart brengen van de klinische en microbiologische aspecten van gastro-enteritis werd behandeld in **hoofdstuk 2**. Niet alle vragen konden echter onderzocht worden met KIzSS gegevens. Zo vereiste het beantwoorden van onderzoeksvraag I.2 (**hoofdstuk 4**) een veel langere periode van follow-up en steekproefomvang van kinderen dan KIzSS kon bieden. Onderzoeksvraag I.2 werd daarom beantwoord met behulp van Deense gegevens (Childcare database). Voor het beantwoorden van onderzoeksvraag I.3 (**hoofdstuk 5**) waren gegevens nodig van gastro-enteritis onder gezinnen met jonge kinderen. Voor deze vraagstelling werd daarom een online enquête ontwikkeld en uitgevoerd onder gezinnen met kinderen in de leeftijd 0-48 maanden (G&G).

Wat is de incidentie van episodes van gastro-enteritis onder kinderen op het kinderdagverblijf, en hoe verhoudt hun huisartsbezoek zich tot dat van kinderen in de algemene bevolking? (I.1)

In **hoofdstuk 3** vonden we dat symptomen van gastro-intestinale infecties (gastro-enteritis, 387 episodes per 1000 kind-jaar) en niet van influenza-achtige ziektebeelden (247 per 1000 kind-jaar) of huidinfecties (59 per 1000 kind-jaar) het meest gemeld werden door kinderdagverblijven. Gastro-enteritis kwam

ongeveer twee keer zo vaak voor onder 0-2 jarigen dan onder 2-4 jarigen (IRR 1.7 [95%CI: 1.5-1.9]). Kinderen in kinderdagverblijven bezochten hun huisarts bijna twee keer zo vaak voor gastro-enteritis dan we zouden verwachten op basis van landelijke schattingen (NIVEL) voor 0-4 jarigen (IRR: 1.7 [95%CI: 1.4-2.0]). Verder gaf een enquête onder kinderdagverblijven in dit hoofdstuk aan dat er ruimte leek voor verbeteringen van relatief eenvoudige infectieziekte preventie maatregelen op het kinderdagverblijf. Zo gaven kinderdagverblijven aan niet altijd de handen van kinderen te wassen voor het eten (34%) of na een wc-bezoek (15%), en meldden ze dat ze de toiletten en keuken niet dagelijks schoonmaakten (17%).

Wat zijn de directe en langdurende effecten van kinderdagverblijf opvang op ziekenhuisopname van een kind met gastro-enteritis, en zijn deze effecten afhankelijk van de hoeveelheid tijd die een kind in het kinderdagverblijf doorbrengt, de leeftijd waarop een kind voor het eerst naar de kinderopvang gaat, en het type verblijf dat het kind bezoekt? (I.2)

In **hoofdstuk 4** bekeken we of kinderopvang directe en langdurende gevolgen had op ernstige episodes van gastro-enteritis die leidden tot ziekenhuisopname. Het risico op hospitalisatie voor gastro-enteritis werd geschat met gegevens uit twee grote cohorten van Deense kinderen die nog niet (< 6 jaar oud) of al wel naar de basisschool gingen (6-10 jaar oud). Samen telden deze twee cohorten 443,872 kinderen,

21,038 ziekenhuisopnames en 1.742.284 kinderen (1994-2011). We vonden dat kinderen die tot 12 maanden hadden doorgebracht in kinderdagopvang een verhoogd risico liepen op ziekenhuisopname voor gastro-enteritis in vergelijking tot kinderen die geen enkele vorm van kinderopvang genoten. Dit risico bleek het hoogst (HR: 1.8 [95%CI: 1.5-2.0]) vlak na het eerste bezoek aan het kinderdagverblijf en nam daarna langzaam af. Na 12 maanden van kinderopvang bleek het bezoeken van een kinderdagverblijf geassocieerd te zijn met een lager risico op ziekenhuisopname. Dit verlaagde risico werd echter alleen waargenomen bij kinderen die voor hun eerste levensjaar met kinderopvang in aanraking kwamen (HR: 0.8 [95%CI 0.7-0.9]). Bovendien was het verlaagde risico alleen aanwezig tijdens en niet na de kinderopvangjaren.

Wat zijn de maatschappelijke kosten voor zorg en behandeling van een kind met gastro-enteritis, en verschillen deze kosten tussen kinderen die wel of niet naar het kinderdagverblijf gaan? (I.3)

In **hoofdstuk 5** gaven we schattingen voor de (verschillen in) maatschappelijke kosten van een gastro-enteritis episode voor een kind dat wel en niet naar het kinderdagverblijf gaat. We stelden vast dat met name erg jonge kinderdagverblijf kinderen (<1 jaar) meer episoden van gastro-enteritis doormaakten dan hun leeftijdsgenoten die thuis werden opgevangen (aIRR 1.6 [95%CI: 1.1-2.7]). Echter, de gemiddelde maatschappelijke kosten die gepaard gingen met de zorg en behandeling

van een dergelijke episode van gastro-enteritis waren met €215.45 ([95%CI: €115.69-€315.02]) ruim twee keer zo hoog dan voor een kind dat niet naar het kinderdagverblijf ging. De hogere kosten waren voornamelijk toe te schrijven aan de verschillen in productiviteitsverlies die ouders ervoeren als ze voor hun zieke kind moesten zorgen. Huishoudens die gebruik maakten van kinderdagopvang bestonden vaker uit twee werkende ouders met een hoger gezamenlijk inkomen. De maatschappelijke kosten die konden worden toegeschreven aan de behandeling en zorg van kinderdagverblijfgelateerde episoden van gastro-enteritis werden geschat op 25 miljoen euro per jaar.

Wat zijn de prevalenties van, een reeks van, enteropathogenen onder kinderen op het kinderdagverblijf, en wat is het verband met leeftijd, seizoen en klinische symptomen? (II.1)

In **hoofdstuk 6** beschreven we de prevalentie van een breed scala aan enteropathogenen in de maagdarmflora van kinderen in kinderdagverblijven. We relateerden de aanwezigheid van deze enteropathogenen aan de leeftijd en gastro-enteritis symptomen van het kind en het seizoen. In 78% van de 5197 geanalyseerde monsters vonden we een of meer enteropathogenen. De kans op het vinden van een viraal of bacterieel enteropathogeen nam af met de leeftijd van het kind, terwijl het omgekeerde verband werd gevonden voor parasitaire enteropathogenen. Virale enteropathogenen vertoonden jaarlijkse seizoensfluctuaties met piekprevalenties

gedurende de wintermaanden, terwijl bacteriële enteropathogen juist meer gedetecteerd werden gedurende de zomermaanden. Parasitaire enteropathogenen vertoonden geen duidelijke seizoenfluctuaties. 95.4% van monsters kwamen van kinderen die geen symptomen van gastro-enteritis vertoonden op het moment van monsterafname. Een meerderheid van de gastro-intestinale infecties onder kinderen op het kinderdagverblijf bleek dus asymptomatisch te verlopen.

Wat zijn de relatieve bijdragen van deze enteropathogenen aan de gastro-enteritis incidentie op het kinderdagverblijf? (II.2)

Hoofdstuk 7 richtte zich op het schatten van het percentage kinderen op het kinderdagverblijf dat gastro-enteritis doormaakte (hoofdstuk 3) als functie van de circulatie van enteropathogenen op het kinderdagverblijf (hoofdstuk 6). We vonden dat rotavirus, norovirus, astrovirus, *Giardia* en *Cryptosporidium* de grootste veroorzakers leken te zijn van gastro-enteritis. Gezamenlijk verklaarden rotavirus (11%), norovirus (10%), astrovirus (7%), *Giardia* (8%) en *Cryptosporidium* (3%) 39% van de gastro-enteritis incidentie gemeten in het KIzSS netwerk. Naar schatting maken 52.000 kinderen in kinderdagverblijven elk jaar gastro-enteritis door als gevolg van een infectie met een van deze vijf enteropathogenen.

Welke kinderdagverblijfskenmerken en -werkwijzes zijn geassocieerd met een hoge/lage gastro-enteritis incidentie op het kinderdagverblijf (II.3)

De wekelijkse incidentie van gastro-enteritis episodes (hoofdstuk 3) en de wekelijkse prevalentie van de vijf belangrijkste veroorzakers van gastro-enteritis (hoofdstuk 7) maakten het mogelijk om risicofactoren (generiek en/of enteropathogeen-specifiek) voor gastro-enteritis in het kinderdagverblijf te onderzoeken in **hoofdstuk 8**. Factoren geassocieerd met een hoge gastro-enteritis incidentie waren: grote kinderdagverblijven met een hoge concentratie aan kinderen, de aanwezigheid van dieren, zandbakken, zwembadjes, centrale verschoonruimten, het roteren van medewerkers over kind-groepen en het niet dagelijks schoonmaken van beddengoed en speelgoed. Factoren geassocieerd met een lage gastro-enteritis incidentie waren: het desinfecteren van oppervlakken met chloor, het opruimen van braaksel met papieren doekjes en allesreiniger, het gescheiden opvangen van zieke kinderen en het weren van zieke kinderen en medewerkers.

Conclusie

De impact van gastro-enteritis gerelateerd aan Nederlandse kinderdagverblijven is aanzienlijk, vooral onder hele jonge kinderen. Het bezoeken van een kinderdagverblijf verdubbelt ruwweg de kans dat een kind een episode van gastroenteritis doormaakt waarvoor het naar de huisarts of ziekenhuis moet. Na 12 maanden van kinderopvang ervaart een kinderdagverblijf kind een lager risico op ziekenhuisopname voor gastroenteritis dan een niet-kinderdagverblijf kind, maar alleen als het voor het eerste levensjaar start met kinderopvang. Daarnaast lijkt dit beschermend effect beperkt te blijven tot de kinderopvangjaren. De gemiddelde maatschappelijke kosten die gepaard gaan met de zorg en behandeling van een episode van gastro-enteritis van een kind dat naar het kinderdagverblijf gaat zijn twee keer zo hoog als van een kind dat niet naar het kinderdagverblijf gaat. De impact van gastroenteritis gerelateerd aan kinderdagverblijven is mogelijk nog groter als toekomstig onderzoek aantoont dat asymptomatisch geïnfecteerde kinderen in de kinderdagopvang bijdragen aan de transmissie van enteropathogenen binnen én buiten de grenzen van het kinderdagverblijf. Dit wordt momenteel onderzocht. Een aanzienlijk deel van de gastroenteritis incidentie wordt in dit proefschrift toegeschreven aan de circulatie van vijf enteropathogenen op het kinderdagverblijf. Verbeterde implementatie van bestaande maatregelen die in dit proefschrift samenhangen met een verlaagde circulatie van deze en andere enteropathogenen zou theoretisch niet alleen

kunnen leiden tot een reductie van de ziektelast, maar ook tot substantiële maatschappelijke kostenbesparingen. Vervolgonderzoek zou zich daarom kunnen richten op het ontwikkelen van interventiestudies die verbeteringen in de implementatie van de in dit proefschrift gevonden risicofactoren toetsen op hun effectiviteit en haalbaarheid in Nederlandse kinderdagverblijven. Momenteel wordt door het Rijksinstituut voor Volksgezondheid en Milieu bekeken wat het draagvlak is voor het verder terugbrengen van de gastro-enteritis ziektelast op kinderdagverblijven in Nederland.

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Remko

Curriculum Vitae

Remko Enserink werd geboren op 22 september 1983 in Wageningen. Na vijf jaar van zijn jeugd te hebben doorgebracht in Afrika, Tanzania, behaalde hij in 2002 zijn vwo diploma in Natuur en Gezondheid aan het Streek Lyceum in Ede. Na zijn propedeuse in Bos- en Natuurbeheer, studeerde hij biologie aan de Wageningen Universiteit. Gedurende zijn studie was hij lid van de studentenvereniging SSR-W en actief in verschillende organisatorische comités en reisde hij 7 maanden door Australië en Nieuw-Zeeland. Hij studeerde in 2009 af. In hetzelfde jaar startte hij een gecombineerde PhD positie aan het Rijksinstituut voor Volksgezondheid en Milieu en het Universitair Medisch Centrum Utrecht. Gedurende zijn PhD was hij actief binnen het PhD-bestuur van het RIVM, reisde hij af naar Denemarken om te werken met collega-wetenschappers en organiseerde hij een internationale workshop. Hij woont nu in Boston, VS.

