Epidemiology of gastroenteritis in the Netherlands

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CHAPTER 1

INTRODUCTION
In this introduction, the public health problem of gastroenteritis is discussed. It is focused on the information required for prevention, and methods of collecting this information.

**Introduction**

Gastroenteritis is an inflammation of the gastrointestinal tract, which can be caused by a wide range of infectious and non-infectious causes. Gastroenteritis is defined by its clinical picture, characterised mainly by diarrhoea and vomiting. Worldwide, gastroenteritis causes substantial mortality and morbidity. An estimated 2.2 million deaths occur annually as a result of diarrhoeal diseases (4% of total deaths), mainly in children under 5 years of age in Africa and Southeast Asia [1]. In industrialized countries the mortality due to the gastroenteritis is limited, primarily as a result of improved hygiene and sanitation, an improved nutritional status of the population, and adequate and timely treatment. In these countries, most gastroenteritis episodes are relatively mild and self-limiting, but due to the high incidence, the morbidity remains high [2]. Apart from direct illness resulting from gastrointestinal infections, several complications can occur, such as dehydration as a result of diarrhoea and vomiting, Haemolytic Uraemic Syndrome (HUS) after an *E. coli* O157-infection, Guillain-Barré syndrome following *Campylobacter* infection, and reactive arthritis following several bacterial infections [3].

In developed countries, one of the main concerns of gastroenteritis is the economical burden [4]. Costs are generated not only by patients seeking medical care, but also by persons missing work due to their illness, or persons missing work caring for an ill person. Although the costs per ill patient are limited, the total costs are substantial due to the high number of persons affected [4,5].

**Case definition**

Although gastroenteritis is defined by its clinical picture, there is no internationally accepted case definition. WHO has a case definition for diarrhoea (three or more loose stools in 24 hours), but this does not include syndromes characterised mainly by vomiting. Syndromes that overlap largely with gastroenteritis and are often considered synonyms are infectious diarrhoea, diarrhoeal disease, and infectious intestinal disease. Foodborne infections are often falsely considered a synonym for gastroenteritis. Several pathogens causing gastroenteritis do not (solely) transmit through food (e.g. rotavirus), and several foodborne pathogens do not cause gastroenteritis (e.g. *Listeria*, Hepatitis A-virus). Based on the clinical picture alone, it is not possible to distinguish infectious from non-infectious causes. Although we are aware that non-infectious gastroenteritis cases can be included in the studies presented in this thesis, we focus on the infectious causes only. A community-based study in 1991 showed that the incidence of gastroenteritis increased fourfold when widening the case definition [6]. Therefore, the lack of an internationally accepted case definition makes comparisons between countries very difficult, and
comparisons are only possible when the case definitions used are clearly presented and differences are taken into account.

**Microbiological etiology of gastroenteritis**

The infectious causes of gastroenteritis include a wide range of bacteria, viruses and parasites. Because different pathogens have different transmission routes, the possibilities for prevention are different for each pathogen. Therefore, to design efficient prevention policies, information on the relative importance of the pathogens is needed along with information about the relative importance of different modes of transmission for the various pathogens.

In previous studies on gastroenteritis, only in a minority of cases, an infectious organism could be detected [7-12]. Also, in cases where a pathogen was detected, it was not certain if this pathogen was the cause of the symptoms, because only limited information is available about the prevalence of these pathogens in healthy individuals. The absence of a detectable pathogen can have several causes. The cause might be non-infectious, the cause can be a known pathogen which is not detected, due to the moment of sampling, the sensitivity of the detection method, or the condition of the sample, or the symptoms might be related to an infection with a unknown pathogen of which the association with gastroenteritis is not established yet. In recent years, several pathogens have been added to the list of causes of gastroenteritis, such as *Cyclospora* and torovirus [13,14]. Distinguishing different infections based on the clinical picture will never be entirely possible, however, clinical symptoms can be indicative for the infectious organisms. So far, pathogens known to be associated with gastroenteritis include *Salmonella*, *Campylobacter*, *Yersinia*, *Shigella*, pathogenic *E. coli*, *Bacillus cereus*, *Staphylococcus aureus*, *Clostridium perfringens*, rotavirus, adenovirus type 40/41, astrovirus, Norwalk-like viruses, Sapporo-like viruses, torovirus, *Giardia lamblia*, *Entamoeba histolytica*, *Cryptosporidium*, *Cyclospora*. Several other pathogens, such as *Dientamoeba fragilis*, have been associated with gastroenteritis, but their ability to cause gastroenteritis has not been proven yet. For most of these pathogens, the incidence in the Dutch population nor in most other populations is unknown.

**Transmission**

The main transmission routes for pathogens causing gastroenteritis are foodborne, waterborne, direct feco-oral transmission, and transmission through contact with animals or animal products. Clarifying the relative importance of each of these transmission routes for specific pathogens will focus preventive activities and make estimates of their effect possible.

Gastroenteritis can occur in individual persons and in related cases involved in outbreaks. Some settings and some pathogens are more prone to induce outbreaks than others. Point source outbreaks and outbreaks spreading from person-to-person both occur.
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Pathogens that are less vulnerable to environmental influences, that need low infectious doses to cause illness, that have a high case-infection ratio, and for which the majority of the population is vulnerable, such as Norwalk-like viruses, are likely to cause outbreaks (epidemic gastroenteritis), whereas pathogens like *Campylobacter*, that need specific environmental circumstances to survive, hardly ever cause outbreaks and are mainly seen as separate cases, also called endemic gastroenteritis. Because, we can never be sure that an individual patient is not related to other cases, the terms individual and sporadic cases are avoided.

**Developments influencing the incidence of gastroenteritis**

Changes in human demographics and behaviour, changes in the food production system and changes in internal travel and trade are likely to have an effect on the incidence of gastroenteritis worldwide and in The Netherlands. Changes in demographics include an increase in households where both adults are working, resulting in higher day-care centre attendance, more eating-out and a higher consumption of ready-to-eat meals [15]. Day-care centres are high-risk settings because of the lack of toilet training of many of the children attending and because of grouping of children lacking immunity [16-19]. The number of children attending whole-day day-care centres has increased fivefold from 1989 to 1998 in the Netherlands [20]. Another demographic change is the ageing of the population, resulting in a large group of relatively vulnerable elderly [21,22]. The percentage of the population older than 80 years has increased almost 5 fold in the last century and is expected to increase more in the next decades [20]. In addition, an increasing percentage of the population is living in homes for the elderly, where again transmission of infections is high, due to crowding, and shared toilet facilities.

Recently the awareness has grown that the intensivation and scale enlargement of the Dutch stock and cattle breeding has passed its limits, with regard to treatment of the animals, the environment, public health risks, and control. Therefore, a commission set up by the Dutch government has formulated a plan to redesign this sector in a less intensive one, on a smaller scale, focusing on durability [23]. Because cattle and poultry are a major source of infections with zoonotic gastrointestinal pathogens, changes in this sector are expected to affect the incidence of infections in humans.

In agriculture, a globalizing trend is occurring, where products grown in one country are consumed all over the world. This globalization of the trade in food products might result in infections rapidly spreading over the world and causing international outbreaks [24-26]. In addition, infections can rapidly spread between countries with humans as the reservoir. Intercontinental traffic has increased rapidly over the past decades, as have vacations to tropical countries [20]. Increased traffic to and from countries where several pathogens that cause severe disease (such *Shigella dysenteriae* and *Vibrio cholerae*) are still endemic poses a risk of reintroduction of these pathogens in developed countries.
In general, an increasing trend in the prevalence of foodborne infections is reported [27].

**Implemented prevention activities**

Prevention can focus on eliminating the pathogen from its reservoir, on stopping transmission from the reservoir to humans, or on preventing illness resulting from infection. The characteristics of the pathogens and the feasibility of different approaches need to be considered before deciding which preventive actions are the most efficient. Several preventive activities have already been implemented in the past years. In 1996, a programme was initiated by the product boards for livestock, meat and eggs (PVE) to decrease infection with *Salmonella Enteritidis* in laying hens to 5%, and to decrease infection with *Salmonella* and *Campylobacter* in meat chicken to 10% and 15% respectively, in three years. The aim of the programme was to decrease the number of infections in humans, because poultry is considered to be the main infection source for *Salmonella Enteritidis* and *Campylobacter* infections in humans. The programme consisted mainly of improving hygiene in poultry farms, continuous monitoring of infections, eliminating infected poultry from the production chain, and decreasing the contamination in the slaughtering process [28,29]. In July 1997, the programme was fully implemented. The studies described in this thesis were partly initiated to evaluate the effects of these programmes on infections in humans. In 2001, a new programme is being prepared to decrease *Salmonella* infections in pigs.

Since 1995, all organizations that work in food preparation, conservation, transportation and distribution have to work according to Hazard Analysis Critical Control Points (HACCP) directives, or, for smaller businesses, follow a standard hygiene code. Control is performed by the Inspectorates for Health Protection and Veterinary Public Health. For private households a separate hygiene code was developed by the Netherlands Nutrition Centre [30].

For rotavirus, preventive activities worldwide are mainly focused on the development of a vaccine. This viral pathogen is one of the major causes of death due to dehydration in developing countries [31]. Also, in developed countries, rotavirus is a major cause of hospitalisations for dehydration in young children. Symptomatic infections occur mainly in young children, whereas infections in adults are usually asymptomatic due to protective immunity acquired at an earlier age [32]. For these reasons, a feasible and effective approach was the development of a vaccine. On 31 August 1998, the first rotavirus vaccine (RRV-TV) was licensed and introduced in the United States [33]. Due to a possible association of vaccination with intussusception, the vaccine was withdrawn from the market and several studies were initiated to investigate this association [34-37].

For Norwalk-like virus, a similar approach was chosen, in spite of the lack of knowledge concerning immunity following infection. Vaccines are currently being developed, but no vaccine has been licensed yet [38].
**Treatment and diagnostics**

The guidelines for general practitioners in The Netherlands concerning gastroenteritis focus mainly on evaluating the hydration situation of the patient [39]. Microbiological testing is recommended only for severely ill patients for whom hospitalisation might follow, and for patients who are at increased risk of infecting others. The first microbiological tests recommended are for *Salmonella*, *Shigella*, and *Campylobacter*. Testing for *E.coli* or viral pathogens are advised against for acute diarrhoea. Testing for protozoa is advised when the patients has symptoms for 10 days or more, when the patients has been in the (sub) tropics or when the patient has a reduced resistance. The guidelines advise treatment with oral rehydration solution (ORS) only for persons at increased risk of dehydration. For some pathogens, antimicrobial treatment is recommended: for *Giardia lamblia* and *Entamoeba histolytica*.

For several pathogens, diagnostic testing methods have improved greatly over the past years. For instance, for Norwalk-like viruses and Sapporo-like viruses, a Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) was developed which greatly increases the sensitivity of testing compared to the formerly used Electron Microscopy [40,41]. For rotavirus, a commercial ELISA-test kit is now available that enables regional laboratories without a specified virological laboratory to perform these tests. More sensitive techniques can help decrease the diagnostic deficit.

For many pathogens, sero- or genotyping methods are currently available, that can help link specific reservoirs to human infections. For instance for *Salmonella*, a comparison of serotyping data from humans and from different animals species provides insight in the sources of human infections with *Salmonella* [42]. Typing techniques are also valuable in detecting clusters of patients and in linking the source to the patients, which is often applied in outbreak investigations as an addition to epidemiological investigation.

**Required information for prevention**

To estimate the magnitude of the total problem, estimates of the incidence of gastroenteritis and the duration and severity of symptoms are required. In general, the incidence is the factor most likely to be subject to change over time and differ between countries, whereas the duration of symptoms and the severity will be more stable in industrialized countries. Therefore, information about the incidence needs to be collected more frequently and country-specific factors should be considered when extrapolating data from other countries, whereas for other estimates, information from earlier years or in other comparable countries can be used.

To collect information about the incidence of the different pathogens, epidemiological information needs to be supplemented with microbiological information. Establishing the importance of different pathogens requires information about the proportion of gastroenteritis caused by this pathogen, and again the severity of disease following
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Infection. Furthermore, information about the relative importance of the different transmission routes of this pathogen is important to determine the feasibility of prevention.

Sources of information

Because gastroenteritis is, in general, a relatively mild disease, only a small proportion of patients seeks medical care and can be traced in the health care system (Figure 1). To be able to use information from patients included at some level in the health care system for estimates about the total burden of gastroenteritis, we first need to study the selection that has occurred in consulting patients compared to all cases. Because only a small proportion of gastroenteritis cases need a hospitalisation or treatment by a specialist, the most appropriate level for monitoring gastroenteritis is the general practitioner, who is also the gate-keeper for more advanced care in the Netherlands [43].

![Pyramid of sources for surveillance of gastroenteritis](image-url)

**Figure 1. Pyramid of sources for surveillance of gastroenteritis**

Laboratory-based surveillance uses existing information obtained for the treatment of an individual patient. Therefore, it provides data on a continuous basis, which enables the study of trends in the different pathogens. Because only an unknown selection of patients is covered by a laboratory surveillance system, no information about the magnitude of the problem can be derived from this. Only a minority of patients with gastroenteritis seeks medical care, and only in a minority of cases the attending physician request microbiological testing of which only a proportion leads to a positive result. When interpreting the data from laboratory-based surveillance, one has to realize that trends can result from actual changes in the incidence of an organism, but also from changes in consultation behaviour, changes in laboratory requests to confirm the diagnosis, or changes in the diagnostic method [43].

In the Netherlands, a laboratory-based surveillance system exists for the bacterial pathogens *Salmonella*, *Campylobacter*, *Yersinia*, *Shigella* and *E. coli* O157, and a separate
system for rotavirus [42,44]. In the bacteriological surveillance, 16 regional public health laboratories report the number of samples tested and the number of positive results on a weekly basis to the National Institute of Public Health and the Environment (RIVM). *Campylobacter* was included from May 1996, and *Yersinia* was included until 1997. Additionally, for *Salmonella* and *E.coli* O157 all isolates are sent to the RIVM for serotyping, accompanied by the age and sex of the patient. For *E.coli* O157 an intensified surveillance system exists in which, for all positive samples, the patient is traced and interviewed. In addition, information from serotyping of samples from different reservoirs, such as farm animals and food products are available at the RIVM. For viral pathogens, a separate system exists in which 17 virological laboratories report the number of positive samples on a weekly basis. Rotavirus is the only viral pathogen included causing gastroenteritis. The majority of these samples are from hospitalised patients. Although this provides information on the total number of positive samples, no information is available on the subtypes of rotavirus that circulate. In addition, an electronic surveillance system is functional in the Netherlands, including more laboratories every year. In this system, called ISIS (Infectious diseases Surveillance Information System), all laboratory results are sent to the RIVM electronically every 24 hours. In 2001, 10 laboratories are linked to the RIVM database.

![Figure 2. Laboratory surveillance 1991-2000. number of positives for Campylobacter, Salmonella, Shigella and Yersinia, and the number of stools tested. For Campylobacter surveillance started in 1997, Yersinia was excluded in 1996.](image)

The number of stool samples tested and the number of positives remains fairly constant over the years, except for *Salmonella* that has shown a decreasing trend from 1996 onwards (figure 2). This trend can almost entirely be attributed to a decrease in *Salmonella* Enteritidis.
Consulting cases

In the Netherlands, the general practitioner (GP) provides the first line treatment and is the gatekeeper to more specialized care. The majority of cases with gastroenteritis seeking medical care consult a general practitioner, and for most cases no additional care is required.

The Netherlands Institute for Health Services Research (NIVEL) maintains a network of sentinel general practices that participate in the continuous morbidity registration [45]. Gastroenteritis was included in the continuous morbidity registration in 1992-1993 and from 1996 onwards. This surveillance system provides information on consultations for the clinical syndrome gastroenteritis, as defined by the case definition mentioned at the end of this chapter. No information is obtained about the causing pathogens. Additional information was obtained in case studies in 1992 and 1993 [12], and in a pilot study in two cities in the Netherlands (Amsterdam and Helmond) from 1987-1991 [11]. These studies estimated the incidence of gastroenteritis at 9 and 15 per 1000 person years, respectively. All stool samples were tested for Salmonella, Campylobacter, and Shigella which were detected in 5%, 14%, and 2%, respectively (Amsterdam Helmond 1987-1991) and 4%, 15%, and 1%, respectively (national study 1992-1993). In addition, samples from 1991 in the study in Amsterdam and Helmond were tested for rotavirus group A and adenovirus type 40/41, which were detected in 6% and 2%, respectively. In both these studies, a pathogen could be detected in less than one third of cases. No information about controls was obtained, so no comparisons could be made between cases and healthy persons.

Non-consulting cases of gastroenteritis

A community-based cohort study is the most appropriate method to obtain information on the incidence of gastroenteritis in the community. Even though gastroenteritis is in the top ten of diseases with the highest incidence in the Netherlands [46], a large cohort has to be included to obtain a sufficient number of cases. Therefore these studies are very expensive and time-consuming.

In May, June and July of 1991, a population-based study on gastroenteritis was performed in four municipal health service regions of The Netherlands [6,7]. Based on this study, the incidence of gastroenteritis was estimated at 45 per 100 person years. The incidence decreased with age from 95 per 100 in the age group of 0-4 years to 30 per 100 in the age group of 60 years and older. Salmonella was detected in 1.5% of cases, Campylobacter in 4.6%. In total, in 94% of cases no etiological agent could be detected. Also, the seasonal trends in pathogens causing gastroenteritis make the interpretation of data covering only three months of the year very difficult. Furthermore, non-response was large and selective in this study. In total, 20% of the cases consulted a general practitioner, half of which by telephone. A comparison of the results of this study with the results of studies performed in general practices, shows that this study estimates a 5-fold higher incidence of consulting cases than the studies in general practice. Since both studies were not performed in the same year, the results cannot be directly compared.
same region, nor in the same period, no hypotheses about the discrepancy in incidences can be tested. Although this study did produce the first estimate of the incidence of gastroenteritis in the Dutch community, crucial information about many pathogens was still lacking [7].

**Hospital discharge diagnosis, mortality registration, statutory notifications**

Hospital discharge diagnoses are recorded by the SIG/Prismant for all hospitals in the Netherlands, based on ICD-codes. The codes 001-009 and 558 all include gastroenteritis cases, but are not restricted to gastroenteritis. In some of these codes the microbiological agent is included, however, most cases by far, are recorded as caused by unknown non-infectious agents (60%) and non-specified infectious agents (10%). Mortality registration has to contend with the same difficulties in coding as the discharge diagnosis. In general, mortality due to gastroenteritis is limited in developed countries.

In The Netherlands, gastroenteritis is notifiable when more than two persons are thought to have been infected by the same source, or when the affected person is working in the food production or distribution, or as a caretaker for others (Figure 3).

![Figure 3. Number of statutory notifications and hospital discharge diagnosis coded as 001-009 and 558, from 1991-2000.](image)

The trends that can be observed in the notifications are most likely due to a change in notification behaviour instead of an actual trend in incidence [47]. The number of discharge diagnosis that include gastroenteritis has remained fairly constant over the years (figure 4). A decrease was observed in the number of hospitalisations for (para)typhoid fever, for diseases due to *Salmonella*, and for diseases due to protozoa and amoeba. However, the less specified ICD-code (of gastroenteritis due to unidentified infectious causes) shows an increase of similar size. Because not much is known about the attitudes of physicians in the coding, we cannot conclude whether *Salmonella* infections have actually decreased or whether they are more often coded under the less detailed code of infectious gastroenteritis.
Outbreaks

A different source of detecting gastroenteritis cases is by studying cases in outbreaks. The Inspectorate for Health Protection and Veterinary Public Health and the Municipal Health Services in the Netherlands are responsible for investigating reported outbreaks. Consumers with symptoms of gastroenteritis that suspect that these symptoms might have been caused by the consumption of food can report this to the Inspectorate for Health Protection and Veterinary Public Health, that investigates these reports, focusing on the (preparation of the) food. Annually, an overview of these outbreaks is composed by the RIVM.

The initial increase in investigated incidents can be attributed to an increasing number of inspectorates participating in the registration. In 1998, a large reorganization from 13 to 5 regional Inspectorates has caused a temporary decrease in the number of incidents reported and investigated. (Figure 4) [47-51]. In 1995 an increase in the number of persons involved was seen.

Outbreaks of gastroenteritis are also reported to Municipal Health Services (MHS), from different sources such as day-care centres, homes for the elderly, or general practitioners who notice a link between different cases. The MHS investigates these outbreaks. There is partial overlap between the outbreaks these two services investigate.

A separate surveillance-project by the National Institute of Public Health and the Environment (RIVM) was initiated in 1995, focusing on NLV in outbreaks with suspected viral gastroenteritis [52,53]. Stool samples of outbreaks investigated by the Municipal Health Services were sent to the RIVM for NLV-testing. In the winter of 1995/1996 an increase was observed in the number of outbreaks caused by NLV, which could mainly be attributed to one new epidemic strain of NLV [41]. This could also have influenced the increase of the number of persons involved as observed in the outbreaks investigated by the Inspectorates for Health Protection and Veterinary Services.
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Information about gastroenteritis from other countries

Although this thesis focuses on gastroenteritis in the Netherlands, information from other countries can (partly) be extrapolated to the Netherlands. The total incidence and the relative contribution of different pathogens can differ between countries, for instance, due to differences in the food patterns, day-care centre attendance, and water purification [54,55]. However, the age distribution and the clinical pictures are likely to be similar in all industrialized countries. Also, incidence data from other countries can be used as references for the incidence estimated for The Netherlands. Furthermore, due to the increasing globalization, the developments in one country influence and are influenced by developments in other countries [56].

A pilot-study in England (Oct 1991-May 1992) estimated the incidence of infectious intestinal disease (loose stools or significant vomiting) in the community at 10 per 100 person years, and in general practice at 2 per 100 person years [10]. A study in Wales (Jan-Mar and Aug-Oct 1992) estimated a higher incidence in the community (48 per 100 person years) and a comparable incidence in general practice (2 per 100 person years), when using a case-definition of three or more loose stools in 24 hours [9]. A study among households in the United States from 1965 to 1971 estimated the incidence of diarrhoea or vomiting at 98 per 100 person years [57]. However, 27% of the episodes coincided with respiratory illnesses, and might have been caused by a respiratory pathogen. A review of the available literature concerning infectious intestinal disease (defined as diarrhoea or vomiting) in the United States in 1988 estimated the incidence in the community at 37 per 100 person years (88 million cases in a population of 270 million), and for consulting cases at 3 per 100 person years [4]. The incidence estimates of gastroenteritis differ greatly between and even within the different countries, whereas the incidence of consulting cases is comparable. The different studies have used very different and, in general, very wide case-definitions, which probably accounts for the different community estimates. The fact that in consulting cases these differences have, for the greater part, disappeared probably results from the fact that for consulting cases the use of a case definition is less relevant, because all cases have severe enough illness to warrant a consultation.

In the English study, the most frequently observed pathogens in general practice-based patients were diarrhoeagenic *E. coli* (15%), *Salmonella* (7%), astrovirus (4%), and *Campylobacter* (3%). *Clostridium perfringens* and *Staphylococcus aureus* were also detected frequently, but even more frequently in controls [10]. In the study of households in the US, bacterial pathogens were detected in 3.3% of cases and rotavirus in 3.8% of cases. Again in the majority of cases no pathogen was detected [8].

Lacking information

Up-to-date information about the incidence of gastroenteritis in the Netherlands is still missing, as is the etiologic information for the majority of cases. Information on trends can be obtained through laboratory surveillance for *Salmonella*, *Campylobacter*, *Shigella*, and
*E. coli* O157, although possible changes in diagnostic practices and consultation behaviour should always be considered. For other pathogens, none or insufficient information is available from laboratory surveillance, due to the lack of a test, or the lack of expertise at regional level, or because testing is hardly ever requested.

To obtain information about the magnitude of the problem, information from laboratory surveillance cannot be used. For *Salmonella* and *Campylobacter* data are available from previous studies on gastroenteritis. However, a preventive programme has been implemented since the most recent information was obtained, and therefore an update for these bacteria is required. For other pathogens, hardly any information is available for The Netherlands nor for other countries.

So far, most of the information for the Netherlands is obtained by general practice-based studies. Therefore, cases included in these studies are a selection of all cases in the community and this selection must be studied before general-practice based data can be extrapolated to community-based estimates. Combining available data from the general practice-based studies and the community-based study has led to contradictory conclusions about the magnitude of the problem. Both studies need to be performed in the same populations and in an overlapping time-period, to enable studying the link between both studies.

To plan effective interventions to prevent gastroenteritis due to specific pathogens, the transmission routes of these pathogens that are relevant in The Netherlands need to be known. Therefore, risk factors and risk groups need to be identified and their impact estimated, in order to predict the effect of a preventive measure. Transmission routes can be studied by studying the cases and their characteristics, and by studying the characteristics of the pathogen in different reservoirs and different settings.

Although the RRV-TV rotavirus vaccine was withdrawn from the market, a new vaccine will probably be available in the near future. To decide whether implementation of this vaccine is effective, information about the epidemiology of rotavirus on different levels of the health care system is needed [44].

To compare the disease burden of a relatively mild but frequent disease like gastroenteritis with that of more severe but less frequent diseases, an objective measure of disease burden is required that includes both the number of cases and the severity of illness. An example of such a measure are Disability Adjusted Life Years (DALYs) or Quality-Adjusted Life-Years (QALYs). The decision on how to spend the limited resources for public health, will partly be based comparisons of the number of DALYs that can be saved by a preventive programme.

The required information was operationalized into the following research questions:

1. What is the incidence of gastroenteritis in the community and in different age groups in The Netherlands? (Chapter 2, 3, 4)
2. What is the relative contribution of the different pathogens to gastroenteritis? (Chapter 2,3)

3. Are there any trends in the incidence of gastroenteritis or of specific pathogens? (Chapter 2.3)

4. What disease-associated or person-associated factors are relevant to distinguish between different infections in gastroenteritis patients? (Chapter 4)

5. What selection of all cases in the community do we study in a general practice-based study? (Chapter 5)

6. What transmission routes are important for the specific pathogens? With a special focus on NLV, SLV and rotavirus. (Chapters 6.7)

7. What is the disease burden of rotavirus-gastroenteritis? Especially focused on hospital admissions due to rotavirus infection. (Chapter 8)

8. What is the disease burden of gastroenteritis estimated in a comparable measure, the DALY, using Campylobacter infection as an example? (Chapter 9)

**Designs of the studies**

Several studies have been conducted to collect data to answer these questions. Details of these studies are described in separate chapters, but a short overview of the studies is presented below:

- From 1996-1999, a general practice-based study was performed in cooperation with the network of sentinel general practices of the Netherlands Institute for Health Services Research. Weekly reporting of all cases consulting for gastroenteritis in all sentinel practices was combined with a nested case-control study in the majority of practices. All cases consulting for gastroenteritis and a consulting control were invited by the general practitioner to complete a questionnaire and submit a stool sample.

- Partly overlapping and in the same population of persons registered at general practices of the network, a prospective community-based cohort study with a nested case-control study, named Sensor, was conducted in 1999. Two consecutive cohorts were followed for six months by weekly reporting of gastroenteritis symptoms and a questionnaire was completed at the start of follow-up. Cases occurring in the cohort were included in a case-control study and a matched control was selected from the cohort. Cases and controls submitted four and two stool samples, respectively, with weekly intervals and completed a questionnaire. Cases also completed a medical diary for four weeks.

These studies used the same case-definition, that was also used in the general practice-based study in 1992 and 1993, which in presented in the box below. Stool samples in these studies were tested for a wide range of pathogens: *Salmonella, Campylobacter, Yersinia, Shigella, Verocytotoxin-producing E.coli, Bacillus cereus, Staphylococcus aureus, Clostridium perfringens*, rotavirus, adenovirus, astrovirus, Norwalk-like viruses (also known as Small Round-Structured Viruses), Sapporo-like viruses, *Giardia lambia, Entamoeba histolytica, Cryptosporidium, Cyclospora, Dientamoeba fragilis* and other non-
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pathogenic parasites. These studies were used to estimate the incidence of gastroenteritis in
the community (Chapter 2) and in general practice (Chapter 3), to study the relative
importance of the associated pathogens (Chapters 2, 3, 4), to study the link between cases in
a general practice-based study and a community-based study (Chapter 5) and to study risk
factors for pathogen-specific gastroenteritis (Chapter 6).

- In addition, the occurrence of an outbreak of Norwalk-like virus gastroenteritis enabled
  the study of the spread of this virus and the impact of a flaw in hygiene (Chapter 7).

- An additional study was performed in cooperation with the Dutch Paediatric
  Surveillance Unit, to estimate the incidence, clinical picture and treatment of children
  admitted with rotavirus. Monthly, a questionnaire was completed by all paediatricians
  about all children admitted with a microbiologically confirmed rotavirus. In addition,
  data from a laboratory-based surveillance system on the weekly number of rotavirus-
  positive samples were combined with data from the National Disease Registry on
  children admitted for gastroenteritis, to obtain an indirect estimate of the incidence of
  hospitalisations for rotavirus. (Chapter 8)

- Data from several epidemiological studies were combined to estimate the disease
  burden of Campylobacter associated gastroenteritis and complications, measured in
  Disability-Adjusted Life Years (DALYs) (Chapter 9).

The results of these studies are described in this thesis, as indicated by the chapter noted
behind every question and behind the description of the studies. When reading through this
thesis, one should take into account that the chapters are not organized according to the
chronological order of the studies.

Case definition of gastroenteritis used:
- three or more loose stool in 24 hours or
- diarrhoea with two or more additional symptoms or
- vomiting with two or more additional symptoms

Additional symptoms could be: abdominal pain, abdominal cramps, nausea, fever, blood in
the stool, mucus in the stool, diarrhoea or vomiting.

An episode had to be preceded by a symptom-free period of two weeks.

The community-based study also included the following criteria:
- three or more times vomiting in 24 hours
References


