Optimizing management of children with acute gastroenteritis: at home and in primary care

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CONTENTS

CHAPTER 1

General introduction

Acute gastroenteritis (AGE) is one of the most common childhood infectious diseases, with an annual incidence of 1.96 episodes per child under the age of five in the Netherlands.[1,2] Although AGE is typically a self-limiting disease, severe symptoms in children can rapidly lead to dehydration.[3] Dehydration is a serious condition and the most important reason for referral to paediatric emergency care.[4] The total costs for children with AGE under five years are estimated at € 77.28 million per year in the Netherlands, predominantly due to referrals, hospitalizations, and parental work absences.[2] Beyond the financial impact, referrals contribute to parental stress, inability in completing household tasks, absence of work and sleep deprivation.[5] There is a critical need to optimize the management for children with AGE, both at home and in primary care, as it is assumed that too many children with AGE at low dehydration risk are referred, or even admitted, to the hospital and receive unnecessary medical interventions.[3,6,7]

This chapter provides an overview of AGE and the challenges associated with its management at home and in primary care. The sequence follows the order of the healthcare professional. We commence with oral rehydration therapy (ORT), followed by (out-of-hours) primary care, safety net advice, and the use of ondansetron. Subsequently, we delve into the broader healthcare system. Finally, an outline of this thesis is provided presenting the objectives of each subsequent chapter.

Acute gastroenteritis

Acute gastroenteritis is characterized by inflammation of the gastrointestinal tract, resulting in the abrupt onset of vomiting and/or diarrhoea, with or without fever.[8] Viruses, particularly rotavirus and norovirus, are the leading cause of AGE in high-income countries.[3] Given its highly contagious nature, AGE often manifests in outbreaks, making it of public health concern.[9] The diagnosis is primarily clinical and stool cultures are rarely necessary.[4] The most important complication is dehydration and its extent can be assessed by the child's weight loss.[3] If the initial weight is unknown, clinical signs can help estimate the degree of dehydration, though these signs have a low predictive value.[10]

The management of children with AGE depends on the severity of symptoms and the risk of dehydration. Most children can be effectively managed at home with guidance or assistance from a healthcare professional as needed.[1] Parents should be encouraged to provide normal fluids in smaller, more frequent portions, and fluid losses should be replenished with ORT.[3] Early home-administered ORT significantly reduces complications, medical visits, hospitalizations, length of hospital stays, and return visits compared to intravenous rehydration.[11–13] Despite these advantages, ORT remains underused, and reasons for this underuse are not fully understood.[8,14,15]

(Out-of-hours) primary care

When parents of children with AGE seek medical attention, they can either contact their regular general practitioner (GP) during standard working hours or utilize out-of-hours primary care services. Out-of-hours primary care centres are regional facilities where multiple GPs work in shifts to provide healthcare services beyond standard working hours.[16] Despite being designed for urgent cases, approximately 80% of out-of-hours contacts relate to non-urgent cases, with parents of sick children classified as frequent users.[17,18] In Norway, the proportion of children under five years with AGE was twice as high at the out-of-ours primary care compared to regular primary care.[19] Specific data on out-of-hours primary care for children with AGE in the Netherlands, including contact and referral rates, as well as ORT prescriptions, are unknown.

Consultations in out-of-hours primary care tend to be more complex than those in regular primary care.[20] One reason for this complexity is the lack of continuity of care, a vital element that facilitates effective communication, ensures adequate follow-up and allows for reconsultations when necessary.[21] Moreover, the absence of an established relationship between GPs and patients at the out-of-hours primary care makes trust, treatment acceptance, and satisfaction more challenging.[20] Knowledge of parental motivations and experiences with the out-of-hours primary care, as well as gaining insight into data on its use and management for children with AGE, could offer opportunities for new interventions aimed at optimizing parental management and the delivery of care in out-of-hours primary care.

Safety net

For children with AGE who do not require a referral, it is recommended that the GP implement a safety net.[1] This safety net should furnish parents with information about the expected disease course, identification of developing red flag symptoms, the importance of ORT use and fluid intake, and guidance on when to seek help.[22] The goal of safety netting is to increase parental confidence in caring for their sick child while ensuring those at risk of complications are re-evaluated. Ideally, safety net advice should be tailored to each child, taking into account the risk of dehydration and the potential for a more complicated course. It has been proven that safety netting reduces primary care revisits for febrile children.[23] Nevertheless, for children with AGE, existing safety net advice remains incomplete due to a lack of knowledge about the expected duration of symptoms in an uncomplicated course and symptom indicators for a complicated course.

Ondansetron

When a GP decides to refer a child with AGE to a paediatric emergency department, a paediatrician may administer ORT along with medication if necessary. Antibiotics and antidiarrheal medications are not recommended for children with AGE.[3] Recently, oral ondansetron, a 5-HT3 serotonin receptor antagonist primarily used to manage chemotherapy-induced vomiting,[24] has been recommended for children with AGE and

vomiting at paediatric emergency departments in order to stop vomiting and therewith improve ORT.[25,26] Compared to placebo, oral ondansetron has demonstrated efficacy in increasing the cessation of vomiting (RR 1.44, 95%-CI 1.29-1.61), improving the feasibility of ORT (RR 1.17, 95%-CI 0.99-1.38), reducing the need for intravenous rehydration therapy (RR 0.41, 95%-CI 0.29-0.59) and decreasing hospitalizations (RR 0.40, 95%-CI 0.19-0.83) in children with AGE and vomiting at emergency departments.[26] In primary care, where 70% of all children with AGE present with vomiting, one suggested reason for the underuse of ORT is that excessive vomiting hinders ORT intake.[8] A safe and effective approach for managing vomiting in primary care could enhance ORT intake and success rates, potentially reducing the number of referrals. However, data on the (cost-)effectiveness of oral ondansetron in primary care are lacking.

Research in primary care is crucial for evidence-based healthcare, yet various challenges exist. The recruitment of children proves challenging, as evidenced by the premature discontinuation of 40% of paediatric randomised controlled trials due to poor recruitment.[27] Moreover, research can be overshadowed by routine clinical practice, as observed in the off-protocol use of GPs.[28] Addressing these challenges is essential to future research involving children in primary care.

Healthcare system

Taking a broader perspective and examining the overall healthcare system, it becomes evident that both an effective public health and clinical care system are essential for addressing the needs of children with AGE. The imperative lies in the ability to proactively prevent and intervene early, thereby mitigating the risk of outbreaks and preventing the symptom deterioration in affected children.[29] The Netherlands and Australia, both top-performing high-income countries where GPs play a pivotal role,[30,31] exhibit variations in the incidence rates and costs per episode for children under five years with AGE (Australia: 1.58 annual episodes; €14,37 per episode | the Netherlands: 1.96 annual episodes; €55,68 per episode).[2,32] Discrepancies in the functions of the healthcare systems may impact the actual delivery of care. Comparative research between these countries holds the potential to strengthen both healthcare systems by identifying, acknowledging, and learning from best practices.[33]

Outline of this thesis

The main aim of this thesis is to optimize the management of children with AGE at home and in primary care. This thesis comprises several chapters, each addressing specific aspects of this aim (Figure 1).

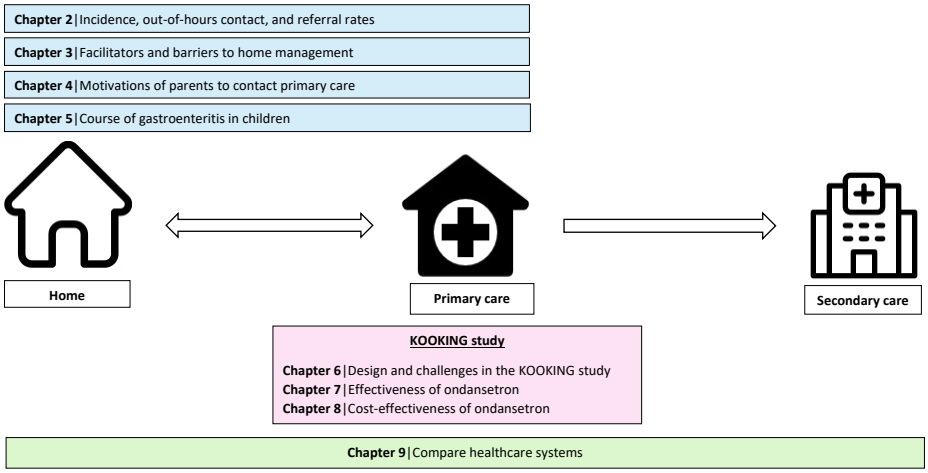

Figure 1. Outline of this thesis

At first in **chapter 2**, we examine trends in the incidence, face-to-face contact, and referrals at the out-of-hours primary care for children with AGE through a retrospective cohort study spanning from 2007 to 2014. In **chapter 3**, we provide a systematic overview of the literature to identify facilitators and barriers to home management for children with AGE, from the perspectives of healthcare professionals and parents. In **chapter 4**, we delve into the motivations of parents when contacting out-of-hours primary care for children with AGE, as well as their expectations and experiences. In **chapter 5**, we provide the symptom course and risk of clinical deterioration for children with uncomplicated AGE who visited the out-of-hours primary care, employing a seven-day prospective follow-up study.

The three subsequent chapters concern the design and analysis of the KOOKING study (KOOKING: *Kosteneffectiviteit ondansetron bij kinderen met acute gastro-enteritis*; translated as *cost-effectiveness ondansetron in children with acute gastroenteritis*). With this randomised controlled trial, we evaluate the (cost-)effectiveness of adding oral ondansetron to standard care for children with AGE at increased risk of dehydration due to vomiting at the out-of-hours primary care. In **chapter 6**, we outline the design of this trial along with the challenges associated with conducting research in children in primary care. In **chapter 7**, we present the effectiveness, and in **chapter 8**, we disclose the results of the cost-effectiveness analysis of this randomised controlled trial. In **chapter 9**, we zoom out and see what one can learn from other healthcare systems. Through a cross-country expert study between Australia and the Netherlands, we evaluate the public health and clinical care management for children with AGE. Finally, in **chapter 10** we conclude this thesis by synthesizing the results of all chapters, conducting a comparative analysis, discussing methodological considerations, exploring clinical implications and presenting strategies for implementation.

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CHAPTER 2

Referral rates for children with acute gastroenteritis: a retrospective cohort study

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ABSTRACT

Background

Hospital admission rates are increasing for children with acute gastroenteritis. However, it is unknown whether this increase is accompanied by an increase in referral rates from GPs due to increased workloads in primary care out-of-hours (OOH) services.

Aim

To assess trends in referral rates from primary care OOH services to specialist emergency care for children presenting with acute gastroenteritis.

Design & setting

This retrospective cohort study covered a period from September 2007–September 2014. Children aged 6 months to 6 years presenting with acute gastroenteritis to a primary care OOH service were included.

Methods

Pseudonymised data were obtained, and children were analysed overall and by age category. X^2 trend tests were used to assess rates of acute gastroenteritis, referrals, face-to-face contacts, and oral rehydration therapy (ORT) prescriptions.

Results

The data included 12 455 children (6517 boys), with a median age of 20.2 months (interquartile range [IQR] 11.6 to 36.0 months). Over 7 years, incidence rates of acute gastroenteritis decreased significantly, and face-to-face contact rates increased significantly (both, $P<0.01$). However, there was no significant trend for referral rates ($P = 0.87$) or prescription rates for ORT ($P = 0.82$). Subgroup analyses produced comparable results, although there was an increase in face-to-face contact rates for the older children.

Conclusion

Incidence rates for childhood acute gastroenteritis presenting in OOH services decreased and referral rates did not increase significantly. These findings may be useful as a reference for the impact of new interventions for childhood acute gastroenteritis.

INTRODUCTION

Most children that are younger than 5 years will suffer from at least one episode of acute gastroenteritis.[1] Although these episodes are generally self-limiting and uncomplicated, they can lead to severe dehydration, particularly in young children.[2] Over the decade from 1999–2010, hospital admission rates for acute gastroenteritis increased by 31% in England.[3] This increase has not been associated with increased severity, with most cases being for short-term admissions (<1 day) that possibly could have been managed in primary care.[3] High emergency admission rates are often thought to be inversely related to primary care quality, but, presumably, a complex interplay of factors is responsible for the observed increase in hospital admission rates.[4]

Primary care OOH services are regional centres in which multiple GPs work in shifts to cover patients outside of normal working hours.[5] Patients in the Netherlands must go through triage by telephone before they are invited for face-to-face contact with a GP in the OOH service. Factors thought to have influenced the increase in hospital admission rates include complicated access to the OOH service, loss of continuity in GP care, a drive for shorter hospital stays (also leading to increased readmission rates), the impact of social media, and the expectations of parents and professionals for the treatment of a sick child.[4] In addition, GPs are experiencing high workloads in OOH services,[6] which may be due to inaccurate triage of children by telephone assistants. In turn, this may contribute to more referrals to paediatric emergency departments and consequent hospital admissions for children who could be better managed at home with ORT.[7]

Although trends in hospital admission rates are known, the authors are not aware of research into the trends in referral rates for children with acute gastroenteritis presenting to primary care OOH services. The authors therefore investigated whether referral rates to paediatric emergency care from a primary care OOH service increased over a 7-year period for children with acute gastroenteritis. In addition, factors potentially related to that trend were explored, focusing on rates of the incidence of acute gastroenteritis, face-to-face contacts, and ORT prescriptions.

METHODS

Study design

This retrospective cohort study was performed using information obtained between September 2007–September 2014. Data for children aged 6 months to 6 years were obtained from the electronic database of a primary care OOH service. The primary outcome was the referral rate from this service to secondary care.

Setting and triage procedure

Pseudonymised data were obtained from the electronic database of a primary care OOH service that included 290 collaborating GPs providing care for approximately 650 000 residents in the north of the Netherlands.[8] Triage was initially performed over the telephone by trained assistants who assessed the urgency of a consultation based on the guidelines of the Dutch College of General Practitioners. They were then able to offer advice over the telephone — including advice to administer ORT — or make an appointment for face-to-face contact with a GP.[9] If the patient was seen by a GP in a face-to-face contact, the GP decided if referral was necessary or if the patient could be managed at home. The assistant and GP record their findings in the patient's medical record, which contains information on the contact date, demographics, symptoms, physical examination, additional testing, diagnosis, prescriptions, and referrals.

Study population and contact selection

The study included children aged 6 months to 6 years who were diagnosed with acute gastroenteritis and seen in the OOH service during the study period. First, all contacts of children aged 6 months to 6 years were selected, and their medical records were extracted and saved in a database. All patient information was pseudonymised by the OOH service. Second, a computer search was performed to select all contacts with the words *'diarrhoea'* and/or *'vomiting'* (or synonyms of these words) in the history record. The results were checked for false negatives by randomly extracting 10% of all OOH service contacts over the study period (n = 5000) and hand checking if any children with diarrhoea and/or vomiting had been missed. The computerised search was then adapted, and the false negative screening was repeated until no eligible contacts were missed. Three researchers (two medical students and a GP) also hand searched all contacts in which the child presented with diarrhoea and/or vomiting to exclude those with chronic diarrhoea (that is to say, those with symptoms for ≥2 weeks).

The study defined a diagnosis of acute gastroenteritis as follows: 1) a registered diagnosis of 'gastroenteritis', or synonyms; or 2) a registered diagnosis of 'viral infection' or 'vomiting' if diarrhoea was a presenting symptom; or 3) if no diagnosis was recorded, but diarrhoea or vomiting was the presenting symptom and other plausible causes were not mentioned. Contact selection was performed by three researchers, and any uncertainties were discussed with an expert panel (two GPs). If children contacted more than once within two weeks, it was counted as one episode. If children contacted more than once, but with an intervening period of more than 2 weeks, this was counted as separate episodes.

Data extraction

The following data were extracted by three researchers using a structured form: contact date, contact type (telephone, face-to-face), age, symptoms and signs, referral, and any medication or ORT prescribed (or self-prescribed). Before starting full data extraction, a pilot was performed to determine the level of agreement between researchers in the extracted data (Cronbach's alpha, ≥0.87). After a consensus meeting, agreement was retested for a random sample of 10% of all of the included contacts (Cronbach alpha, ≥0.85). Thus, there was a good level of agreement in the information extracted between researchers.

Outcomes

The primary outcome was the referral rate, with the total number of contacts per year as the denominator. Secondary outcomes were to analyse the incidence rate of acute gastroenteritis, the rate of each contact type (for example, face-to-face or telephone), and the rate of ORT prescriptions.

Statistical analysis

Descriptive data are reported as medians and IQRs, or as numbers and percentages. Trends were evaluated for all primary and secondary outcomes. In addition, subgroup analyses were performed for age categories of 6 to 12 months and 1 to 6 years. All trend analyses were conducted using the X^2 test (two-sided), and were considered significant if $P<0.05$. Data were analysed using IBM SPSS (version 25.0).

RESULTS

Patient characteristics

In total, 171 967 contacts with the OOH service were recorded for children aged 6 months to 6 years during the study period. Among these, 34 860 were for diarrhoea and/or vomiting, and a subset of 12 455 (9432 children) were diagnosed with acute gastroenteritis (Figure 1). For those with acute gastroenteritis, multiple contacts were recorded in 3023 cases (specifically, two times for 1613 children, three times for 396 children, four times for 112 children, five times for 45 children, six times for 13 children, seven times for five children, and eight times for one child).

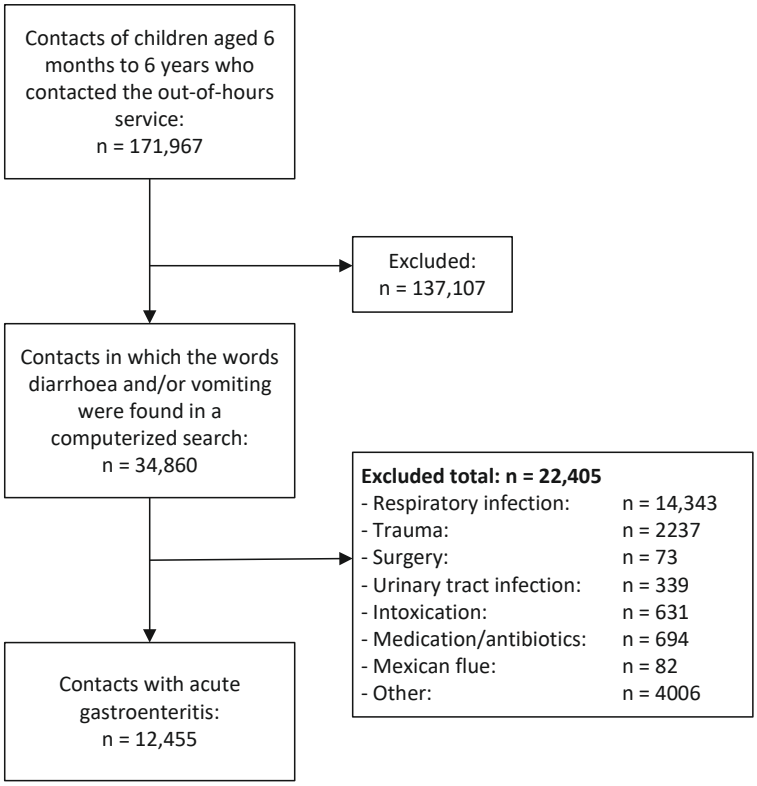

Figure 1. Flowchart of patient selection

The median age was 20.2 months (IQR 11.6 to 36.0), and boys accounted for 6517 contacts (52.3%). Regarding presentation, 2678 (21.5%) contacts had only diarrhoea, 3934 (31.6%) had only vomiting, and 5843 (46.9%) had both diarrhoea and vomiting. In total 9777 (78.5%) contacts presented with vomiting and 6614 (53.1%) with diarrhoea (Table 1). For the 1036 contacts (8.3%) referred with acute gastroenteritis, age and sex were comparable to those in the overall cohort, but a higher proportion had both diarrhoea and vomiting.

Table 1. Characteristics of Dutch children aged 6 months to 6 years with acute gastroenteritis who were seen in primary care out-of-hours service (2007-2014)

Characteristics	Total (n = 12 455)	Referred children (n = 1036)
Male sex, n (%)	6517 (52.3)	556 (53.7)
Median age, months (IQR)	20.2 (11.6 to 36.0)	18.0 (12.0 to 32.0)
Age categories		
6 months to <1 year, n (%)	3229 (25.9)	249 (24.0)
1 to 6 years, n (%)	9226 (74.1)	787 (76.0)
Presenting symptoms		
Diarrhoea only, n (%)	2678 (21.5)[a]	106 (10.2)[b]
Vomiting only, n (%)	3934 (31.6)[c]	214 (20.7)[d]
Diarrhoea and vomiting, n (%)	5843 (46.9)	716 (69.1)

[a]No information about vomiting in patient record (n = 1621). [b]No information about vomiting in patient record (n = 73). [c]No information about diarrhoea in patient record (n = 2006). [d]No information about diarrhoea in patient record (n = 112). Abbreviation: IQR = interquartile range.

Trend analyses

Table 2 presents the results of the trend analyses overall and for the two age subgroups over the 7-year study period. In both the overall and subgroup analyses, no significant increase in the trend for referral rates was found (overall median 8.1%). However, there was an increasing trend in face-to-face contact rates for all children with acute gastroenteritis (P<0.01). Subgroup analyses confirmed that this increasing trend was only statistically significant for children aged 1–6 years (P <0.01). ORT prescription rates did not change significantly (P = 0.82). Finally, there was a significantly decreasing trend in the incidence rate of acute gastroenteritis presenting to the OOH service in both the overall and the subgroup analyses (P <0. 01) .

Table 2. Trend analyses for Dutch children aged 6 months to 6 years with acute gastroenteritis seen in a primary care OOH service (2007 to 2014), grouped by the total cohort (n = 12 455), age <1 year (n = 3229), and age ≥1 year (n = 9226)

	2007/2008	2008/2009	2009/2010	2010/2011	2011/2012	2012/2013	2013/2014	Total	*P* value
Total number of contacts[a]	24 920	25 088	27 772	24 466	24 459	22 923	22 339	171 967	–
6 months to 6 years, n **(%)**[b] (*n* = 12 455)	2298 (9.2)	1994 (7.9)	1902 (6.8)	1648 (6.7)	1612 (6.6)	1784 (7.8)	1217 (5.4)	12455	<0.01
Referred, *n* (%)[c]	195 (8.5)	162 (8.1)	147 (7.7)	154 (9.3)	127 (7.9)	163 (9.1)	88 (7.2)	1036	0.87
Face-to-face contact, *n* (%)[c]	1186 (51.6)	1025 (51.4)	927 (48.7)	885 (53.7)	809 (50.2)	994 (55.7)	672 (55.2)	6498	<0.01
ORT prescription, *n* (%)[c]	533 (23.2)	415 (20.8)	424 (22.3)	343 (20.8)	367 (22.8)	432 (24.2)	242 (19.9)	2756	0.82
Subgroup analyses									
6 months to <1 year, n **(%)**[b] (*n* = 3229)	545 (2.2)	554 (2.2)	568 (2.0)	438 (1.8)	413 (1.7)	416 (1.8)	295 (1.3)	3229	<0.01
Referred, *n* (%)[c]	33 (6.1)	52 (9.4)	42 (7.4)	47 (10.7)	30 (7.3)	21 (5.0)	24 (8.1)	249	0.73
Face-to-face contact, *n* (%)[c]	297 (54.5)	298 (53.8)	274 (48.2)	243 (55.5)	233 (56.4)	231 (55.5)	172 (58.3)	1748	0.10
ORT prescription, *n* (%)[c]	135 (24.8)	129 (23.3)	128 (22.5)	91 (20.8)	109 (26.4)	99 (23.8)	61 (20.7)	752	0.58
1 year to 6 years, n **(%)**[b] (*n* = 9226)	1753 (7.0)	1440 (5.7)	1334 (4.8)	1210 (4.9)	1199 (4.9)	1368 (6.0)	922 (4.1)	9226	<0.01
Referred, *n* (%)[c]	162 (9.2)	110 (7.6)	105 (7.9)	107 (8.8)	97 (8.1)	142 (10.4)	64 (6.9)	787	0.98
Face-to-face contact, *n* (%)[c]	889 (50.7)	727 (50.5)	653 (49.0)	642 (53.1)	576 (48.0)	763 (55.8)	500 (54.2)	4750	<0.01
ORT prescription, *n* (%)[c]	398 (22.7)	286 (19.9)	296 (22.2)	252 (20.8)	258 (21.5)	333 (24.3)	181 (19.6)	2004	0.93

[a]Total number of contacts including all children aged 6 months to 6 years visiting the OOH service. [b]Denominator is total number of contacts 6 months to 6 years. [c]Denominator is total number of contacts with acute gastroenteritis in each specific age category. Abbreviations: OOH = out-of-hours; ORT = oral rehydration therapy.

DISCUSSION

Summary

This study gives important insights into referral rates for childhood acute gastroenteritis from a primary care OOH service to paediatric specialist care between 2007 and 2014, a period during which there was no change in guidelines. Incidence rates for childhood acute gastroenteritis decreased and this study could not show a trend in referral rates in both the overall and subgroup analyses. The median referral rate was 8.1%. The study found a statistically significant increasing trend in face-to-face contact rates. This was mainly due to a significant increasing trend in face-to-face contact rates in children aged 1–6 years. Referral was more likely for children reporting both diarrhoea and vomiting, and almost one in five children received advice or a prescription for ORT.

Strengths and limitations

The main strength was the inclusion of a relatively large number of patient contacts. Data were then obtained in a structured manner with good reliability among the raters and discussion of doubtful contacts. Missing data were also minimised because Dutch law (The Medical Treatment Agreement Act) requires that information on referrals and prescriptions be recorded. Moreover, when the authors screened a random sample for false negatives, they confirmed that few children with diarrhoea and/or vomiting were missed by the computerised selection method.

Some limitations do need to be considered, such as the decision to include only those aged 6 months to 6 years, and to perform subgroup analysis at a cut-off of 1 year. The overall age range was chosen because it corresponded to the peak incidence of acute gastroenteritis[10] and the group that most often contacts primary care OOH services.[5] Younger children were excluded because they are at increased risk of dehydration, meaning that any referral decisions may only reflect age.[11] In the subgroup analyses, age groups were predefined based on their assumed risk for a complicated course. However, this age cut-off was arbitrary, and it may have been preferable to use the 2-year cut-off advised in the 2014 revision of Dutch guidelines.[10] Furthermore, multiple contacts were recorded in 3023 cases, which might have influenced the magnitude of the referral rate.

The health care system in the Netherlands is comparable to those in Denmark, Sweden, the UK, Australia, and New Zealand, which are based on the GP serving as a gatekeeper to further care.[12] However, watchful waiting is a common strategy in the Netherlands, with emphasis on telephone advice and relatively few people getting face-to-face contact with the GP.[13] For example, 5% and 22% of community cases visit their GP because of acute gastroenteritis in the Netherlands and New Zealand, respectively.[14] Therefore, trends in referral rates in the Netherlands could also differ from those in other countries.

Comparison with existing literature

It was notable that there was no statistically significant increase in referral rates from the OOH service to the emergency department, which ran counter to the authors' expectation based on a previous report on increasing hospital admission rates.[3] The findings may indicate that parents attend the paediatric emergency department directly, possibly because of easier access to advice without the need for telephone triage.[4] This could account for the increase in hospital admission rates of children that could be managed in primary care, despite referral rates from OOH services remaining stable. However, this does not seem a plausible explanation. Given that prognosis was worse among those self-referred with fever, parents appear to be capable of accurately evaluating the severity of illness and need for emergency paediatric care.[15]

The increasing trend in face-to-face contact rates for acute gastroenteritis in children was consistent with the findings of a Dutch study showing a similar increase in face-to-face contact rates to OOH services for other problems between 2009 and 2016.[6] This may indicate a change in telephone triage practices at OOH services. In the Netherlands, most OOH services use a validated standard for triage to increase its efficiency and patient safety.[9] However, unknown patients, anxious parents, high work pressures,[16] and differing views of disease and illness can make triage challenging. Furthermore, it has been shown that telephone triage may be especially suboptimal for children with gastrointestinal complaints.[17] These challenges may be associated with the increase in face-to-face contact rates for children with benign prognoses. This in turn, may contribute to the high work pressure experienced by GPs in these services, even while the absolute number of children presenting with acute gastroenteritis decreases.[6]

Subgroup analyses showed that the increase in face-to-face contact rates was only significant for children aged 1–6 years, in whom the risks of complications were low to moderate. It is unlikely that risk actually increased over time to justify this change, indicating that more children with a benign prognosis were allowed through to face-to-face contacts. Indeed, despite the increase in face-to-face contact rates, secondary triage by GPs did not result in a corresponding increase in referral rates. The likelihood of referral was increased if the child had an increased risk of dehydration, with referral rates being highest for those presenting with both vomiting and diarrhoea. This finding indicates that the quality of GP triage remained appropriate.

ORT is the recommended first line treatment for children at risk of dehydration or with mild, moderate, or severe dehydration, with proven efficacy.[2] In the present study, the change in ORT prescribing rates was statistically insignificant, with approximately 22% receiving advice or a prescription, and non-prescribing justified by the presence of vomiting in about 80% of patients.[7] This is consistent with the justifiable fear that vomiting will hamper the intake of ORT and may affect compliance. In referred children, ondansetron is an effective antiemetic, which could increase ORT uptake and compliance.[18] As such, this medication

may have a role in primary care, with the potential to prevent referrals to secondary care and manage patients in primary care.

The incidence rate of acute gastroenteritis in children almost halved during the study period (Table 2). However, this finding should be interpreted with caution because the annual incidence fluctuates widely for a range of reasons, with each of these having the potential to explain the observed variations.[19] Moreover, only the first and last years of this study showed markedly different incidence rates, with relative stability observed in the intervening period. An explanation for the lower incidence and referral rates for acute gastroenteritis in 2013–2014 could be the lower reported incidence of rotavirus infections in that year.[20] Given that rotavirus is known to be associated with a particularly complicated course,[21] a lower incidence could be associated with fewer contacts and referrals.

Implications for research and practice

These results showed that the trend in referral rates to secondary care is not significant. There are five aspects in the management of children with acute gastroenteritis that could potentially affect these rates in the future. First, the introduction of point-of-care tests for pathogens of acute gastroenteritis may affect management. Triaging children with gastrointestinal complaints based on their clinical signs and symptoms is challenging. It is therefore unsurprising that GPs have difficulties in distinguishing between children who will have uncomplicated courses and those who will have complicated courses requiring referral. Current guidelines do not recommend stool microbiological investigation for acute gastroenteritis in children.[10,11] Research could therefore evaluate if specific pathogens are associated with a more severe course of acute gastroenteritis, and if demonstrated, should assess the added value of point-of-care tests in daily practice.

Second, rotavirus is the most common pathogen among children presenting with acute gastroenteritis in primary care,[10] yet children had not been vaccinated against it during the study period. Implementing this vaccination in the future will influence the risk of a complicated course in children with acute gastroenteritis. This will influence the need for referral.

Third, although referral rates remained constant at a median of 8.1%, the percentage that was subsequently admitted to hospital was unknown. It would be interesting to know whether treating vomiting specifically could facilitate greater ORT intake in primary care, and thereby decrease referral rates. Ondansetron is often used with good efficacy as an antiemetic, and to increase ORT uptake and compliance in paediatrics.[18] For now, ondansetron has only been shown to have benefit in hospital settings, at the more severe end of the spectrum, especially in children who are deemed unsuitable for discharge from emergency department. It might be argued that ondansetron may not be warranted, safe, or cost-efficient in children presenting to primary care. Concerns about diarrhoea, prolongation of QT-interval on electrocardiogram, and prescribing for minimal clinical

benefit may challenge uptake in primary care. A study addressing the impact of ondansetron in primary care, focusing on children with acute gastroenteritis and prominent vomiting, is therefore highly needed.

A fourth management aspect is that not enough is known about the adherence to prescriptions for ORT. The presence of vomiting in around 80% of contacts in this study could result in poor compliance with ORT, or to GPs fearing poor compliance. Further research into ORT adherence, including qualitative research into the barriers to adherence, is therefore warranted.

Finally, the reasons for the increase in face-to-face contact by older children requires further research. Important questions in this research will include the reasons for parents contacting OOH services, the validity of telephone triage, and the availability of adequate and appropriate information about when parents should contact the OOH service.

In a 7-year period from 2007 to 2014, incidence rates for childhood acute gastroenteritis presenting at OOH services decreased, and referral rates remained stable. These findings may be useful as a reference against which the impact of new interventions for childhood acute gastroenteritis can be measured.

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CHAPTER 3

Facilitators and barriers to home management for children with acute gastroenteritis: systematic review

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ABSTRACT

Objective

To identify facilitators and barriers to home management for children with acute gastroenteritis from the perspective of healthcare professionals and caregivers, utilizing the Theoretical Domains Framework (TDF).

Study design

A systematic review was performed using the following databases: PubMed, Embase, Web of Science and CINAHL. Studies from high-income countries published from 2003 to 2023 who included children with acute gastroenteritis under six years, treated via home management, and addressed facilitators or barriers from the perspective of healthcare professionals or caregivers were eligible for inclusion. All studies were independently reviewed for inclusion, data extraction (to the TDF), and quality assessment.

Results

4476 studies were screened with 16 meeting the inclusion criteria. Facilitators for healthcare professionals included knowledge of guidelines and management, enhanced skills, and clinical decision support systems. For caregivers, lack of knowledge created a barrier for home management, while access to information resources, with positive emotions and beliefs in caregivers' own capabilities served as facilitators.

Conclusions

Optimizing home management for children with gastroenteritis is a complex process and should focus on incorporating combined process changes (increasing knowledge, skills and implementing clinical decision support systems) for healthcare professionals. For caregivers, the focus should be on increasing knowledge, resources targeting education and reassurance. By addressing these aspects, an effective strategy could be established, potentially allowing more children to be treated at home.

INTRODUCTION

Acute gastroenteritis is one of the most common childhood diseases and can be effectively managed at home in children aged over six months.[1,2] Especially in high-income countries, where most children present without severe dehydration, effective home management can reduce the burden of gastroenteritis on children and the healthcare system.[2–4] Yet home management remains suboptimal.[3-5]

Optimal home management for children with acute gastroenteritis involves preventing dehydration through symptom monitoring, adequate rehydration, and the use of ORT, with ondansetron if needed.[1] Early home-administered oral rehydration therapy (ORT) can reduce complications, healthcare visits, and hospitalizations[5,6] but it remains underused in high-income countries.[7] Caregivers play a vital role in appropriate home management, either with or without the intervention of a healthcare professional who can guide them in management.[5,8] In 2003, an overview of factors influencing ORT revealed barriers including parental and healthcare professionals' knowledge deficits, cultural practices, preferences for intravenous rehydration therapy, and the perception that vomiting contraindicates ORT.[9] However, in recent years, management approaches have changed, with the implementation of ondansetron – an anti-emetic medication - supporting home management. Oral ondansetron is now recommended in addition to ORT for children with increased risk of dehydration due to vomiting.[10-12] An overview of current data on facilitators and barriers to home management for children with acute gastroenteritis, from the perspective of the two most important stakeholders, healthcare professionals and caregivers, is lacking.

Understanding the facilitators and barriers and mapping them to theoretical mechanisms of behaviour change may help identify tailored, effective approaches for increasing home management.[13] Therefore, we aimed to systematically review the published literature on facilitators and barriers to home management for children with acute gastroenteritis, from the perspective of healthcare professionals and caregivers.

METHODS

Design

This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis.[14] The study protocol was developed a priori and registered in the International Prospective Register of Systematic Reviews on April 9, 2023 (CRD42023412777).

Literature Search

A systematic literature search was performed with the input of medical librarians by using the following databases: PubMed, Embase via Ovid, Web of Science and CINAHL. The search strategy was piloted and peer-reviewed by all authors. It was adapted to each specific database and performed on April 10, 2023 (Appendix 1). The search included peer-reviewed studies published in the last 20 years, written in languages known to the research team (English, Dutch, German, French).

Study Selection

Results from database searches were exported to Covidence and duplicates were removed.[15] Inclusion criteria were: 1) children with acute gastroenteritis aged six months to six years, 2) treated via home management, 3) addressed facilitators or barriers from the perspective of healthcare professionals or caregivers, and 4) conducted in high-income countries, as defined by the World Bank.[16] Studies reporting data of children admitted to hospital were excluded. Single case reports, protocols, guidelines, opinions, book reviews, and conference abstracts were also excluded. Extraction of title and abstracts, followed by full-text screening was independently performed by two authors (JL (paediatrician) and AW (PhD-student)). Disagreements were resolved through discussion and within the research group. The reference lists of all included studies were screened for relevant studies.

Data Extraction, Quality Assessment, and Analysis

Data including aim, study design and methods, healthcare professionals' or caregivers' perspectives, child characteristics and facilitators or barriers were extracted independently by two authors (AW and JL) and re-coded on an extraction template in Covidence.

The quality of included studies was assessed independently by the same two authors using the standardized critical appraisal instruments from the Joanna Briggs Institute Critical Appraisal Tools for each specific study design.[17-20] Questions were scored as yes, no, unclear or not applicable.

All raw data relating to facilitators and barriers experienced by healthcare professionals or caregivers were independently mapped against the Theoretical Domains Framework (TDF). A preliminary summary of the TDF-mapped themes was prepared and discussed within the research team. The TDF comprises 14 theoretical domains synthesized from 33

behaviour change theories and 84 theoretical constructs, offering a systematic and theory-based approach for identifying individual, social, and environmental influences on behaviour (Appendix 2).[13,21] A narrative approach was used to describe the facilitators and barriers mapped to the TDF.

RESULTS

Characteristics of included studies

The search strategy yielded 4476 records of which 104 were reviewed in full text, 16 met the inclusion criteria and were included in the analysis (Figure 1). Of these studies, eight reported healthcare professionals' (primary care paediatricians, paediatric emergency medicine physicians, and emergency department nurses)[22-29] and eight reported caregivers'[30-37] perspectives. A summary of study characteristics is presented in Table 1.

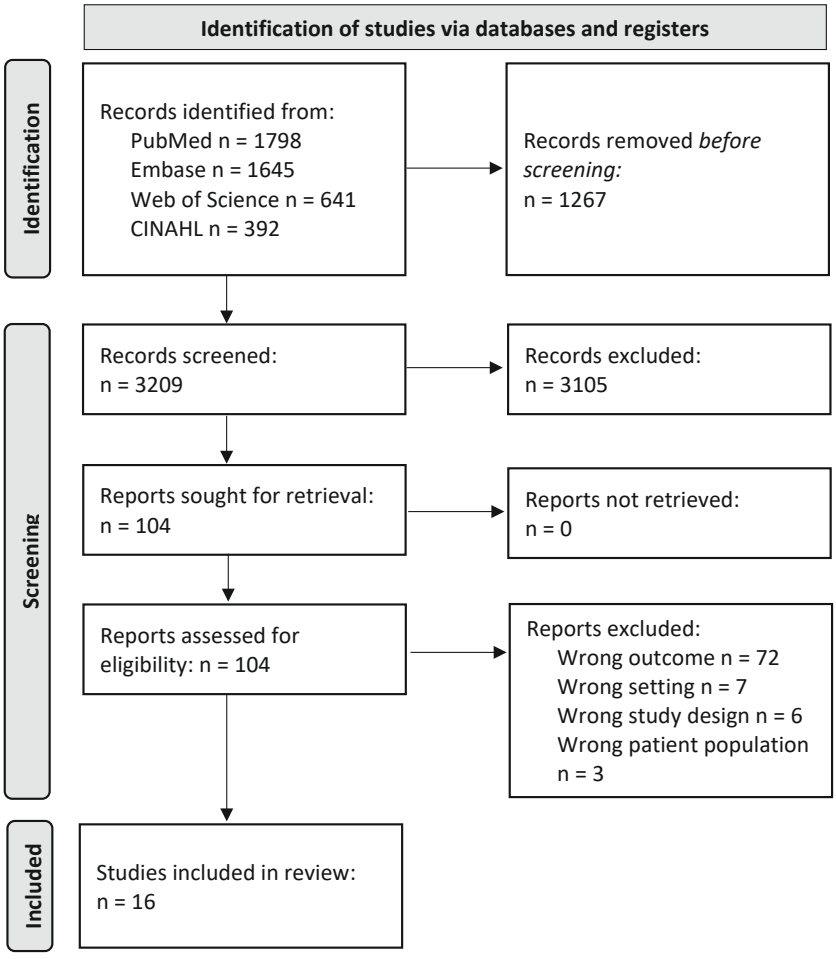

Figure 1. Study Flow Diagram

Table 1. Characteristics of included studies (n = 16)

Author, Year of publication	Country	Aim	Study design and methods	Study population	Characteristic of included children
Albano et al, 2010	Italy	To evaluate the applicability and efficacy of guidelines for managing acute gastroenteritis in pediatricians undergoing specific training.	Randomized controlled trial. Intervention: 2-hour course about recommendations in the guidelines for acute gastroenteritis.	150 primary care pediatricians.	1309 children, 17 months (mean), mild to moderate dehydration.
Albrecht et al, 2017	Canada	To describe caregivers' experiences of pediatric acute gastroenteritis and identify their information needs, preferences, and priorities.	Qualitative study. Methods: semi-structured interviews.	15 caregivers.	15 children, <5 years (93%).
Bahm et al, 2016	Canada	To evaluate the impact of clinical decision tools in pediatric acute gastroenteritis.	Retrospective cohort study. Methods: linked survey data.	Pediatric emergency medicine physicians.	57.921 children, 5.0 years (mean).
Bender et al, 2007	United States	To examine attitudes towards the use of oral rehydration therapy by pediatric emergency medicine physicians before and after being given recent data about guidelines.	Non-randomized interventional study. Intervention: data refuting the barriers to the use of oral rehydration therapy.	445 pediatric emergency medicine physicians.	3 scenarios: child <2 years with mild, moderate or severe dehydration.
Eriksson et al, 2015	Sweden	To describe parents' experiences of monitoring calls in telephone advice nursing, in children with gastroenteritis.	Qualitative study. Methods: in-depth interviews.	10 caregivers.	10 children, aged 8-23 months.
Freedman et al, 2008	Canada	To describe the reliability and validity of a caregiver gastroenteritis knowledge questionnaire and to identify specific knowledge deficits.	Analytical cross-sectional study. Methods: questionnaire with 38 true/ false questions.	80 caregivers.	80 children, 3 months – 4 years.

Table 1. Characteristics of included studies (n = 16) (continued)

Author, Year of publication	Country	Aim	Study design and methods	Study population	Characteristic of included children
Freedman et al, 2011	Canada and United States	To examine practices, knowledge, and beliefs regarding the treatment of toddlers and young children with acute gastroenteritis in the emergency department.	Analytical cross-sectional study. Methods: online survey.	324 pediatric emergency medicine physicians.	Scenario about toddlers and young children with acute gastroenteritis.
Geurts et al, 2017	Netherlands	To evaluate the feasibility and impact of a clinical decision support system for managing of children with acute gastroenteritis at the emergency department.	Randomized controlled trial. Intervention: nurse-guided clinical decision support system.	Emergency department nurses.	222 children, 1.4 years (median), mild to moderate dehydration.
Graham et al, 2010	Canada	To examine parental motivations for bringing their child with symptoms of gastroenteritis to the emergency department.	Qualitative study. Methods: structured survey via telephone.	10 caregivers.	10 children, 3 months – 3 years.
Haines et al, 2012	United States	To evaluate outcomes associated with a discharge action plan employing single-dose home use of ondansetron in patients with acute gastroenteritis.	Case series. Methods: clinical-conducted telephone call 3-5 days after emergency visit.	29 caregivers.	29 children, 5.15 years (mean).
Hendrickson et al, 2018	Unites States	To determine if a triage-based, nurse-initiated protocol for early provision of ondansetron and oral rehydration therapy could safely improve the care of children with gastroenteritis at the emergency department.	Non-randomized interventional study. Intervention: triage-based, nurse-initiated protocol.	Emergency department triage nurses.	128 children, 2.01 years (mean), no and mild dehydration.

Table 1. Characteristics of included studies (n = 16) (continued)

Author, Year of publication	Country	Aim	Study design and methods	Study population	Characteristic of included children
Jove-Blanco et al, 2021	Spain	To evaluate if the addition of a video discharge instruction to usual verbal information improved the comprehension of information provided to caregivers of patients who consult in pediatric emergency department for acute gastroenteritis.	Randomized controlled trial. Intervention: video discharge instructions.	139 caregivers.	139 children, 2 years (median) 87.3% no, 9.3% mild, and 5% moderate dehydration.
Nicastro et al, 2015	11 European countries	To assess the impact of a five-module e-learning course about clinical practice guidelines for acute gastroenteritis on physicians' knowledge and clinical practice.	Non-randomized interventional study. Intervention: e-learning course including five learning modules addressing the five key areas of acute gastroenteritis management.	149 physicians (95% pediatricians, 5% general practitioners)	545 children, 21 months (median).
Nir et al, 2013	Israel	To evaluate parents' attitudes towards rehydration methods used in pediatric emergency departments.	Analytical cross-sectional study. Methods: questionnaires.	100 caregivers.	100 children, >50% 0-3 years, mild to moderate dehydration.
Small et al, 2005	Northern-Ireland	To compare clinical outcomes of admitted and home treated children with acute gastroenteritis presenting at Accident and Emergency Departments.	Prospective cohort study. Methods: medical records.	116 caregivers.	116 children, 1.85 years (mean).
Zolotor et al, 2007	United States	To improve the quality and reduce cost associated with the care of gastroenteritis for children covered by Medicaid in the AccessCare network.	Non-randomized interventional study. Intervention: education sessions for healthcare professionals, free oral rehydration solution, patient education video, and feedback on oral rehydration use.	20 pediatric practices.	3367 children, <5 years.

Facilitators and barriers

Facilitators and barriers were categorized across 11 domains of the TDF (Table 2). Facilitators were identified in eight domains, with two domains being relevant from both perspectives, two from healthcare professionals' and four from caregivers' perspective. Barriers were mapped across ten domains, including four domains relevant to both perspectives and six domains specific to caregivers' perspective.

Table 2. Facilitators and barriers relevant to healthcare professionals and caregiver for home management of children with acute gastroenteritis mapped to the TDF

TDF domains		Healthcare professionals	Caregivers
Knowledge	**Facilitators**	Knowledge of guidelines[22] Knowledge of effectiveness of ORT and impact on length of stay[24] E-learning about guideline management[28]	Learning about effective treatments[30] New knowledge would impact their future actions and decisions[30]
	Barriers	Lack of awareness of guidelines[22] Lack of knowledge about ondansetron[25]	Lack of understanding of signs and symptoms, course, and dehydration[30] Misconceptions about home management[30] Lack of knowledge for indications to see a physician, solid intake/ refeeding, and medication use[30] Lack of knowledge about treatment, aetiology, signs, and degree of dehydration[33] More likely to attend by first child[33] Lack of knowledge about duration of symptoms[34]
Skills	**Facilitators**	Nursing initiation of ORT[23,29] Collaborating with other emergency departments[29]	
	Barriers	Sites treating fewer children[23]	Exhausting own repertoire of treatments did not work[33]
Beliefs about capabilities	**Facilitators**		Confirmation[31] Share worries and responsibilities[31] Getting positive feedback[22]
	Barriers		Multiple sick family members[30] Primary caregiver for sick child and multiple children[30] Illness out of keeping with their own expectations[33] Hesitating without a medical opinion[33]

Table 2. Facilitators and barriers relevant to healthcare professionals and caregiver for home management of children with acute gastroenteritis mapped to the TDF (continued)

TDF domains		Healthcare professionals	Caregivers
Beliefs about consequences	**Facilitators**		ORT improved symptoms[30]
	Barriers	Misbeliefs that ORT would increase length of stay[24]	Child's symptoms not improving, worsening symptoms[30] Nothing seemed to help[30] Prolonged illness and worry about long-term consequences[33] Parental perception of illness severity[37]
Optimism	**Barriers**		Magical place – kids always improve after visiting the emergency department[33]
Intentions	**Facilitators**		Agree ORT if diarrhoea[36]
	Barriers		Decline ORT if child is vomiting or refuses to drink[36]
Goals			
Memory, attention and decision processes	**Barriers**	Increased number of years in practice decreased change of ORT[24]	Previous experience with similar illness requiring emergency care[30] Previous dissatisfaction with telephone health advice service[30] Previously intravenous treatment, tendency to not agree to ORT[36]
Emotion	**Facilitators**		Feeling of comfort, security, confidence and reassurance[31] Being taken seriously[31] Feeling of being important[31]
	Barriers		Higher parental stress[37] Feeling scared, worried, uncertain, powerless[30] Anxiety about aetiology and alternate diagnosis[33] Feeling helplessness when child is suffering[33]
Behavioural regulation	**Facilitators**	Clinical decision tool with medical directive for ORT[23] Clinical decision support system[26] Triage nurse-based protocol[27] Nurse triage system for dehydration[29] Protocol for ORT administration and monitoring[29]	

Table 2. Facilitators and barriers relevant to healthcare professionals and caregiver for home management of children with acute gastroenteritis mapped to the TDF (continued)

TDF domains		Healthcare professionals	Caregivers
Social/professional role and identity			
Social influences	**Barriers**		Advice from other parents, spouse or partner, day care staff, neighbours, and the internet[33]
Environmental context and resources	**Facilitators**	Free ORT distribution[29]	Use of information sheets from the hospital[29,30] Video discharge instructions[35] Monitoring calls[31] Ondansetron provided before going home[34]
	Barriers		No formal, written information[30] Latest technology in the emergency department[30] Regular physician unavailable for advice[30,33]
Reinforcement			

Abbreviation: ORT = oral rehydration therapy.

Quality of studies

The overall quality of included studies was appropriate (Table 3). For healthcare professionals, all facilitators (11/11) and 80.0% (4/5) of barriers were derived from quantitative studies. Conversely, for caregivers, a smaller proportion of facilitators (14.2%, 2/14) and barriers (1.7%, 3/28) related to home management were sourced from quantitative studies.

Table 3. Quality assessment of the included articles

Analytical cross-sectional studies	**In- exclusion**	**Study sample**	**Validity exposure**	**Measurement condition**	**Confounders**	**Strategies for confounders**
Freedman 2008	Y	Y	Y	Y	Y	Y
Freedman 2011	Y	Y	Y	Y	N	N
Nir 2013	Y	Y	Y	Y	N	N
Cohort studies	**Group similarity**	**Exposures measured**	**Validity exposure**	**Confounders**	**Strategies for confounders**	**Free of outcome start**
Bahm 2016	Y	Y	Y	Y	Y	Y
Small 2005	Y	Y	Y	Y	Y	NA
Qualitative studies	**Perspective - methods**	**Methods - objectives**	**Methods - data collection**	**Methods - analysis**	**Methods - results**	**Researcher's background**
Albrecht 2017	Y	Y	Y	Y	Y	N
Eriksson 2015	Y	Y	Y	Y	Y	Y
Graham 2010	Y	Y	Y	Y	Y	N
Randomized controlled trials	**Randomization**	**Allocation concealed**	**Group similarity**	**Participants blinded**	**Delivering treatment blinded**	**Identical treated**
Albano 2010	Y	Y	Y	Y	N	Y
Geurts 2017	Y	Y	Y	U	N	Y
Jove- Blanco 2021	Y	Y	Y	N	N	Y
Case series	**In- exclusion**	**Measurement condition**	**Validity methods**	**Consecutive inclusion**	**Complete inclusion**	**Participant's demographic**
Haines 2012	Y	Y	Y	Y	Y	Y
Non-randomized interventional studies	**Cause and effect**	**Group similarity**	**Identical treated**	**Control group**	**Multiple measures**	**Follow-up complete**
Bender 2007	Y	Y	Y	N	Y	Y
Hendrickson 2018	Y	N	Y	Y	Y	Y
Nicastro 2014	Y	Y	Y	N	Y	Y
Zolotor, 2007	Y	Y	Y	N	Y	Y

Yes, No, Unclear, or Not Applicable

Validity measurement	Analysis
Y	Y
Y	Y
Y	Y

Validity measurement	Follow-up sufficient	Follow-up complete	Strategies incomplete follow-up	Analysis
Y	Y	Y	Y	Y
Y	Y	Y	Y	Y

Researcher's influence	Participants	Ethics	Conclusion
N	Y	Y	Y
N	Y	Y	Y
Y	Y	Y	Y

Assessors blinded	Same outcomes measured	Reliable outcomes measured	Follow-up complete	Analysis allocated group	Analysis	Design
U	Y	Y	Y	Y	Y	Y
U	Y	Y	Y	Y	Y	Y
U	Y	Y	N	Y	Y	Y

Reporting clinical information	Reporting outcomes	Reporting sites	Analysis
Y	Y	N	Y

Same outcomes measured	Reliable outcomes measured	Analysis
Y	Y	Y
Y	Y	Y
Y	Y	Y
Y	Y	Y

Facilitators experienced by healthcare professionals and caregivers

Knowledge

Healthcare professionals who had more knowledge of acute gastroenteritis management guidelines, either through a 2-hour course or e-learning, were more likely to adhere to recommended practices. As a result, this facilitated home management (i.e., increased ORT prescription, decreased unnecessary dietary changes, avoidance of unapproved probiotics, and decreased inappropriate use of anti-emetics and antibiotics).[21,27] Children treated by healthcare professionals with increased knowledge about guidelines had shorter durations of diarrhoea at home.[22] Additionally, healthcare professionals with knowledge of ORT effectiveness and its non-impact on prolonging emergency department stays were more inclined to integrate ORT into their practices, facilitating the home management.[24]

For caregivers, a facilitator for home management was knowledge about effective treatments and a better understanding of symptoms and dehydration.[22] Caregivers started acting sooner, which included providing fluids and ORT earlier.[22] Moreover, caregivers with more experience and disease-related knowledge felt more confident in managing less severe symptoms at home and were willing to wait longer before seeking emergency care.[22]

Environmental context and resources

Information sheets provided by hospitals facilitated caregivers in managing gastroenteritis at home. These sheets guided caregivers through the necessary steps and aided in identifying signs of dehydration.[29,30] Also the use of video discharge instructions improved caregivers' understanding of discharge instructions, although it did not impact parental satisfaction or emergency department return visit rate.[35]. Monitoring calls from telephone nurses were valued by caregivers as a valuable resource for additional information and an opportunity to ask questions during different stages of the child's illness at home.[31] Practical advice, tips, and information about gastroenteritis symptoms and risks were appreciated by caregivers in their home management.[31] Caregivers also found value in receiving care and guidance via a monitoring call, without the need to travel.[31]

Providing ondansetron to caregivers as part of the discharge action plan in the emergency department, rather than issuing a prescription, facilitated home management as seen by improved compliance and usage of ondansetron at home.[34].

For healthcare professionals, establishing a system to distribute free ORT during gastroenteritis visits, as part of numerous process changes, increased the average ORT use and reduced admission rates.[29]

Facilitators experienced by healthcare professionals

Skills and behavioural regulation

Skilled nursing initiation of ORT via a clinical decision tool with medical directive for ORT facilitated home management, as seen by an increased ORT use and reduced emergency department revisits.[23] Several process changes aimed at enhancing healthcare professionals' skills and behavioural regulation also facilitated home management, evidenced by increased ORT utilization and a 45% decline in gastroenteritis admissions.[29] These process changes included designating an 'ORT nurse' to train clinical staff, collaborating with local emergency departments to promote ORT use, implementing a nurse triage system for dehydration assessment, and establishing a protocol for ORT administration and monitoring based on guidelines.[29] Furthermore, the implementation of a clinical decision support system, featuring a dehydration scale and management guidelines, facilitated home management as seen in a significant rise in appropriate ORT use.[26] Another home management facilitator was a nurse-initiated protocol based on triage, aimed at assessing dehydration and initiating ORT and ondansetron when needed. This protocol led to a significant increase in timely administration of ORT and ondansetron.[27] Additionally, it reduced the use of intravenous fluids and blood tests but had no impact on the return visit or hospitalization rates.[27]

Facilitators experienced by caregivers

Beliefs about capabilities, consequences, intentions and emotions

Monitoring calls acted as a facilitator for caregivers in managing their child with gastroenteritis at home.[31] These calls offered confirmation, support, feedback and an opportunity to share worries, which led to increased confidence in management at home, strengthening their beliefs about their own capabilities.[31] If ORT was well-accepted by the child at the emergency department, caregivers were more likely to agree to continue treatment at home, highlighting the domain beliefs about consequences.[30] When diarrhoea was the main symptom, caregivers were more willing to initiate ORT at home, highlighting their intentions based on symptom presentation.[36] Emotions experienced by caregivers such as comfort, security, confidence and reassurance due to personal contact with a telephone nurse facilitated management at home.[31] Feeling taken seriously, as the nurse showed genuine interest in the child, asked questions and considered the whole family situation, was another facilitator for home management.[31] Caregivers described the feeling of being important when the nurse took time to call back, as a key aspect of home management.[31]

Barriers experienced by healthcare professionals and caregivers

Knowledge

Healthcare professionals' lack of knowledge about guidelines and clinical benefits of oral ondansetron posed a barrier to home management, evidenced by an increased use of non-recommended interventions (i.e., inappropriate dietary changes, prescription of unnecessary medication) and decreased administration of oral ondansetron.[22,25]

Similarly, caregivers' lack of knowledge (about the course of the disease, aetiology, dehydration signs and symptoms, where to purchase necessary items, and what to communicate to their child about gastroenteritis) impeded their ability to manage their child at home.[22,33] Furthermore, caregivers had limited knowledge about when to seek healthcare professional assistance, appropriate solid intake and refeeding, and correct medication use.[32] Common misconceptions impeded home management, such as providing children juice, milk and ice cream, and a misunderstanding of the role of water in combating dehydration.[22] First-time caregivers were more likely to seek medical attention addressing the lack of knowledge.[33]. A lack of understanding of the degree of dehydration caused caregivers to inaccurately believe that their child was in danger.[33] Additionally, a lack of knowledge of duration of symptoms, particularly diarrhoea, presented a barrier for home management and contributed to return visits.[34]

Skills

Barriers to home management included the skill level of healthcare professionals, with sites treating fewer children showing higher revisit rates.[23] Barriers in the skill domain identified among caregivers, were exhausting their own repertoire of treatments without observing significant improvements in their child's symptoms.[33]

Beliefs about consequences

For healthcare professionals, beliefs about the consequences of ORT, such as potential prolonged emergency stays, acted as a barrier to home management evidenced by a reduced likelihood of initiating ORT.[24]

Caregivers opted to bring their child to the emergency department instead of treating them at home when they felt that the child's symptoms were not improving quickly or when the symptoms worsened without relief.[30] Concerns about prolonged illness and worries about long-term consequences or damage were also reasons for not treating the child at home.[33] An increased perception of illness severity by parents was a barrier of treating the child at home.[37]

Memory, attention, and decision processes

In the domain of memory, attention and decision processes, healthcare professionals with more years of practice were more likely to follow their own practice and less likely to incorporate ORT in management, acting as a barrier to home management.[24]

Caregivers who had encountered a similar illness in the past that necessitated emergency care were inclined to seek assistance at the emergency department, acting as barrier to home management.[30] Dissatisfaction stemming from prior encounters with telephone health services also created a barrier for successful home management.[30] Moreover, there was a tendency to not agree to ORT among caregivers whose children had previously undergone intravenous treatment.[36]

Barriers experienced by caregivers

Beliefs about capabilities

Additional stressors, such as having multiple sick family members or being the primary caregiver for multiple children, barriered home management for caregivers.[30] Other barriers included situations where the child's illness did not align with their expectations and hesitation without a medical opinion.[33]

Emotion

Emotions played an important role in home management for caregivers, with higher parental stress levels associated with a barrier to home management.[37] Caregivers felt scared and worried about their child, leading to uncertainty about how to proceed with managing gastroenteritis at home.[30] The symptoms of the illness, coupled with a sense of powerlessness, compelled them to seek help.[30] Anxiety about potentially missing a serious condition when the illness lasted longer than they expected, as well as a fear of alternative diagnosis barriered home management.[33]

Environmental context and resources

The lack of resources, such as written information provided to caregivers, created a barrier to home management, making it difficult for them to remember discharge and care instructions for current and future episodes.[30] A caregiver preferred not to manage gastroenteritis at home and instead desired the use of the latest technology in the emergency department for diagnosis, management and treatment.[30] When regular healthcare professionals were unavailable for discussion or advice, caregivers were more likely to visit the emergency department instead of managing the illness at home.[30,33]

Optimism, intentions and social influences

In the optimism domain, a barrier emerged whereby caregivers perceived the hospital as a 'magical place' where their children always improved upon arrival. This perception led them to refrain from treating the child at home.[33] The use of ORT declined when the child presented with vomiting or refused to drink.[36] Advice from other caregivers or day-care staff posed a barrier to home management, as the course of the disease did not align with the information received from the surrounding environment.[33]

DISCUSSION

Key findings

Optimal home management for children with acute gastroenteritis involves preventing dehydration through symptom monitoring, adequate rehydration, and the use of ORT, with ondansetron if needed. This systematic review identified facilitators and barriers perceived by healthcare professionals and caregivers among 11 domains of the TDF. Healthcare professionals benefited from knowledge about guidelines and management. The implementation of tools to regulate healthcare professionals' behaviour and skills, such as ORT administration protocols and a nurse triage system, facilitated the home management as well. For caregivers, lack of knowledge about the disease, symptoms, and management barriered home management, while access to information resources, along with positive emotions and beliefs in caregivers' own capabilities served as facilitators for managing their child with gastroenteritis at home.

Synthesis of data

Healthcare professionals

Healthcare professionals' knowledge of guidelines and the efficacy of ORT facilitated home management reflected by increased guideline adherence and ORT prescription. This is consistent with research involving older children with gastroenteritis (average age 8 years), where educating medical trainees led to increased appropriate ORT and ondansetron use.[38] Conversely, a lack of awareness among healthcare professionals about the benefits and side effects of ondansetron barriered home management as seen in reduced ondansetron administration. Recent studies have shown that oral ondansetron is (cost-)effective and safe in primary care.[12,39] However, it did not impact ORT use, a crucial aspect of home management, or referral and hospitalization rates.[12,39]

In this review, we found that implementing a combination of process changes designed to increase skills of healthcare professionals and regulate their behaviour facilitated home management. This was evident in increased use of ORT and a 45% decline in admission rates.[29] Among these process changes, offering free ORT during visits for gastroenteritis, was impactful. This finding aligns with previous research, which showed that providing ORT to families during their visits significantly enhanced ORT use and reduced unscheduled return visits.[40] Notably, single process changes increased appropriate ORT use but did not affect revisit or hospitalization rates. Previous research on practice changes revealed that combining multiple process changes produces better outcomes compared to single changes.[41,42] Therefore, it is advisable to incorporate several process changes to optimize home management for children with acute gastroenteritis. Nonetheless, it remains intriguing to explore factors influencing return visits and hospitalizations as with single process changes appropriate ORT usage, and therefore home management, improves.

Caregivers

Central to home management is the caregivers' fear of missing something serious and concerns about the child's safety.[33] This review highlights the impact of negative emotions, such as stress, worry, uncertainty, and helplessness, acting as barriers to optimal home management, while positive emotions, including feelings of comfort, security and being taken seriously, facilitate home management. Previous research found that fears and concerns for childhood diseases are often influenced by personal experiences, stories from others, and information sourced from the internet.[43,44] Therefore, there is a critical need for consistent and reliable information, as supported by this review, where the availability of resources facilitated home management for caregivers. Bernhardt et al. found that mothers, especially in the first few years following delivery, tend to be information seekers especially on the internet.[45] In this review, we found that resources providing information in various forms, such as video instructions, information sheets, and monitoring calls, are facilitators for managing children with gastroenteritis at home. However, no impact was evaluated on the emergency department return visit rate. For childhood fever, caregivers who had access to an illness-focused interactive booklet on childhood fever had a significant reduction in their intention to reconsult for similar illnesses.[46] It would be interesting to see what kind of information resource would facilitate home management the most for children with acute gastroenteritis. By evaluating information resources, it is important to keep in mind that only 61% of caregivers can identify more than one sign of dehydration and the definition of diarrhoea is not completely understood.[47] In this review, we found information deficits in various areas, including aetiology of the disease, recognizing signs and (alarm) symptoms (of dehydration), knowing management options, and determining when to seek professional help. This information should therefore be included in the information resources.

Limitations

This review has some potential limitations. First, only peer-reviewed studies written in languages familiar to the research team were included, spanning from 2003-2023. As guidelines on gastroenteritis and home management have undergone changes in recent years, we believe that studies published more than 20 years ago are less applicable to the current context. Also, in 2003 an overview of barriers for ORT was already published.[9] Second, the search strategy employed in our systematic review did not include healthcare professionals in the search terms, potentially resulting in the omission of relevant articles. However, manual searches conducted in the literature did not yield additional studies beyond those already included in our systematic review. Lastly, the broad and subjective definition of facilitators and barriers for home management has a degree of interpretive variability. To reduce this bias, data extraction and mapping them to the TDF was independently performed by two researchers and discussed within the research team in case of discrepancies.

Quality assessment

The overall quality of the included studies was appropriate. Upon evaluating study design, most of the facilitators and barriers as perceived by healthcare professionals were drawn from quantitative studies, whereas a predominant proportion for caregivers' perspectives stemmed from qualitative studies. In terms of level of evidence, quantitative studies possess a higher rating if performed correctly.[48] Noyes et al. concluded that combining quantitative and qualitative evidence within reviews can offer enhanced insight into understanding complex interventions and underlying implementation systems.[49] Nonetheless, as qualitative studies exploring healthcare professionals' view are missing and further research is needed in this area.

Conclusions

Optimizing home management for children with acute gastroenteritis is a complex process involving both healthcare professionals and caregivers. For healthcare professionals, it is advisable to incorporate combined process changes focusing on increasing their knowledge (about guidelines, ORT, and ondansetron effectiveness), improving their skills (e.g., ORT nurse), providing ORT during visits, and implementing clinical decision support systems. For caregivers, the focus should be on increasing knowledge (about gastroenteritis and dehydration), resources targeting education (e.g., written information about home management) and reassurance (e.g., monitoring call from a nurse). By addressing these aspects, an effective strategy for optimizing home management for children with acute gastroenteritis could be established, potentially allowing more children to be treated at home.

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Appendix 1. Search strategies by data source

PubMed

1	"Gastroenteritis"[Mesh:NoExp] OR "Gastritis"[Mesh] OR Gastroenteritis[tiab] OR Gastroenteritides[tiab] OR Gastritis[tiab]
2	"Child"[Mesh] OR "Infant"[Mesh] OR child*[tiab] OR infan*[tiab] OR pediatr*[tiab] OR paediatr*[tiab] OR school*[tiab] OR preschool*[tiab] OR toddler*[tiab] OR kids[tiab] OR neonat*[tiab] OR young adult*[tiab] OR early life[tiab] OR early in life[tiab] OR early age[tiab] OR younger age[tiab] OR young age[tiab] OR "Family"[Mesh] OR parent*[tiab] OR mother*[tiab] OR father*[tiab] OR caregiver*[tiab] OR famil*[tiab] OR grandparent*[tiab]
3	"Home Care Services"[Mesh] OR home[tiab] OR homes[tiab] OR homecare*[tiab] OR "Self Care"[Mesh] OR "self care"[tiab] OR house*[tiab] OR "Patient Care Management"[Mesh] OR "preadmission management"[tiab] OR "nursing management"[tiab] OR "Fluid Therapy"[Mesh] OR fluid*[tiab] OR ors[tiab] OR oral rehydration*[tiab] OR advice*[tiab] OR educat*[tiab] OR inform*[tiab] OR "Diet"[Mesh] OR diet*[tiab] OR safety net*[tiab] OR antibiot*[tiab] OR "Antiemetics"[Mesh] OR antiemetic[tiab]
4	"Norway" OR "Switzerland" OR "Ireland" OR "Hong-Kong" OR "Iceland" OR "Germany" OR "Sweden" OR "Australia*" OR "Netherland*" OR "Dutch" OR "Denmark" OR "Singapore" OR "Finland" OR "United-Kingdom" OR "New-Zealand" OR "Belgium" OR "Canada" OR "United-States" OR "Austria" OR "Liechtenstein" OR "Japan" OR "Israel" OR "Slovenia" OR "Luxembourg" OR "South-Korea" OR "Andorra" OR "Latvia" OR "Portugal" OR "Slovakia" OR "Spain" OR "France" OR "Czech*" OR "Malta" OR "Italy" OR "Estonia" OR "United-Arab-Emirates" OR "Greece" OR "Cyprus" OR "Lithuania" OR "Poland" OR "UK" OR "US" OR "USA" OR "UAE" OR "NZ" OR "Greenland" OR "United-States" OR "Hong-Kong" OR "HK" OR "Croatia" OR "developed-countr*" OR "developed-nation*" OR "industrialized-countr*" OR "industrialized-nation*" OR "industrialised-countr*" OR "industrialised-nation*"
5	booksdocs[Filter] OR casereports[Filter] OR comment[Filter] OR editorial[Filter] OR guideline[Filter] OR letter[Filter] OR practiceguideline[Filter] OR preprint[Filter] (1 AND 2 AND 3 AND 4) NOT 5 Filter: from 2003-3000/12/12

Embase (via Ovid)

1	gastritis/ or acute gastroenteritis/ or gastroenteritis/ or viral gastroenteritis/
2	(Gastroenteritis or gastroenteritides or gastritis).tw,kf,dq.
3	(Child* or infan* or pediatr* or paediatr* or school* or preschool* or toddler* or kids or neonat* or young-adult* or early-life or early-in-life or early-age or younger-age or young-age or Family or parent* or mother* or father* or caregiver* or famil* or grandparent*).tw,kf,dq,hw.
4	exp home care/
5	exp self care/
6	exp patient care/
7	exp fluid therapy/
8	exp diet/
9	exp antiemetic agent/
10	(home or homes or homecare* or self-care or house* or Patient-Care-Management or preadmission-management or nursing-management or fluid* or ors or oral-rehydration* or advice* or educat* or inform* or diet* or safety-net* or antibiot* or antiemetic).tw,kf,dq.
11	exp developed country/
12	(Norway or Switzerland or Ireland or Hong-Kong or Iceland or Germany or Sweden or Australia* or Netherland* or Dutch or Denmark or Singapore or Finland or United-Kingdom or New-Zealand or Belgium or Canada or United-States or Austria or Liechtenstein or Japan or Israel or Slovenia or Luxembourg or South-Korea or Andorra or Latvia or Portugal or Slovakia or Spain or France or Czech* or Malta or Italy or Estonia or United-Arab-Emirates or Greece or Cyprus or Lithuania or Poland or UK or US or USA or UAE or NZ or Greenland or United-States or Hong-Kong or HK or Croatia or developed-countr* or developed-nation* or industrialized-countr* or industrialized-nation* or industrialised-countr* or industrialised-nation*).tw,kf,dq,hw.
13	(1 or 2) and 3 and (4 or 5 or 6 or 7 or 8 or 9 or 10) and (11 or 12)
14	case report/
15	limit 14 to (conference abstract or conference paper or “conference review” or editorial or letter or “preprint (unpublished, non-peer reviewed)”)
16	13 not (14 or 15)
17	limit 16 to yr=”2003 -Current”

Web of Science

1	Gastroenteritis OR gastroenteritides OR gastritis
2	Child* OR infan* OR pediatr* OR paediatr* OR school* OR preschool* OR toddler* OR kids OR neonat* OR young-adult* OR early-life OR early-in-life OR early-age OR younger-age OR young-age OR Family OR parent* OR mother* OR father* OR caregiver* OR famil* OR grandparent*
3	home OR homes OR homecare* OR self-care OR house* OR Patient-Care-Management OR preadmission-management OR nursing-management OR fluid* OR ors OR oral-rehydration* OR advice* OR educat* OR inform* OR diet* OR safety-net* OR antibiot* OR antiemetic
4	Norway OR Switzerland OR Ireland OR Hong-Kong OR Iceland OR Germany OR Sweden OR Australia* OR Netherland* OR Dutch OR Denmark OR Singapore OR Finland OR United-Kingdom OR New-Zealand OR Belgium OR Canada OR United-States OR Austria OR Liechtenstein OR Japan OR Israel OR Slovenia OR Luxembourg OR South-Korea OR Andorra OR Latvia OR Portugal OR Slovakia OR Spain OR France OR Czech* OR Malta OR Italy OR Estonia OR United-Arab-Emirates OR Greece OR Cyprus OR Lithuania OR Poland OR UK OR US OR USA OR UAE OR NZ OR Greenland OR United-States OR Hong-Kong OR HK OR Croatia OR developed-countr* OR developed-nation* OR industrialized-countr* OR industrialized-nation* OR industrialised-countr* OR industrialised-nation*
#1 AND #2 AND #3 AND #4 and 2003-2023	

CINAHL

1	(MH "Gastroenteritis") OR (MH "Gastritis")
2	Gastroenteritis or gastroenteritides or gastritis
3	Child* or infan* or pediatr* or paediatr* or school* or preschool* or toddler* or kids or neonat* or young-adult* or early-life or early-in-life or early-age or younger-age or young-age or Family or parent* or mother* or father* or caregiver* or famil* or grandparent*
4	(MH "Home Health Care+")
5	(MH "Self Care+")
6	(MH "Patient Care+")
7	(MH "Fluid Therapy+")
8	(MH "Diet+")
9	(MH "Antiemetics+")
10	home or homes or homecare* or self-care or house* or Patient-Care-Management or preadmission-management or nursing-management or fluid* or ors or oral-rehydration* or advice* or educat* or inform* or diet* or safety-net* or antibiot* or antiemetic
11	(MH "Developed Countries")
12	Norway or Switzerland or Ireland or Hong-Kong or Iceland or Germany or Sweden or Australia* or Netherland* or Dutch or Denmark or Singapore or Finland or United-Kingdom or New-Zealand or Belgium or Canada or United-States or Austria or Liechtenstein or Japan or Israel or Slovenia or Luxembourg or South-Korea or Andorra or Latvia or Portugal or Slovakia or Spain or France or Czech* or Malta or Italy or Estonia or United-Arab-Emirates or Greece or Cyprus or Lithuania or Poland or UK or US or USA or UAE or NZ or Greenland or United-States or Hong-Kong or HK or Croatia or developed-countr* or developed-nation* or industrialized-countr* or industrialized-nation* or industrialised-countr* or industrialised-nation*
13	(s1 or s2) and s3 and (s4 or s5 or s6 or s7 or s8 or s9 or s10) and (s11 or s12) Limit 2003 – present; peer reviewed

Appendix 2. Theoretical Domains Framework

TDF Domains	Definition
Knowledge	An awareness of the existence of something
Skills	An ability or proficiency acquired through practice
Beliefs about capabilities	Acceptance of the truth, reality, or validity about an ability, talent, or facility that a person can put to constructive use
Beliefs about consequences	Acceptance of the truth, reality, or validity about outcomes of a behaviour in a given situation
Optimism	The confidence that things will happen for the best or that desired goals will be attained
Intentions	A conscious decision to perform a behaviour or a resolve to act in a certain way
Goals	Mental representations of outcomes or end states that an individual wants to achieve
Memory, attention and decision processes	The ability to retain information, focus selectively on aspects of the environment and choose between two or more alternatives
Emotion	A complex reaction pattern, involving experiential, behavioural, and physiological elements, by which the individual attempts to deal with a personally significant matter or event
Behavioural regulation	Anything aimed at managing or changing objectively observed or measured actions
Social/professional role and identity	A coherent set of behaviours and displayed personal qualities of an individual in a social or work setting
Social influences	Those interpersonal processes that can cause individuals to change their thoughts, feelings, or behaviours
Environmental context and resources	Any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence, and adaptive behaviour
Reinforcement	Increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimulus
Knowledge	An awareness of the existence of something
Skills	An ability or proficiency acquired through practice
Beliefs about capabilities	Acceptance of the truth, reality, or validity about an ability, talent, or facility that a person can put to constructive use
Beliefs about consequences	Acceptance of the truth, reality, or validity about outcomes of a behaviour in a given situation
Optimism	The confidence that things will happen for the best or that desired goals will be attained

TDF Domains	Definition
Intentions	A conscious decision to perform a behaviour or a resolve to act in a certain way
Goals	Mental representations of outcomes or end states that an individual wants to achieve
Memory, attention and decision processes	The ability to retain information, focus selectively on aspects of the environment and choose between two or more alternatives
Emotion	A complex reaction pattern, involving experiential, behavioural, and physiological elements, by which the individual attempts to deal with a personally significant matter or event
Behavioural regulation	Anything aimed at managing or changing objectively observed or measured actions
Social/professional role and identity	A coherent set of behaviours and displayed personal qualities of an individual in a social or work setting
Social influences	Those interpersonal processes that can cause individuals to change their thoughts, feelings, or behaviours

Abbreviation: TDF = Theoretical Domains Framework.

CHAPTER 4

Acute gastroenteritis: a qualitative study of parental motivations, expectations, and experiences during out-of-hours primary care

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ABSTRACT

Purpose

Acute gastroenteritis is a common infectious disease in children younger than 6 years of age. Although it is a self-limiting disease, it nevertheless has a high consultation rate in primary care, especially during out-of-hours primary care (OOH-PC). Reasons for this high consultation rate remain unclear.

Methods

The aim of this qualitative study was to explore parental motivations, expectations, and experiences of OOH-PC contacts for children with acute gastroenteritis. We conducted 14 semi structured interviews with parents who contacted OOH-PC in the Netherlands. Interviews were audio-recorded, transcribed, and analysed using elements of grounded theory and a constant-comparison approach.

Results

Unusual behaviour of the sick child, absent micturition, and ongoing vomiting and/or diarrhoea, with decreased or no fluid intake, motivated parents to contact OOH-PC. Parents initiated contact to prevent symptom deterioration and to be reassured by a general practitioner (GP), expecting them to perform a thorough physical examination, provide information, and make follow-up plans. Parents reported dissatisfaction if they felt unheard, misunderstood, or not taken seriously, and this increased their likelihood of seeking another consultation. General practitioners did not always meet parental expectations.

Conclusion

Multiple factors affect the decision for parents to contact OOH-PC for their child with gastroenteritis. There is a mismatch between parental expectations and actions of the GP. Awareness regarding parental feelings and understanding their expectations can guide GPs in the interaction with parents, which could improve satisfaction with primary health care and OOH-PC specifically.

INTRODUCTION

Acute gastroenteritis is among the top 5 most common reasons for parents consulting a general practitioner (GP) or out-of-hours primary care (OOH-PC) service with a sick child.[1-3] However, we know little about what motivates parents, or indeed, what they expect and experience during OOH-PC consultations for this indication.

During the period 2007 to 2014 in the Netherlands, the incidence of acute gastroenteritis in young children decreased, while the incidence of face-to-face contact with OOH-PC increased from 51.6% to 55.2%.[4] Referrals for children with acute gastroenteritis increased by an average of 3% per year,[5] but it has been suggested that 45% of these could have received treatment at home.[6] In high- and middle-income countries, acute gastroenteritis is a self-limiting disease, with good treatment options at home.[7] Parental motivations for contacting primary care have been investigated for other childhood diseases (e.g., acute otitis media and respiratory tract symptoms) or have been conducted in settings where children are more seriously ill (e.g., emergency departments).[8-11] Parental motivations regarding other childhood diseases cannot be directly translated to childhood gastroenteritis because this disease presents with other symptoms, affecting parents differently.

Knowledge of parental motivations, expectations, and experiences could improve GP care and increase parental satisfaction with OOH-PC contacts, treatments, and outcomes, while providing opportunities to increase self-management by parents. In this study, we aimed to explore parental motivations, expectations, and experiences of OOH-PC contacts for children with acute gastroenteritis.

METHODS

We performed a qualitative study using semi structured interviews, following the Consolidated Criteria for Reporting Qualitative Research and the Standards for Reporting Qualitative Research.[12,13] The Medical Ethics Committee of the University Medical Centre Groningen approved the study (registry No. 202000674).

Setting

Out-of-hours primary care services in 3 cities in the north of the Netherlands (Groningen, Assen, and Zwolle) took part. In the Netherlands, large-scale cooperatives provide OOH-PC services that cover primary care during evenings, nights, and weekends. These services provide an extension of the gatekeeping function to secondary care outside of normal working hours. When people call the OOH-PC, triage nurses assess the urgency of the health problem by telephone and triage all contacts into 1 of 3 options: telephone advice, consultation at the OOH-PC, or home visit by a GP[14]

Study Population

Parents contacting OOH-PC for a child younger than 6 years with acute gastroenteritis were eligible for inclusion and approached by telephone within 3 weeks of their contact with OOH-PC. We only included Dutch-speaking participants who provided written informed consent. They received information regarding the study and were asked to take part. We used purposive sampling to obtain representation of the following characteristics: contact type (telephonic or in-person consultation), gender and age of the child (<1 year, 1-2 years, 2-3 years, >3 years).[15] At inclusion, we assessed gender and age of the parents, parental work status (employed or unemployed), parental education level (low, intermediate, or high vocational), household composition (1 or 2 parents), and number of children.

Data Collection

We collected data from January 2021 to March 2021 using a semi structured interview guide. We used grounded theory with sensitizing concepts for the construction of the interview guide.[16] Sensitizing concepts can direct researchers in certain ways and can provide starting points for building analysis and creating an interview guide.[17] Based on the literature[18-25] and discussions within the research group, we formulated the following concepts: parental motivations, expectations, and experiences when contacting OOH-PC for a child with acute gastroenteritis (arranged chronologically before, during, and after the contact). In the interviews, we addressed these concepts with open questions. Based on the interview guide (Table 1), a trained researcher (A.A.H.W.) conducted semi structured audio-visual online interviews. Another trained researcher (J.T.) observed the interviews and added questions as necessary. We performed interviews until thematic saturation appeared to be achieved by iterative data analysis. We completed 4 additional interviews in which no new codes were found. All interviews were audio-recorded, transcribed verbatim, and anonymized. Each parent received a written summary for response validation.

Analysis

We analysed the data using the constant-comparison method, marked by an iterative process, in which each code was constantly compared with other codes.[16,26] First, open coding was performed by 2 researchers (A.A.H.W. and J.T.), in which a large number of codes were developed to describe the data. The 2 researchers had different backgrounds (Appendix 1) to enhance the reliability of the results by focusing on topics from different perspectives. A third researcher (I.J.B.) checked all of the interview coding for inconsistencies. Thereafter, axial coding was used to investigate the relations between codes that were developed in the open coding process, resulting in different categories. Selective coding was then used to group all different categories into overarching themes. During data collection and analysis, experts in the research group with different backgrounds discussed the codes, categories, and overarching themes and made adjustments as necessary (Appendix 1). We used Atlas.ti software version 8.4 (Scientific Software Development GmbH) for analysis.

Table 1. Interview guide

Questions asked in relation to contact	
Before	Could you tell me what happened before you contacted the OOH-PC? Could you tell me about what you did prior to contacting the OOH-PC? What were your feelings before the contact? Did you have previous experience with a sick child? What was the impact of the illness of your child? What was the trigger to contact the OOH-PC? What other things did you do or think to do before contacting the OOH-PC? What were your expectations from the contact?
During	And then you had the contact, could you tell me what happened next? What did the general practitioner do? How was the contact with the general practitioner? How was it for your child?
After	What was the course of the disease after the contact? How do you look back at the contact? Did you have any positive or negative experiences with the contact? What would you do next time? Were your expectations fulfilled? What advice would you give to the OOH-PC?

Abbreviation: OOH-PC = out-of-hours primary care.

RESULTS

Figure 1 provides an overview of the categories, with overarching themes and their interactions.

Participants

Fourteen parents took part in single semi structured interviews, which lasted 30 to 45 minutes. These included 11 mothers (78.6%) and 3 fathers (21.4%) with an average age of 32 years (range, 22-46 years). Table 2 summarizes their key characteristics.

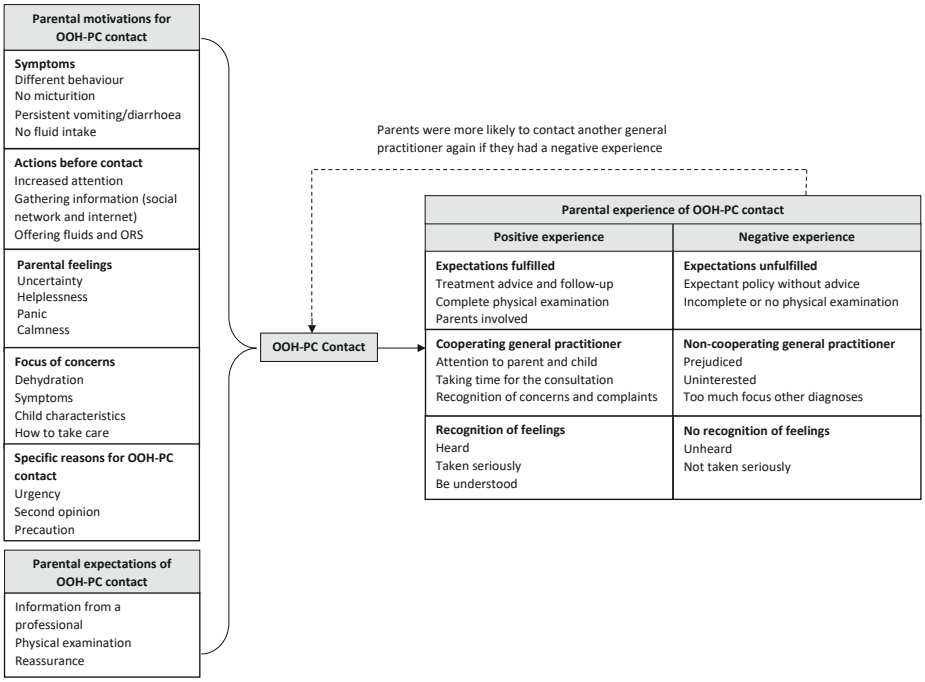

Figure 1. Overarching themes and their interactions

Abbreviations: OOH-PC = out-of-hours primary care. ORS = oral rehydration solution.

Table 2. Participant characteristics (n = 14)

Characteristic	Number (%)
Child sex, female	6 (42.9)
Child age, y	
<1	5 (35.7)
1–2	4 (28.6)
2-3	4 (28.6)
>3	1 (7.1)
Contact Type	
Telephonic	3 (21.4)
Consultation	11 (78.6)
First born child	10 (71.4)
Parent sex, female	11 (78.6)
Parent age, y	
20–29	5 (35.7)
30–39	8 (57.1)
40–49	1 (7.1)
Contacting parent employed	12 (85.7)
Educational level	
Intermediate vocational	6 (42.9)
Higher vocational	8 (57.1)
Type of household	
Single-parent	3 (21.4)
Two-parent	11 (78.6)
Number of children	
1	7 (50.0)
2	5 (35.7)
3	2 (14.3)

Parental Motivations for OOH-PC Contact

Multiple factors affected parental motivation to contact OOH-PC. These included their child's symptoms, the actions taken before contact, and their feelings, concerns, and specific reasons for OOH-PC contact (e.g., urgency, second opinion, or precaution).

Symptoms

Parents immediately sought OOH-PC contact for 3 major symptoms. The most important was a change in their child's behaviour, including the child becoming almost unresponsive, but lack of micturition for a while and the combination of ongoing vomiting and/or diarrhoea with decreased or no fluid intake also prompted contact. Although fever could be present, it was not the main motivator.

> "I thought, now I am going to call because this is no longer my child." (Parent A06, age 27 years, female)

Actions Before Contact

To manage symptoms, parents often performed various actions before contacting OOH-PC. These comprised paying extra attention to their sick child, gathering information from their social network and/or the internet, and offering fluids and/or oral rehydration solution more frequently and in different ways. Seeking information reassured some parents but caused anxiety for others. Failure to respond to increased fluid offerings often prompted consultation.

> "We worried way too much about what was said on the internet, especially about how much she should drink." (Parent G03, age 35 years, male)

Parental Feelings

Parental feelings of uncertainty, helplessness, and panic were important motivations for OOH-PC contact. Uncertainty focused on a range of questions including, Are we on the right track?, What is it?, Will the symptoms ever stop?, and When should we call?, with particular uncertainty expressed about whether they could call OOH-PC with the current symptoms. Parents felt helpless when fluid loss continued and when their child did not want to drink or take oral rehydration solutions. Some parents reached the stage of panic when their child became less alert, or the vomiting did not stop. In addition, emotions during OOH-PC contact differed between parents seen face-to-face and by telephone, with parents who had telephone contact being calmer.

> "You feel helpless because you see your child is suffering. You just don't know what to do anymore. There is nothing you can do." (Parent A01, age 22 years, female)

Focus of Concerns

Parents expressed concerns about 4 general aspects of the illness and its management. First, they reported concerns about dehydration, given that their child kept losing fluids because of vomiting and/or diarrhoea without replenishing those losses with suitable fluid intake. Second, the duration of fever, change in their child's behaviour, and perceived pain also increased their concerns. Third, the household type and child's age appeared to influence the amount of parental concern, with younger child age and parental inexperience (i.e., first child) associated with greater worry.

> "You worry, of course. It is your first child, so it is also the first experience. You rely purely on your feelings." (Parent G04, age 35 years, female)

Fourth, given that acute gastroenteritis is a contagious disease, parents who also got sick expressed concern about how to take care of their child while sick themselves.

Specific Reasons for OOH-PC Contact

Most parents contacted OOH-PC instead of their own GP because of the perceived urgency, reporting that they felt a consultation could not wait until the next working day. Other parents reported contacting the OOH-PC service because they felt that their own GP had not listened to them adequately.

> "Then we thought, we want someone to look at our child. If our own general practitioner is not willing to do that, we will go to the out-of-hours primary care." (Parent Z01, age 30 years, female)

Others cited doing so as a precaution, reporting fear that symptoms might worsen, a desire to prevent dehydration, and/or not wanting to take any risk.

Parental Expectations of OOH-PC Contact

Parents expected to receive information, for their child to undergo a physical examination, and to be reassured by a GP. Specifically, they wanted information regarding different aspects of the disease such as the required amount of fluid intake, the symptoms to be aware of, and what to do in given situations. In addition, they expected the GP to perform an adequate investigation, including physical examination of their child. Reassurance varied from excluding other diagnoses to reassurance about the amount of dehydration.

> "We hoped to get answers to the questions, What is it? What is going on? What should we do? What can we do to get her through this? When does it go wrong?" (Parent G02, age 32 years, male)

Parental Experience of OOH-PC Contact

The actions and attitudes of GPs affected parental experiences. In general, parents experienced the contact as satisfying if their expectations were met and they felt the GP cooperated and recognized their feelings. If this did not happen, parents reported dissatisfaction with the OOH-PC contact.

Fulfilment of Expectations

Parents thought that GPs should identify parental expectations and that if met, the experience will be more positive. Parents reported satisfaction if they received information and advice on how to improve fluid intake, alarm symptoms, what to expect over the course of the disease, and when and whom to call.

> "Advice for the general practitioner: explain to parents how the body works when the child has gastroenteritis and where it comes from. Try to explain this well, so that parents feel better when they end the contact. A very important thing, I think, is to ask if the parents are reassured before they go. Just ask, reassure the parents, and then let them go. Did the parents receive an answer to their question, or do they have further questions? Treat them like humans and not a number." (Parent A04, age 35 years, female)

By contrast, parents reported dissatisfaction if they received no information about the disease or follow-up.

> "The general practitioner said, 'she is not dehydrated, so we cannot do anything for her.' So, basically, I went [to the out-of-hours primary care] for nothing." (Parent A07, age 29 years, female)

Parents felt satisfied when their child received a complete physical examination and when the GP involved them in the examination. Parents appreciated it when the GP thoughtfully described the next steps. By contrast, they reported dissatisfaction when the GP performed little or no physical examination.

Attitude of the General Practitioner

Parents also mentioned the importance of the GPs' attitude, reporting greater satisfaction when the GP paid attention to both the parent(s) and the child. This included the GP being empathetic and showing sympathy for the situation. Parental satisfaction also increased when they perceived that the GP had taken enough time and had acknowledged their concerns about their child's symptoms.

> "They saw she was really sick. The general practitioner said, 'it is good that you came,' and that recognition for the visit is quite nice to hear." (Parent A09, age 27 years, female)

The GP could generate parental dissatisfaction by presenting an attitude indicating that they had a prejudice (i.e., a young mother or single parent), showing no interest (i.e., appearing nonchalant or uncaring), or focusing too much on another diagnosis that the parent had neither presented with nor complained about.

> "The first question the general practitioner asked was, 'Is this your first child?' Even if it had been my third child, I would still have gone there. I did not experience that as very pleasant…The general practitioner just had certain statements and a way of communicating. I am a young mother and sometimes people look at that, that happens, and that is very annoying." (Parent A01, age 22 years, female)

Feelings of Parents

Satisfaction with the contact improved if parents felt heard, taken seriously, and understood by the GP.

> "The general practitioner listened very carefully. She did everything, [did a] full check from head to toe and really listened. I sat there for a long time, I think like 25 minutes. I felt really heard." (Parent A04, age 35 years, female)

In retrospect, parents reported dissatisfaction with the contact because they felt unheard or not taken seriously. This applied, for example, when the GP focused more on the computer than on the parent, did not acknowledge parental worries, and did not recognize the child's complaints. Parents often said that they know their own child best and felt that their authority was denied if the GP expressed an alternative opinion.

> "Then the general practitioner said, 'I don't think your son is drowsy, don't worry.' He wanted to explain to me what a drowsy child was. I don't think I am stupid, and I thought my child was drowsy, and I wanted someone to look at him." (Parent A01, age 22 years, female)

Parents reported that failure to take their concerns seriously had a significant effect on their negative feelings. They sometimes felt that the GP judged them as being overprotective parents, which they considered very unpleasant.

> "I was not taken seriously at all. I got the feeling like, oh god, there you have her again." (Parent A02, age 34 years, female)

If satisfied with the contact by having their expectations met, parents felt that they would be less likely to contact their own GP or OOH-PC again. They also said that good advice about acute gastroenteritis and dehydration could help them with future illnesses and perhaps even prevent GP or OOH-PC contact.

DISCUSSION

In this qualitative study, we investigated parental motivations, expectations, and experiences regarding OOH-PC contacts for children with acute gastroenteritis. Parental motivations to contact OOH-PC were a change in their child's behaviour, absent micturition, and a combination of persistent vomiting and/or diarrhoea with decreased or no fluid intake. These features led to parental concern and OOH-PC contact to prevent symptom deterioration. In addition, we found that most parents became dissatisfied with OOH-PC when they felt unheard, misunderstood, or not taken seriously. In turn, this dissatisfaction made them more likely to seek another consultation with a GP. Parents mainly expected to be reassured by the GP, which could be achieved by providing information, making follow-up plans, and performing thorough physical examinations. Unfortunately, GPs did not always fulfil these expectations.

Strengths and Limitations

A strength of this study is that the same interviewer completed all of the interviews to ensure consistency. The interviewer was not employed at the OOH-PC to optimize objectivity. In addition, the research group in which codes were discussed and analysed comprised a range of experts with different backgrounds, helping to improve the analysis. The fact that we performed interviews online, owing to the coronavirus disease 2019 pandemic, could be a limitation, though research has shown similar parent responses with audio-visual media and in-person interviews.[27]

Comparison With Existing Literature

Parental Motivations for OOH-PC Contact

This study found that a different behaviour of the child motivated parents to contact OOH-PC. A prior study of rotavirus gastroenteritis revealed a greater effect on parents' daily activities and greater parental distress with increased changes in the child's behaviour.[28] Our findings add to the hypothesis that behavioural changes might increase anxiety and therefore cause parents to contact OOH-PC (Figure 1). In addition, we found that ongoing vomiting and/or diarrhoea with decreased or no fluid intake and absent micturition caused parents to contact OOH-PC. Interestingly, fever was not a main motivator for parents of children with gastroenteritis to contact OOH-PC. This might be explained by the fact that in the Netherlands, parents have easy access to well-designed and trustworthy information regarding how to handle fever.[29] This might decrease the feeling of helplessness regarding childhood diseases.

With respect to childhood diseases, parents actively search for information before contacting the GP.[20] For parents of children with gastroenteritis, we found that internet, personal network, or prior consultations for the same condition were important sources of information before contacting OOH-PC. Prior studies of childhood fever revealed that

an informative booklet for parents decreased the intention to reconsult for similar feverish illnesses.[30,31] Increasing knowledge and providing reliable information might increase self-management and decrease anxiety and helplessness for parents.

Parental Expectations of OOH-PC Contact

In accordance with the existing literature, we found that parents expected to receive information, a physical examination of their child, and to be reassured by a GP.[9,25] Research has shown that a physical examination is valued as an important component of a consultation and is reassuring for parents.[20,32] A new finding of the present study was the specific information parents of children with gastroenteritis need about different aspects of the disease such as the required amount of fluid intake, the symptoms to be aware of, and what to do in given situations.

Parental Experience of OOH-PC Contact

Regarding the actions of the GP, parents were generally satisfied if they received adequate treatment advice with follow-up appointments. A previous study concluded that parents of children with gastroenteritis were satisfied with telephone nursing advice if a follow-up call was offered and felt more secure if someone called them back.[33] We also found increased parental satisfaction when the GP paid attention to both the parents and the child, which is supported by qualitative research investigating how to facilitate consultations with children aged 1 to 2 years.[34] Parents reported a positive experience with OOH-PC if they felt heard, taken seriously, and understood by a GP. General practitioners could facilitate this by showing interest in wanting to know what the parent had to say, taking time to manage the child, listening carefully, and asking questions that the parents felt applied to them. We conclude that the general principles of good communication are especially important when dealing with parents of children with acute gastroenteritis. This is critical, given that parents are the principal caregivers of their child and are in a unique position to provide an informed overall view of their health.[35]

Implications

The results of this study indicate that it is important for GPs to keep in mind that some children are not severely sick or dehydrated, but parents might be worried and want to prevent severe illness. In addition to reassurance, parents are in need of clear, practical information regarding the natural course of the disease, alarm symptoms, and when to contact again. For childhood fever, it appears that access to an illness-focused interactive booklet decreased the intention to consult again for a similar illness.[31] This could also be valuable for childhood gastroenteritis. Studies have shown that effective communication with parents requires GPs to have a better understanding of parental concerns and their causes.[36,37] When parents feel that their needs are met, they are more likely to accept GPs' advice and decisions, even when this differs from their expectations.[32] This simple focus on communication could be all that is needed to improve the therapeutic relationship, improve parental satisfaction, and perhaps decrease reattendance. Moreover, if correctly triaged

based on both clinical and parental need, a telephone call could be sufficient when parents only require information and not necessarily a physical examination.

Conclusions

This study provides important information regarding parental motivations, expectations, and experiences that could serve as a reminder for GPs to provide more appropriate care, strengthened by listening to parents, taking them seriously, and understanding their feelings and worries. The parents of children with acute gastroenteritis have valid worries, and when the symptoms of their child reach a certain point, they will search for reassurance from GPs. Parents will have a more positive experience when a GP performs a complete physical examination, provides clear information about the disease course, discusses alarm symptoms, and meets parental expectations. Delivering on these preferences might improve parental satisfaction and decrease reattendance in primary care.

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Appendix 1. Backgrounds of the research group members

Name researcher	Background
Anouk AH Weghorst	MD/PhD candidate, BSc
Marian J van den Brink	General Practitioner, PhD, epidemiologist
Irma J Bonvanie	Trainee paediatrician, MD, PhD
Jolanda Tuinstra	Sociologist, health and well-being, PhD
Maria v Gosliga	Remedial educationalist, behavioural scientist, MD
Gea A Holtman	Epidemiologist, PhD
Elleke Landeweer	Empirical ethics researcher, PhD
Marjolein Y Berger	Professor of general practice, general practitioner, MSc, Epidemiology.

CHAPTER 5

Course of uncomplicated acute gastroenteritis in children presenting to out-of-hours primary care

Anouk AH Weghorst
Irma J Bonvanie
Gea A Holtman
Michiel R de Boer
Marjolein Y Berger

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ABSTRACT

Background

The aim of this article is to describe the courses of vomiting, diarrhoea, fever, and clinical deterioration, in children with uncomplicated gastroenteritis at presentation. This study was performed as a 7-day prospective follow-up study in an out-of-hours primary care service. The course of vomiting, diarrhoea, and fever was analysed by generalized linear mixed modelling. Because young children (≤ 12 months) and children with severe vomiting are at increased risk of dehydration, the potentially more complicated courses of these groups are described separately. The day(s) most frequently associated with deterioration and the symptoms present in children who deteriorated during follow-up were also described.

Results

In total, 359 children presented with uncomplicated acute gastroenteritis to the out-of-hours primary care service. Of these, 31 (8.6%) developed a complicated illness and needed referral or hospitalization. All symptoms decreased within 5 days in most children (> 90%). Vomiting and fever decreased rapidly, but diarrhoea decreased at a somewhat slower pace, especially among children aged 6–12 months. Children who deteriorated during follow-up had a higher frequency of vomiting at presentation and higher frequencies of vomiting and fever during follow-up.

Conclusions

The frequency of vomiting, not its duration, appears to be the more important predictor of deterioration. When advising parents, it is important to explain the typical symptom duration and to focus on alarm symptoms. Clinicians should be vigilant for children with higher vomiting frequencies at presentation and during follow-up because these children are more likely to deteriorate.

INTRODUCTION

Acute gastroenteritis is a common childhood disease that contributes significantly to the burden of primary care consultations.[1-3] Characterized by vomiting and/or diarrhoea with or without fever,[4,5] it typically results in an uncomplicated minor illness that can be managed safely at home.[3,6] However, it can also lead to severe dehydration, particularly in young children and in children with severe vomiting. [5,7] Given these risks, safety netting is recommended for children with acute gastroenteritis who do not require referral.[8]

Safety netting advice should include clear parental education about the expected disease course, possible alarm symptoms, and when and where to seek further help.[9] The goal of safety netting is to increase parental self-efficacy to take care of their ill child while ensuring that children who deteriorate are re-evaluated.[10] Ideally, advice should be tailored to each child, taking into account risk factors for dehydration and a more complicated illness course, such as young age (≤ 12 months) and severe vomiting.[5,8] There is evidence that safety netting reduces the reattendance of febrile children in primary care.[10] However, a lack of knowledge about the expected duration of symptoms in an uncomplicated disease course means that current advice is not comprehensive. It is also unclear when deterioration occurs, and indeed, what symptoms are typically present at that time. Improving the knowledge of the expected course of acute gastroenteritis could help both general practitioners (GPs) and parents to distinguish children in need of re-evaluation or referral from among the vast number who will have an uncomplicated course.

In this study, we aimed to describe the courses of vomiting, diarrhoea, fever, and clinical deterioration in children for 7 days after presenting to primary care with uncomplicated gastroenteritis.

METHODS

Design and setting

This study used data obtained for a previous cohort study and a randomised controlled trial (RCT) for evaluating the (cost-)effectiveness of oral ondansetron added to care-as-usual.[11,12] The original research was conducted at three out-of-hours primary care (OOH-PC) centres in the north of the Netherlands from 2015 to 2018. A detailed description of the study design has been described elsewhere.[13] All parents of the included children gave written informed consent. The Medical Ethics Review Committee of the University Medical Centre of Groningen approved this study (NL5830).

Participants

Children were included in the RCT if they were aged 6 months to 6 years, had a diagnosis of acute gastroenteritis, and were considered at risk of dehydration,[5] which was based on two criteria: 1) ≥ 4 vomiting episodes in the 24 h before attending the OOH-PC centre; and 2) ≥ 1 vomiting episode in the 4 h before attending the OOH-PC centre. Antiemetic use or prescription in the 6 h before presentation was the main exclusion criteria for the RCT. Included children were randomly allocated to either care-as-usual (oral rehydration therapy) or care-as-usual plus one dose of 0.1 mg/kg oral ondansetron.[11,12] The only inclusion criteria for the parallel cohort were that the child was age 6 months to 6 years and had a diagnosis of acute gastroenteritis. All parents of children from the cohort study and RCT completed a diary for 7 days.

Data of children included in the RCT and cohort were included in the current study if the children had uncomplicated acute gastroenteritis at presentation. A complicated illness was defined as requiring referral to, or hospitalization in, a paediatric emergency department immediately after presentation. Children referred at baseline were therefore excluded.

Patient recruitment and baseline assessment

Parents of consecutive children presenting to the OOH-PC with vomiting and/or diarrhoea were informed about the studies by a research assistant before the GP consultation. If parents were interested, the research assistant started baseline assessment and collected demographic and medical data. Subsequently, the GP confirmed or refuted the diagnosis of acute gastroenteritis and assessed the degree of dehydration. Children were included by the research assistant based on the GP's diagnosis, the baseline data, and receipt of informed consent from parents.

Outcomes

The primary outcome was to describe the courses of vomiting, diarrhoea, and fever over the 7-day follow-up period among children with uncomplicated acute gastroenteritis. Secondary outcomes were the day on which deterioration occurred and the prevalence of each symptom on the day of deterioration.

Measurements

Parents were asked to complete a diary for 7 days. In the first 4 h, they were asked to report on their child's progress and any health care use each hour; thereafter, they reported on these daily until 7 days after presentation. Data from the first day of the diary were omitted from analysis because they only accounted for the first 4 h and not a full 24-h period, as reported for all other days.

In the diary, parents state if each symptom had been present in the past 24 h (yes/no). A vomiting episode was defined as the forceful expulsion of stomach contents.[14] Diarrhoea was defined as the passage of three or more loose or liquid stools per day (Bristol type 6 or 7).[5,8] Fever was defined as a body temperature of 38.0 °C or more. Because young children (≤ 12 months) and those with severe vomiting are at increased risk of dehydration, and thereby a complicated course, the courses for these groups were described separately.[5,8] Deterioration was defined as referral or admission to hospital during follow-up. We recorded the day of deterioration and the symptoms present on the follow-up days.

Statistical analysis

Descriptive statistics were used to report the baseline characteristics, including the risk factors and alarm symptoms of dehydration. Baseline data are reported as medians and interquartile ranges (IQR) or as numbers and percentages.

The courses of vomiting, diarrhoea, and fever were analysed by generalized linear mixed models (GLMMs). First, we created a new variable with child subgroups from a 2 × 2 cross-tabulation of age (≤ 12 months versus > 12 months) and severe vomiting (yes versus no). This new variable, time (in days), the interaction between these variables, and ondansetron use (yes versus no), were set as fixed effects. Ondansetron use was included to adjust for potential confounding by medication use. As ondansetron was associated with an increase in episodes of diarrhoea, we additionally checked this for our population.[15] We accounted for repeated measures by including a random intercept at the child level, and we assumed missing data to be missing at random. Estimated percentages and 95% confidence intervals are presented for the GLMM.

Frequency of deterioration is described by day of follow-up, using bar charts, and we describe the differences in baseline characteristics between children who did and did not deteriorate during follow-up. In addition, the presence of vomiting, diarrhoea, and fever were compared between groups.

Data were analysed using IBM SPSS, version 25.0 (IBM Corp., Armonk, NY, US).

RESULTS

Participant flow and baseline characteristics

Participant flow is shown in Figure 1. In total, 1061 children were screened for eligibility at one of the three participating OOH-PC centres. Finally, data for 359 children were used in the analyses. Their median age was 1.5 years (IQR, 0.9–2.2 years) and 184 (51.3%) were female.

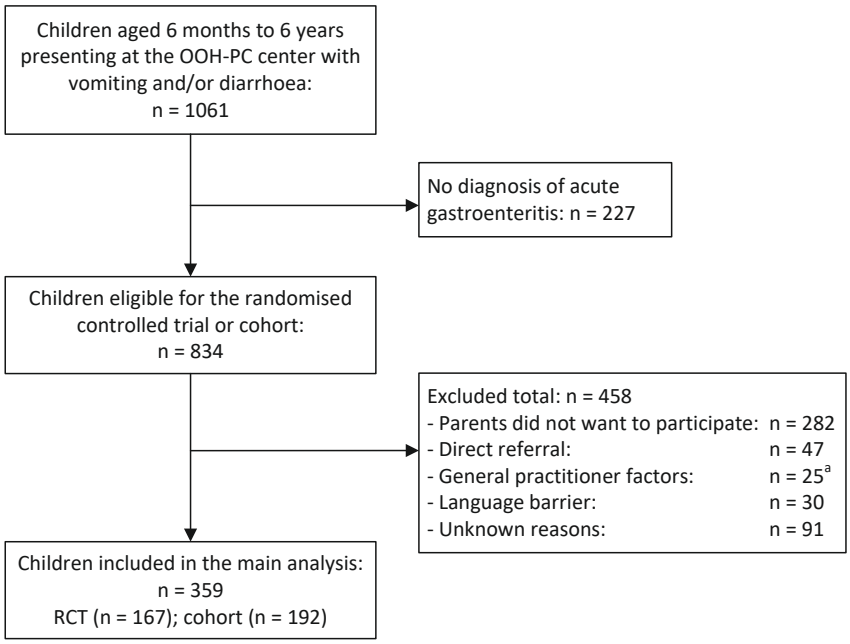


Figure 1. Flow of participants

[a]GP objected to ondansetron use (n = 16) or did not agree with inclusion (n = 9). Abbreviations: GP = general practitioner. OOH-PC = out-of-hours primary care. RCT = randomised controlled trial.

The median duration of vomiting before presentation was 2 days (IQR, 1.0–3.0 days). Diarrhoea was present in 181 (50.7%) children and the median duration before presentation was 3 days (IQR, 2.0–4.0 days) (Table 1). Severe vomiting and age 6–12 months were the most common risk factors for dehydration, being present in 244 (68.0%) and 103 (28.7%) children, respectively. The most frequent alarm symptom for dehydration was no urine output for 24 h, which was present in 45 (13.3%) children (Table 2).

Table 1. Baseline characteristics

Baseline characteristics	n	Included	n	Deterioration follow-up	n	Hospitalized follow-up
Gender (female)	359	184 (51.3)	31	15 (48.4)	18	8 (44.4)
Age in years	359	1.5 (0.9-2.2)	31	1.6 (0.8-2.5)	18	1.5 (0.8-2.0)
Weight in kg	296	11.1 (9.5-14.0)	29	11.5 (9.5-13.6)	17	10.0 (9.5-12.8)
Vomiting present	357	328 (91.9)	31	29 (93.5)	18	17 (94.4)
Duration of vomiting prior to presentation OOH-PC in days	326	2.0 (1.0-3.0)	29	2.0 (1.0-3.0)	17	1.0 (0.9-2.5)
Frequency of vomiting past 24 hours	311	5.0 (3.0-8.0)	29	6.0 (3.0-17.0)	17	9.0 (3.5-18.0)
Diarrhoea present	357	181 (50.7)	31	14 (45.2)	18	10 (55.6)
Duration of diarrhoea prior to presentation OOH-PC in days[a]	180	3.0 (2.0-4.0)	13	2.0 (1.5-3.0)	9	3.0 (1.5-5.0)
Frequency of diarrhoea in past 24 hours[a]	167	5.0 (4.0-7.0)	14	5.0 (3.0-8.5)	10	5.0 (3.0-8.5)
Dehydration assessed by GP (0-100%)	339	20.0 (9.0-35.0)	31	20.0 (10.0-45.0)	18	20.0 (7.8-54.5)
Additional risk factors for dehydration[b]	357		31		18	
1		131 (36.7)		13 (41.9)		7 (38.9)
≥2		30 (8.4)		3 (9.6)		2 (11.1)
Alarm symptoms of dehydration[c]	357		31		18	
1		50 (14.0)		8 (25.8)		6 (33.3)
≥2		8 (2.2)		1 (3.2)		1 (5.6)

Results are shown as Median (IQR) or N (%). [a]Numbers are only presented for participants with diarrhoea. [b]Risk factors assessed at baseline: ≥ 6 watery stools or diarrhoea, fever, and reduced intake. [c]Alarm symptoms assessed at baseline: confusion or decreased consciousness, bradycardia, weak peripheral heartbeat pulsations, capillary refill > 4 s, skin pitch > 4 s, extremities cold/marbled, and no urine output for 24 hours. Abbreviations: OOH-PC = Out-of-hours primary care. GP = General practitioner. IQR = interquartile range.

Table 2. Risk factors and alarm symptoms of dehydration

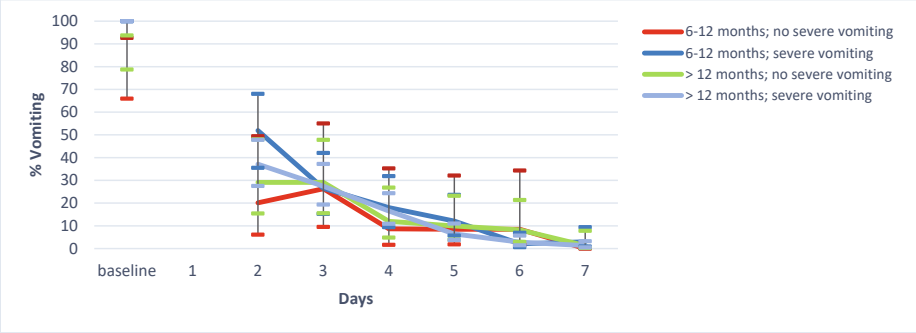
	n	Included	n	Deterioration follow-up	n	Hospitalized follow-up
Risk factors for dehydration						
Age 6–12 months	359	103 (28.7)	31	8 (25.8)	18	5 (27.8)
Severe vomiting[a]	359	244 (68.0)	31	25 (80.6)	18	15 (83.3)
≥ 6 watery stools	355	81 (22.8)	31	6 (19.4)	18	5 (27.8)
Fever (≥38°C)	346	84 (24.3)	31	11 (35.5)	18	4 (22.2)
Reduced intake in the last 12 hours	353	28 (7.9)	31	3 (9.7)	18	3 (16.7)
Alarm symptoms of dehydration						
Confused or decreased consciousness	357	10 (2.8)	31	2 (6.5)	18	2 (11.1)
Bradycardia	354	1 (0.3)	31	0 (0.0)	18	(0.0)
Weak peripheral pulse	353	0 (0.0)	31	0 (0.0)	18	(0.0)
Capillary refill > 4 s	356	1 (0.3)	31	1 (3.2)	18	1 (5.6)
Skin pitch > 4 s	356	1 (0.3)	31	1 (3.2)	18	1 (5.6)
Extremities cold/marbled	356	7 (2.0)	31	0 (0.0)	18	(0.0)
No urine output for 24 hours	338	45 (13.3)	29	6 (20.7)	16	4 (25.0)

Results are shown as n (%). [a]Severe vomiting is defined as at least four episodes of vomiting in the 24 hours before presentation and at least one episode of vomiting in the 4 hours before presentation.

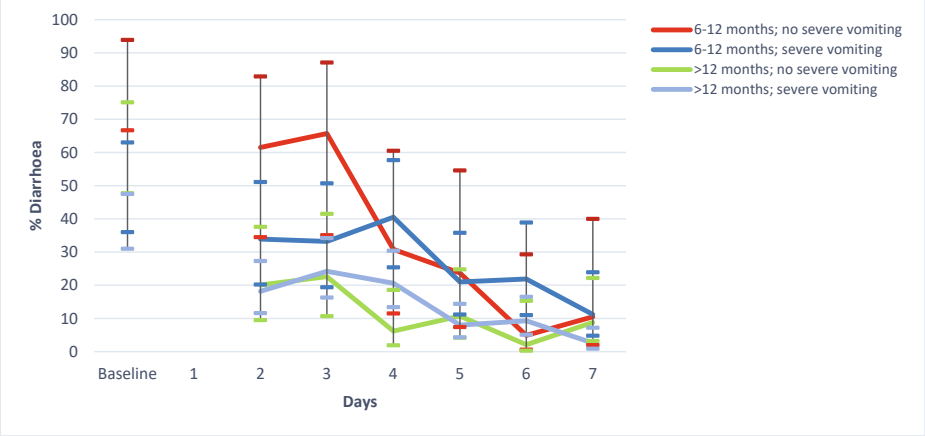
Presence of symptoms

Grouping children by age and vomiting severity produced four groups: age 6–12 months without severe vomiting (n = 32), age 6–12 months with severe vomiting (n = 71), age > 12 months without severe vomiting (n = 83), and age > 12 months with severe vomiting (n = 173). Estimated percentages and 95% confidence intervals for vomiting, diarrhoea, and fever are presented in Figure 2 and Appendix 1.

(a) Estimated mean percentage (95%CI) of children with vomiting per day



(b) Estimated mean percentage (95%CI) of children with diarrhoea per day



(c) Estimated mean percentage (95%CI) of children with fever per day

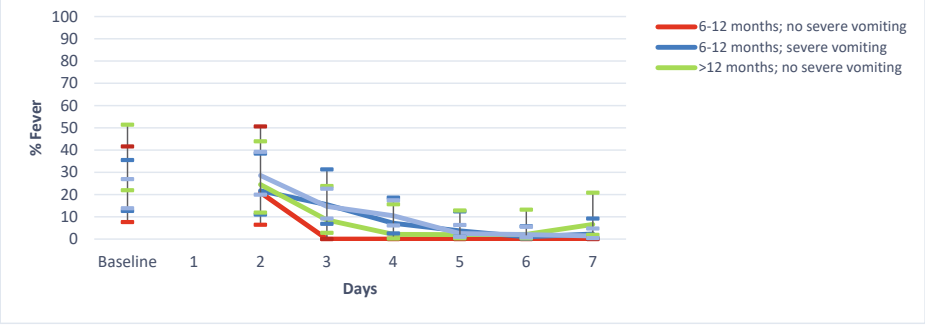


Figure 2. Estimated percentages of children with vomiting, diarrhoea, and fever over time *Abbreviation: 95%CI = 95% confidence interval.*

Most children presented with vomiting, and 20%–50% of these were still vomiting by day 2 after presentation, with the highest percentages among children with severe vomiting at presentation. By day 5, irrespective of risk group, these percentages had decreased to 10% (Figure 2a).

The percentage of children with diarrhoea at presentation varied by age and the presence of severe vomiting. The lowest percentage was 38.9% for children aged > 12 months with severe vomiting and the highest was 84.7% for children aged 6–12 months without severe vomiting. Notably, 10% of children aged > 12 months had persistent diarrhoea by day 5, but this threshold was only reached by day 7 for children aged 6–12 months (Figure 2b). There was no association found between ondansetron use and an increase in diarrhoea episodes.

Fever was present in 20%–40% of children at presentation, with < 10% having persistent fever at day 4. The course of fever was broadly comparable in all groups (Figure 2c).

Deterioration: referral or hospitalization

During follow-up, 31 children (8.6%) were referred to the emergency department and 18 (5.0%) of these were hospitalized. Most children deteriorated on days 2 and 3 after presenting (Appendix 2). Children who were hospitalized had a median of 1 day of vomiting prior to presentation compared to 2 days in children who were not hospitalized during follow-up; however, hospitalized children had higher median frequencies of vomiting at presentation (9 vs 5 in 24 h) (Table 1). During follow-up, children who deteriorated had higher frequencies of vomiting and fever, but the frequencies of diarrhoea throughout follow-up were similar to those of children who did not deteriorate (Appendix 3).

DISCUSSION

Summary

This study described the courses of vomiting, diarrhoea, and fever over 7 days, together with the pattern of clinical deterioration, among children who present to OOH-PC centres with uncomplicated acute gastroenteritis. In total, 8.6% of children developed a complicated illness that required referral and 5.0% were hospitalized. Symptoms decreased by day 5 in > 90% of the children, except for diarrhoea in children aged 6–12 months. Vomiting and fever decreased rapidly while diarrhoea decreased at a slower pace, especially among younger children. There was a higher frequency of vomiting at presentation, and the symptoms of vomiting and fever persisted for longer, among children who deteriorated.

Limitations and strengths

A limitation of this is study is that the RCT focused on children who presented with excessive vomiting, indicating that children with severe vomiting could have been overrepresented, which in turn, could have influenced the observed course of the illness and its deterioration. However, we formed several analysis subgroups and separately evaluated the illness courses of children with and without severe vomiting. This design has the added benefit of enabling us to give advice tailored to a child's specific situation.

Despite this limitation, the study benefited from using prospectively collected data on daily progress and healthcare use for 359 children who presented with an uncomplicated course at the OOH-PC. The use of a parental diary over 7 days enabled us to gain insight into the courses of vomiting, diarrhoea, and fever among children with uncomplicated illnesses at presentation.

Comparison with existing literature

In this study, we tried to provide good safety netting advice for children with acute gastroenteritis in primary care. Thompson et al. already found that no diagnostic test or clinical decision rule in general practice is 100% sensitive.[9] The course of diseases differs between individuals and safety netting is therefore extremely important to give a diagnostic strategy to deal with diseases in primary care.

Over 90% of children stopped vomiting within 5 days after presentation in this study. Chow et al. reported that vomiting persisted for a mean duration of 1.84 days, which is far shorter than in our study. One reason for this discrepancy might be the difference in aetiology, with rotavirus known to cause illness that typically persists for 5 to 7 days.[16] Leung et al. reported that vomiting was almost four times more common and tended to be prolonged among children with rotavirus gastroenteritis compared with other etiological agents.[16,17] Given that an inclusion criterion for our RCT was severe vomiting, it is possible that more children with rotavirus gastroenteritis were included. However, the distribution of pathogens was not recorded in our study. Another possible reason for the longer duration of vomiting in our study is that we only included children who consulted a GP, whereas other studies also included children who did not consult a physician. A multicentre study that included 12 European hospitals previously demonstrated that vomiting was present in 20% of children on day 2 and in < 10% on day 5.[18] These secondary care data are comparable with ours for primary care.

The studies by Roslund et al. and Reeves et al. showed that diarrhoeal episodes persisted for 5 to 7 days after discharge from emergency departments.[19,20] This is consistent with the results of our study in primary care, although we add to this by providing insight into the roles of age and vomiting as a risk factor. Of note, 90% of children were free of diarrhoea on day 5 in the group aged > 12 months compared to day 7 in the group aged 6–12 months. We also found no association between ondansetron use and the increase in episodes of diarrhoea, as the circulating concentration of ondansetron is expected to reach 50% of its maximum serum level at 3 h after oral dosing.[21]

At presentation, ≤ 40% of children had a fever, consistent with the expected course of rotavirus gastroenteritis in which low-grade fever is typically seen in 30%–50% of children.[16] Also supporting existing literature on the uncomplicated course of childhood fever in primary care, fever resolved after 4 days in 90% of children.[22]

Most of the children who deteriorated did so on days 2 and 3 after presentation, in line with the findings of Friesema et al. who reported a median of 3 days to hospitalization.[23] In our study, children who deteriorated during follow-up showed higher frequencies of vomiting at presentation and during follow-up than children who recovered (9 vs 5 episodes in 24 h). In a study by Stephen et al., children with gastroenteritis referred to paediatric emergency departments also had 9 episodes of vomiting in the preceding 24 h.[14] This indicates that the frequency of vomiting is especially predictive of referral to the emergency department. Indeed, vomiting is one of the most important symptoms for considering failure of oral rehydration therapy.[24] GPs should therefore take particular care to note the frequency of vomiting at each assessment of a child with acute gastroenteritis.

Conclusions and implications for clinicians and policymakers

To provide good safety netting advice, it is necessary that we provide a full description of the expected duration of symptoms in an average uncomplicated course of acute gastroenteritis, detailing the predictors of deterioration whenever possible. Based on the present study, we recommend that GPs at the OOH-PC educate parents about the duration of symptoms and what alarm symptoms to monitor as part of this safety netting advice. It seems reasonable to advise that vomiting should resolve within 5 days and that fever should resolve within 4 days of presentation in 90% of children. Regarding diarrhoea, however, it is important to differentiate advice by the age of the child: children aged ≤ 12 months may have diarrhoea for a further 7 days, but children aged > 12 months should recover within 5 days. GPs may need to monitor closely those children who have higher frequencies of vomiting at presentation because these children deteriorated more often in our study. Although further research is needed to confirm these results, the advice is consistent with good practice and the results of other research in this field.

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Appendix 1. Estimated percentages and confidence intervals for symptoms by age and severity of vomiting

(a) Vomiting

Day	Age and severe vomiting[a]	Estimated percentages	95% CIs	
			Lower	Upper
Baseline	6–12 months; no severe vomiting	83.2	65.9	92.6
	6–12 months; severe vomiting	100.0	–	–
	> 12 months; no severe vomiting	88.1	78.7	93.7
	> 12 months; severe vomiting	100.0	–	–
2	6–12 months; no severe vomiting	20.1	6.1	49.4
	6–12 months; severe vomiting	51.9	35.5	68.0
	> 12 months; no severe vomiting	29.1	15.4	48.0
	> 12 months; severe vomiting	37.1	27.5	47.8
3	6–12 months; no severe vomiting	26.3	9.5	55.0
	6–12 months; severe vomiting	26.5	15.2	42.0
	> 12 months; no severe vomiting	29.1	15.5	47.8
	> 12 months; severe vomiting	27.4	19.3	37.2
4	6–12 months; no severe vomiting	8.7	1.6	35.2
	6–12 months; severe vomiting	18.0	9.4	31.8
	> 12 months; no severe vomiting	12.0	4.8	26.8
	> 12 months; severe vomiting	16.5	10.9	24.3
5	6–12 months; no severe vomiting	8.5	1.8	32.1
	6–12 months; severe vomiting	12.1	5.7	23.6
	> 12 months; no severe vomiting	9.9	3.9	23.2
	> 12 months; severe vomiting	6.4	3.7	11.0
6	6–12 months; no severe vomiting	8.5	1.6	34.3
	6–12 months; severe vomiting	2.1	0.6	6.9
	> 12 months; no severe vomiting	8.2	2.9	21.3
	> 12 months; severe vomiting	2.8	1.4	5.7
7	6–12 months; no severe vomiting	0.0	–	–
	6–12 months; severe vomiting	3.0	0.9	9.4
	> 12 months; no severe vomiting	1.3	0.2	7.8
	> 12 months; severe vomiting	1.3	0.5	3.2

(b) Diarrhoea

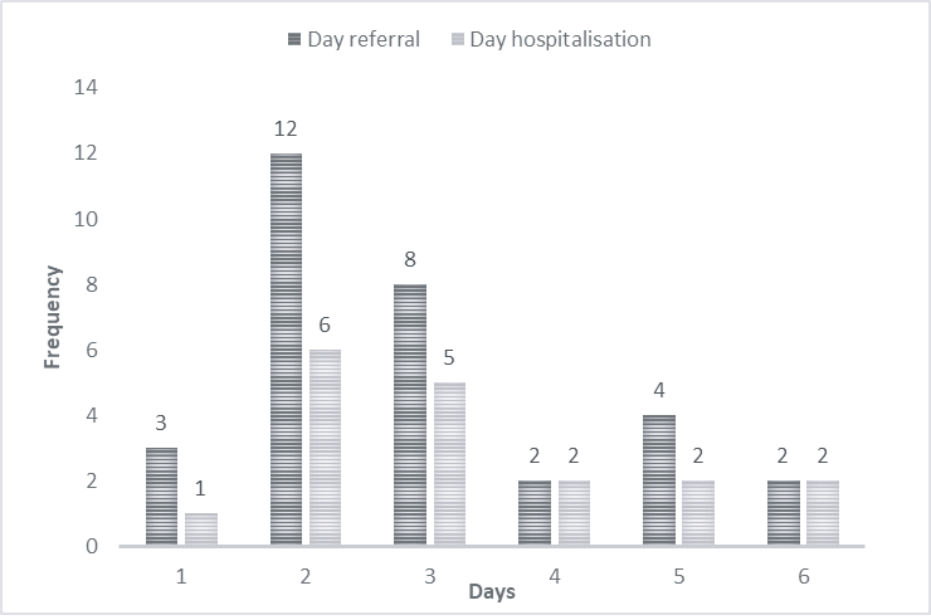
Day	Age and severe vomiting[a]	Estimated percentages	95% CIs	
			Lower	Upper
Baseline	6–12 months; no severe vomiting	84.7	66.7	93.9
	6–12 months; severe vomiting	49.5	36.0	63.0
	> 12 months; no severe vomiting	62.4	47.7	75.1
	> 12 months; severe vomiting	38.9	31.0	47.5
2	6–12 months; no severe vomiting	61.5	34.5	82.9
	6–12 months; severe vomiting	33.9	20.2	51.1
	> 12 months; no severe vomiting	20.1	9.5	37.6
	> 12 months; severe vomiting	18.2	11.6	27.3
3	6–12 months; no severe vomiting	65.7	35.1	87.1
	6–12 months; severe vomiting	33.2	19.4	50.7
	> 12 months; no severe vomiting	22.6	10.7	41.5
	> 12 months; severe vomiting	24.2	16.3	34.2
4	6–12 months; no severe vomiting	30.8	11.5	60.5
	6–12 months; severe vomiting	40.5	25.4	57.7
	> 12 months; no severe vomiting	6.2	1.9	18.6
	> 12 months; severe vomiting	20.6	13.4	30.4
5	6–12 months; no severe vomiting	23.7	7.4	54.6
	6–12 months; severe vomiting	21.0	11.2	35.8
	> 12 months; no severe vomiting	10.7	4.2	24.8
	> 12 months; severe vomiting	8.0	4.3	14.4
6	6–12 months; no severe vomiting	4.9	0.6	29.3
	6–12 months; severe vomiting	21.9	11.0	38.9
	> 12 months; no severe vomiting	2.1	0.3	15.3
	> 12 months; severe vomiting	9.3	5.1	16.5
7	6–12 months; no severe vomiting	10.5	2.0	40.0
	6–12 months; severe vomiting	11.2	4.8	23.9
	> 12 months; no severe vomiting	8.8	3.2	22.2
	> 12 months; severe vomiting	2.6	0.9	7.2

(c) Fever (≥38°C)

Day	Age and severe vomiting[a]	Estimated percentages	95% CIs	
			Lower	Upper
Baseline	6–12 months; no severe vomiting	19.5	7.6	41.6
	6–12 months; severe vomiting	21.9	12.6	35.5
	> 12 months; no severe vomiting	35.3	21.9	51.4
	> 12 months; severe vomiting	19.5	13.8	26.9
2	6–12 months; no severe vomiting	20.9	6.4	50.6
	6–12 months; severe vomiting	21.7	11.0	38.4
	> 12 months; no severe vomiting	24.5	11.9	43.9
	> 12 months; severe vomiting	28.6	19.9	39.2
3	6–12 months; no severe vomiting	0.0	–	–
	6–12 months; severe vomiting	15.5	6.8	31.3
	> 12 months; no severe vomiting	8.6	2.8	23.8
	> 12 months; severe vomiting	14.7	9.2	22.6
4	6–12 months; no severe vomiting	0.0	–	–
	6–12 months; severe vomiting	7.1	2.5	18.6
	> 12 months; no severe vomiting	2.1	0.2	15.6
	> 12 months; severe vomiting	10.5	6.1	17.4
5	6–12 months; no severe vomiting	0.0	–	–
	6–12 months; severe vomiting	3.7	1.0	12.4
	> 12 months; no severe vomiting	2.0	0.3	12.8
	> 12 months; severe vomiting	2.5	1.0	6.3
6	6–12 months; no severe vomiting	0.0	–	–
	6–12 months; severe vomiting	1.0	0.2	5.7
	> 12 months; no severe vomiting	2.1	0.3	13.2
	> 12 months; severe vomiting	2.0	0.7	5.5
7	6–12 months; no severe vomiting	0.0	–	–
	6–12 months; severe vomiting	2.3	0.5	9.2
	> 12 months; no severe vomiting	6.6	1.9	20.8
	> 12 months; severe vomiting	1.4	0.4	4.7

[a]Persistent vomiting was based on; 1) at least four episodes of vomiting 24 hours before presenting to the OOH-PC centre; and 2) at least one episode of vomiting in the 24 hours before presenting to the OOH-PC centre. All the measurements were corrected for medication. Abbreviations: 95% CI = 95% Confidence Interval. OOH-PC = out-of-hours primary care.

Appendix 2. Day of deterioration requiring hospital referral or admission



Appendix 3. Symptoms present by day of follow-up in children who deteriorated

	Baseline	2	3	4	5	6	7
Deterioration follow-up (n = 31)							
Vomiting	29 (93.5)	18 (58.1)	19 (61.3)	14 (45.2)	7 (22.6)	3 (9.7)	1 (3.2)
Diarrhoea	14 (45.2)	11 (35.5)	12 (38.7)	13 (41.9)	8 (25.8)	5 (16.1)	0 (0.0)
Fever	11 (35.5)	14 (45.2)	11 (35.5)	9 (29.0)	3 (9.7)	3 (9.7)	2 (6.5)
Hospitalised follow-up (n = 18)							
Vomiting	17 (94.4)	9 (50.0)	12 (66.7)	11 (61.1)	3 (16.7)	1 (5.6)	1 (5.6)
Diarrhoea	10 (55.6)	4 (22.2)	9 (50.0)	8 (44.4)	5 (27.8)	2 (11.1)	0 (0.0)
Fever	4 (22.2)	8 (44.4)	5 (27.8)	5 (27.8)	2 (11.1)	2 (11.1)	1 (5.6)

Results are shown as n (%)

CHAPTER 6

Recommendations for clinical research in children presenting to primary care out-of-hours services: a randomised controlled trial with parallel cohort study

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ABSTRACT

Background

Research in primary care is essential, but recruiting children in this setting can be complex and may cause selection bias. Challenges surrounding informed consent, particularly in an acute clinical setting, can undermine feasibility. The off-protocol use of an intervention nearing implementation has become common in pragmatic randomised controlled trials (RCTs) set in primary care.

Aim

To describe how the informed consent procedure affects study inclusion and to assess how off-protocol medication prescribing affects participant selection in a paediatric RCT.

Design & setting

A pragmatic RCT evaluating the cost-effectiveness of oral ondansetron in children diagnosed with acute gastroenteritis (AGE) in primary care out-of-hours services and a parallel cohort study.

Methods

Consecutive children aged 6 months to 6 years attending primary care out-of-hours services with AGE were evaluated to assess the feasibility of obtaining informed consent, the off-protocol use of ondansetron, and other inclusion and exclusion criteria.

Results

The RCT's feasibility was reduced by the informed consent procedure because 39.0% (n = 325/834) of children were accompanied by only one parent. GPs prescribed ondansetron off-protocol to 34 children (4.1%) of which 19 children were eligible for the RCT. RCT-eligible children included in the parallel cohort study had fewer risk factors for dehydration than children in the RCT despite similar dehydration assessments by GPs.

Conclusion

The informed consent procedure and off-protocol use of study medication affect the inclusion rate, but had little effect on selection. A parallel cohort study alongside the RCT can help evaluate selection bias, and a pilot study can reveal potential barriers to inclusion.

INTRODUCTION

Outcomes from RCTs are essential for GPs to provide evidence-based health care.[1] However, recruiting sufficient numbers of representative participants can be difficult, especially for acute paediatric management.[2] This is illustrated by the fact that 40% of paediatric RCTs are discontinued prematurely owing to poor recruitment.[2–4] Besides that, GPs who are aware of the effectiveness of the intervention may use this intervention, which can cause selection bias.[5]

Primary care is not an easy place to conduct research.[6] Although GP involvement in case recruitment can decrease the chance of successful inclusion,[1] not involving them is not always feasible and can be costly. In out-of-hours primary care centre (OOH-PC), GPs must also evaluate patients with whom they are unfamiliar, which may further decrease their willingness to recruit children into a trial and worsen the inclusion rate.[1] When trials are discontinued, authors rarely report how and by whom participants were recruited, which prevents any lessons learnt being applied when planning trials in other settings.[2] Ideally, authors would report the recruitment process of their trial in sufficient detail to help avoid the repetition of mistakes.[5] Pilot studies can be used to uncover reasons for recruitment failure.[5]

A pragmatic RCT was performed to investigate the cost-effectiveness of adding a single dose of oral ondansetron to care-as-usual (CAU) in an OOH-PC on the frequency of vomiting in children aged 6 months to 6 years with AGE. Despite a pilot study, child recruitment was challenging. In this report, the recruitment efforts are described, focusing on how the informed consent procedure and the use of off-protocol prescribing affected the inclusion rate and child selection, respectively.

METHODS

Study design

In the pragmatic RCT, participants were enrolled from December 2015 to January 2018 at three OOH-PCs in the north of the Netherlands (Groningen, Zwolle, and Assen). After a pilot study (NL4700) from December 2015 to October 2016, in agreement with the medical ethical committee (METc), the primary outcome was changed from 'referral rate' to 'proportion of children who continued vomiting in the first 4 hours after randomisation' because this was considered a more patient-oriented outcome by both the METc and the parents involved. The primary and secondary outcomes of the RCT are detailed in Appendix 1. The written informed consent procedure was also adapted because it could not be feasibly obtained from both parents, severely restricting inclusion. The METc agreed that children could be included from the pilot study in the amended RCT (NL5830), and a parallel cohort study was added. The parallel cohort study provides insight into the representativeness of the trial population and helps to assess the external validity in a non-invasive manner.[7,8] Follow-up was for 7 days after randomisation.

Participants

Inclusion criteria: RCT Children aged 6 months to 6 years were included who presented at the OOH-PC with vomiting and for whom the GP diagnosed AGE. Specifically, children were included if: 1) they reported at least four episodes of vomiting 24 hours before presentation; 2) they reported at least one episode of vomiting 4 hours before presentation; and 3) written informed consent was obtained from both parents. If the child was accompanied by one parent, that parent could give written informed consent and the second parent could give oral informed consent via a telephone call in the presence of the research assistant (RA). The written informed consent from the second parent had to be sent by post.

Exclusion criteria: RCT Children were excluded if: 1) they had used or been prescribed antiemetics in the previous 6 hours; 2) they had renal failure or hypalbuminaemia; 3) they had diabetes mellitus or inflammatory bowel disease; 4) they had a history of abdominal surgery that could explain the current symptoms according to the GP; 5) they had sensitivity to 5-HT3 receptor antagonists; 6) they had a prolonged QT interval or were using QT-prolonging medication; or 7) they had previously been enrolled.

Inclusion criteria: parallel cohort study Children aged 6 months to 6 years and diagnosed with AGE, but whose parents did not give written informed consent for the RCT, were asked if they were willing to participate in a parallel cohort study in which written informed consent was only needed from one parent.

Patient recruitment and baseline assessment

Parents were informed about the study by an RA before the GP consultation. If parents were interested, the RA started baseline assessments (Appendix 2) and the GP then assessed the child (confirming or refuting a diagnosis of AGE and assessing the degree of dehydration) and their suitability for participating based on the inclusion and exclusion criteria. The RA asked the parents of eligible children for written informed consent (Figure 1).

Randomisation and blinding

After obtaining at least one written and one oral informed consent from parents, children were block randomised (1:1 allocation) to intervention groups by a computer programme and were stratified by age (6–24 months or >24 months) and dehydration status (see Table 1: 'at risk' if no alarm symptoms, or 'dehydrated' if ≥1 alarm symptom). Allocation was not generated before inclusion to ensure concealment. Treatment allocation was not blinded to the parents, the child, the GP, or the RA. The researcher who performed the statistical analyses was blinded to treatment allocation.

Interventions

Control group and parallel cohort study: CAU Children received CAU (Figure 1) that comprised instructions to buy oral rehydration solution and how to use it, as described in the acute diarrhoea guideline of the Dutch College of General Practitioners.[9] That involved 10 ml/kg compensation when at risk of dehydration (that is, all children) and 15 ml/kg for 4 hours when assessed as dehydrated. Parents were informed about the expected course, alarm symptoms, and when and how to contact their GP.

Intervention group: ondansetron plus CAU Children in the intervention group received CAU plus a single weight-based dose of oral ondansetron syrup (0.1 mg/kg) according to the Dutch Paediatric Formulary.[10] If the child vomited within 15 minutes, the dose was given a second time only.

Follow-up assessment

Parents used a structured diary to record symptoms (that is, diarrhoea, vomiting, and fever), oral rehydration therapy and fluid intake, medication use, adverse reactions, healthcare use, hours missed from work, and satisfaction with treatment during follow-up. The diary was to be completed every hour for the first 4 hours and daily thereafter for 7 days. Parents could return the diary on paper with the enclosed envelope. If parents did not return the diary after multiple requests, information was collected about the primary outcome by telephone.

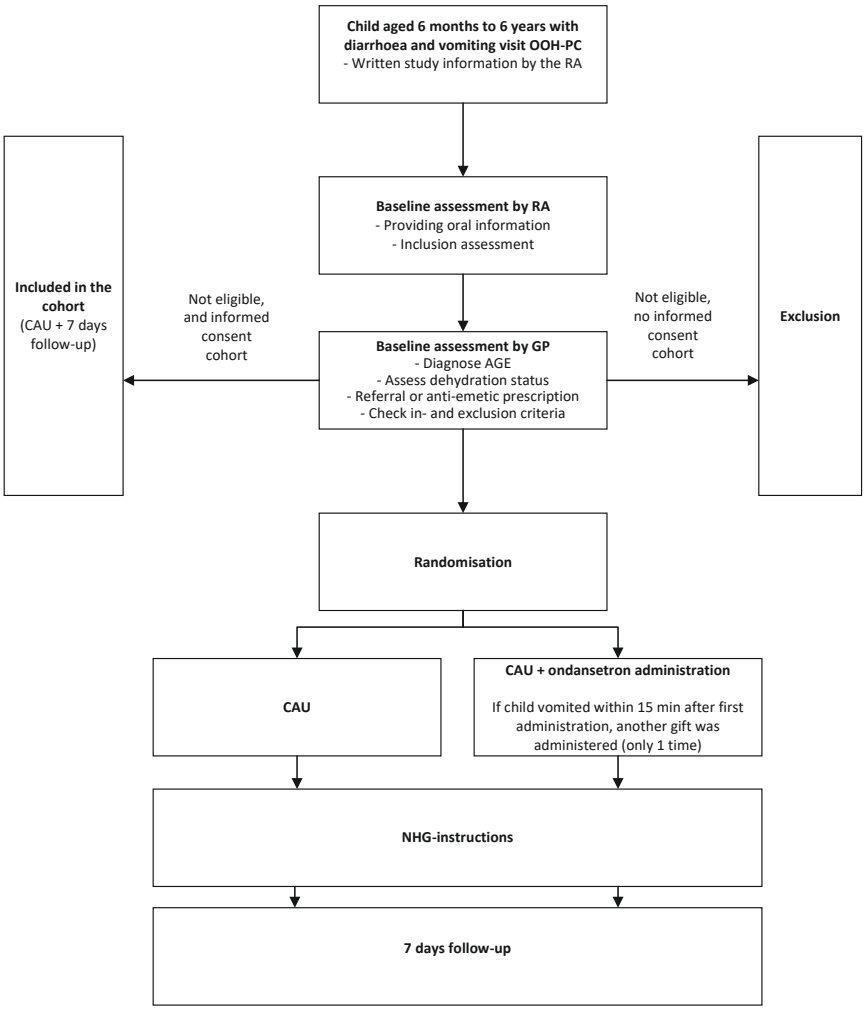

Figure 1. Study design

Abbreviations: AGE = acute gastroenteritis. CAU = care-as-usual. GP = general practitioner. OOH-PC = out-of-hours primary care. RA = research assistant.

Table 1. Alarm symptoms and risk factors for dehydration

Alarm symptoms of dehydration	Risk factors for dehydration
Confused or decreased consciousness	≥6 watery stools or diarrhoea
Bradycardia	Fever (>38°C)
Weak peripheral pulse	Reduced intake in the last 12 hours
Capillary refill >4 s	
Skin pitch >4 s	
Extremities cold/marbled	
Reduced urine output in the last 24 hours	

Sample size

Based on a systematic review, it was estimated that 85% and 64% of children in the CAU and ondansetron groups would continue vomiting after 4 hours,[11] indicating that a difference of 21% in the proportion of children with persistent vomiting was clinically relevant. Therefore, 89 children per arm needed to be included for a power of 90% and an α of 0.05, allowing for a 10% loss to follow-up.

Statistical analysis

The following baseline characteristics were assessed: age, sex, AGE symptoms (weight, duration or frequency of vomiting and/or diarrhoea), dehydration alarm symptoms, dehydration risk factors (see Table 1),[9] and degree of dehydration assessed by the GP (0–100 scale). To evaluate the impact of the informed consent procedure on the inclusion rate, the number of children with AGE who visited the OOH-PC with only one parent was reported. To evaluate the impact of the off-protocol prescription of ondansetron on the selection of children in the RCT, baseline characteristics of RCT-eligible children included in the parallel cohort study and for whom the GP prescribed ondansetron were non-statistically compared with children included in the RCT. To understand the overall level of selection bias, the baseline characteristics of RCT-eligible children included in the parallel cohort study were statistically compared with the baseline characteristics of children included in the RCT. Continuous variables were compared with non-parametric tests (Mann–Whitney U test) and dichotomous variables were compared by logistic regression. Statistical significance was defined by a two-tailed P value of <0.05, and all analyses were performed using SPSS (version 25).

RESULTS

Study population

The eligibility of 1061 children meeting the enrolment criteria were assessed. Of these, 834 had a GP diagnosis of AGE, with 194 ultimately randomised in the RCT and 201 included in the parallel cohort study. In total, 70 children were eligible for both the RCT and parallel cohort study and were included in the study analysis (Figure 2).

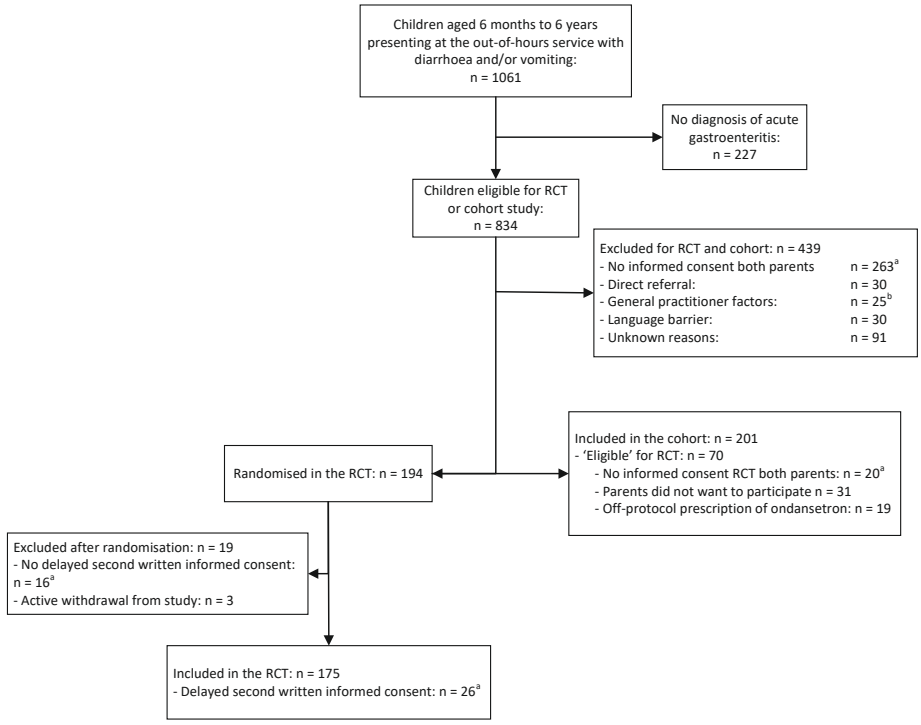

Figure 2. Study flow diagram

[a]Only one parent was present (n = 325). [b]GP objected to ondansetron use (n = 16) or did not agree with inclusion (n = 9). Abbreviation: RCT = randomised controlled trial.

Informed consent

In 39.0% (n = 325/834) of cases, only one parent accompanied the child with AGE. Adapting the consent procedure increased the inclusion rate from seven to 10 cases per month. Of the 194 randomised children, 42 were accompanied by only one parent (21.2%) and 16 (8.3%; eight from each RCT group) did not send the second written informed consent after giving verbal permission, so were excluded (Figure 2).

Table 2. Baseline characteristics of all children and those in each analysed subgroup of children

		Valid n	All included children (n = 175)	Valid n	Eligible, but included in parallel cohort study (n = 70)	Valid n	GP prescribed ondansetron (n = 19)
Demographics							
Median age, years (IQR)		175	1.50 (0.9–2.1)	69	1.5 (1.0–2.1)	18	2.0 (1.0–3.0)
Females, n (%)		175	88 (50.3%)	70	36 (51.4%)	19	10 (52.6%)
Symptoms							
Median weight, kg (IQR)		169	11.0 (9.5–14.0)	61	11.0 (9.1–13.5)	16	12.7 (11.0–16.5)
Median vomiting duration, days (IQR)		174	2.0 (1.0–3.0)	70	2.0 (1.0–3.0)	19	3.0 (2.0–4.0)
Median vomiting frequency per 24 hours (IQR)		171	5.0 (4.0–10.0)	66	7.0 (4.0–10.0)	19	8.0 (6.0–10.0)
Diarrhoea present, n (%)		174	124 (71.3%)	70	49 (70.0%)	19	13 (68.4%)
Median diarrhoea duration, days[a] (IQR)		124	2.0 (1.0–3.0)	49	1.0 (0.0–3.3)	13	3.0 (1.0–4.0)
Median diarrhoea frequency per 24 hours[a] (IQR)		123	3.0 (2.00– 5.0)	44	1.0 (0.0–4.0)	13	1.0 (0.0–4.0)
Management							
Median GP-assessed degree of dehydration (0–100), (IQR)		170	20.0 (10.0–40.0)	64	25.0 (10.0–39.0)	16	38.0 (30.0–58.0)
Use of concomitant medication		175	65 (37.1%)	66	19 (28.8%)	19	10 (52.6%)
Risk factors and alarm symptoms							
Dehydration: risk factors[b]	1	175	63 (36.0%)	70	22 (31.4%)	19	7 (36.8%)
	≥2	175	**18 (10.3%)**	70	**2 (2.9%)**	19	0 (0.0%)
Dehydration: alarm symptoms[c]	1	175	32 (18.3%)	70	5 (7.1%)	19	0 (0.0%)
	≥2	175	2 (1.1%)	70	3 (4.3%)	19	0 (0.0%)

***Bold** = result with a significant difference. .[a]Numbers only presented for those participants with diarrhoea. [b]Risk factors assessed at baseline were as follows: ≥6 watery stools or diarrhoea, fever (>38°C), and reduced intake in the last 12 hours. [c]Alarm symptoms assessed at baseline were as follows: confused or decreased consciousness, bradycardia, weak peripheral heartbeat pulsations, capillary refill >4 s, skin pitch >4 s, cold/marbled extremities, and reduced urine output in the last 24 hours. Abbreviations: GP = general practitioner. IQR = interquartile range.*

Off-protocol ondansetron prescribing

GPs prescribed ondansetron off-protocol to 34 (4.1%) of the 834 children with AGE, and 19 of these were eligible for participation in the RCT. There were no clinically relevant differences in baseline characteristics compared with children in the RCT, except that GPs estimated the degree of dehydration to be almost twice as high in these 19 cases compared with those in the RCT (38 versus 20; Table 2).

Selection bias

Compared with children in the RCT, the baseline characteristics of the 70 RCT-eligible children in the parallel cohort study did not differ with statistical significance except for the risk factors of dehydration. Children in the parallel cohort study had less risk factors for dehydration compared to children in the RCT (odds ratio = 0.22; 95% confidence interval = 0.11 to 1.00), but the median GP-assessed dehydration level did not differ with statistical significance (P = 0.302) (Table 2).

DISCUSSION

Summary

Almost 40% of all children attended with one parent, making it difficult to obtain informed consent as required and, thereby, complicating inclusion. GPs also prescribed off-protocol ondansetron if they suspected more severe dehydration, but this did not correspond with known dehydration risk factors or alarm symptoms. Children in the parallel cohort study had fewer additional risk factors for dehydration compared with children in the RCT.

Strengths and limitations

The authors are aware of no prior research assessing the pitfalls of the trial recruitment process in an OOH-PC. Consecutive children were screened presenting to one of the three OOH-PC over a period spanning more than 2 years, making this study highly representative of the population. Lessons have been learnt from the pilot, and a parallel cohort study has been added in which the children included have been evaluated. However, a limitation is that the RCT-eligible children in the parallel cohort study — to whom GPs prescribed ondansetron — was small (n = 19), precluding statistical testing with the children in the RCT. It should also be noted that the recommendations are based on the data from one RCT and a parallel cohort study.

Comparison with existing literature

Informed consent

Based on guidance for research involving humans, the METc decided that both parents must sign a parental consent form.[12] However, the risk for children in this RCT was deemed low to moderate, with sufficient evidence of effect in referred children and extremely low risk of adverse events.[13–15] In this study, almost 40% of children diagnosed with AGE at the

OOH-PC were accompanied by only one parent, but the acuteness of the clinical problem meant that inclusion and randomisation could not be delayed to obtain the second consent, potentially resulting in study exclusion. This problem with obtaining informed consent from both parents has been reported in other paediatric RCTs.[16,17]

Based on the results of a pilot study that confirmed the above, the METc agreed to an adapted procedure that increased the inclusion rate by three children per month. The adaptation allowed for one parent to give written informed consent and the second to give initial oral informed consent by telephone, with confirmation of written informed consent obtained by post. A second written informed consent for 16 children was not received despite calling repeatedly; but these children were randomised, eight received the study medication, and some even returned their diary. Nevertheless, they were excluded for protocol deviation, raising ethical concerns given that they had been randomised, had completed study activities, and had received the study medication.

Off-protocol ondansetron prescribing

Implementation of the study protocol created more awareness of the potential efficacy of ondansetron for children with AGE. In 34 children, GPs prescribed ondansetron off-protocol despite not being recommended in national guidelines.[9] After the pilot study, fearing that the effect of ondansetron would be diluted if prescribed in both study arms, it was decided to not include eligible children from the RCT if a GP prescribed ondansetron before randomisation. Their follow-up was monitored in the parallel cohort study instead.

A clinically relevant difference existed in the level of dehydration estimated by the GP between groups, but owing to the small group size (n = 19), this was without statistical significance. Among children receiving off-protocol ondansetron, the GP estimated dehydration to be almost twice that in children in the RCT (38 versus 20). Given that it was intended to assess the effect of ondansetron in children at increased risk of dehydration, excluding these may have resulted in an underestimation of the true effect of ondansetron. However, the study demonstrated no differences in risk factors or alarm symptoms of dehydration. Therefore, the level of dehydration estimated by the GP alone should be interpreted with caution.

Selection bias

The baseline characteristics of RCT-eligible children in the parallel cohort study did not differ from those of children in the RCT, except that those in the parallel cohort study had fewer risk factors for dehydration. This could imply that the parents of more severely dehydrated children were more willing to participate in the RCT. However, the median dehydration level assessed by the GP did not differ statistically between groups. Other studies have shown that there is no structured way of assessing dehydration in children with AGE,[18,19] meaning that determining the course of AGE and the risk of dehydration remain important challenges. Further research is needed to evaluate the prognostic value of risk factors and

GP-based assessments of dehydration. Given the number of additional risk factors and the GP estimates, the authors are confident that they included children at mild-to-moderate risk of dehydration, as intended.

Implications for practice

The authors' experiences indicate that there are four areas in which study designs like theirs need improving. First, there is a need to reconsider if written informed consent is required of both parents in pragmatic RCTs involving low risk to the child, especially in acute settings. There is need for future observational research to see how often both parents visit the OOH-PC with their child, as often the other parent stays at home for other caring responsibilities. By identifying the exact numbers for multiple childhood diseases, the need to reconsider this ethical decision increases even more. Consistent with this study's approach, it is thought that obtaining the written informed consent of one parent and the oral consent of the second parent, in the presence of the first parent and an RA, is ethically more responsible than excluding a child who otherwise engages in the study but for whom a second written consent form is not received. Second, GPs should receive information that starting with the intervention (or on a paediatrician's recommendation) during an RCT can seriously bias the outcomes. Communication with all stakeholders, to assess the barriers to protocol compliance, should be routine when performing (pragmatic) RCTs. Third, the authors recommend initiating a parallel cohort study to run alongside RCTs to ensure follow-up when parents do not want to participate in the RCT. This allows comparison of the characteristics of children who did and did not participate, and gives an opportunity to assess if the right population was included. Finally, initiating a pilot study before an RCT offers an invaluable opportunity to evaluate potential barriers to study inclusion and patient selection.

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CHAPTER 7

Oral ondansetron for paediatric gastroenteritis in primary care: a randomised controlled trial

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ABSTRACT

Background
Acute gastroenteritis (AGE) affects almost all children aged ≤5 years. In secondary care, ondansetron was found to be effective at reducing vomiting.

Aim
To determine the effectiveness of adding oral ondansetron to care as usual (CAU) to treat vomiting in children with AGE attending out-of-hours primary care (OOH-PC).

Design and setting
A pragmatic randomised controlled trial at three OOH-PC centres in the north of the Netherlands (Groningen, Zwolle, and Assen), with a follow-up of 7 days.

Methods
Children were included if they were: aged 6 months–6 years; AGE diagnosed by a GP; ≥4 reported episodes of vomiting in the 24 hours before presentation; ≥1 reported episode of vomiting in the 4 hours before presentation; and written informed consent from both parents. Children were randomly allocated to either the control group or the intervention group. The control group received CAU, namely oral rehydration therapy. The intervention group received CAU plus one dose of oral ondansetron (0.1 mg/kg).

Results
In total, 194 children were included for randomisation. One dose of oral ondansetron decreased the proportion of children who continued vomiting within 4 hours from 42.9% to 19.5%, with an odds ratio of 0.37 (95% confidence interval [CI] = 0.20 to 0.72, number needed to treat: four). Ondansetron also decreased the number of vomiting episodes within 4 hours (incidence rate ratio 0.51 [95% CI = 0.29 to 0.88]) and improved overall parental satisfaction with treatment (P = 0.027).

Conclusion
Children with AGE and increased risk of dehydration due to vomiting could be treated with ondansetron in primary care to stop vomiting more quickly and increase parental satisfaction with treatment. These results could be used to improve the quality and efficacy of general practice medicine.

INRODUCTION

Acute gastroenteritis (AGE) is common in young children and, although it is typically self-limiting, severe dehydration is an important complication.[1] Approximately 5% of all GP consultations with children in the Netherlands are for AGE.[2] Among those seen in primary care, 8.1% are referred to specialist care and 8000 are admitted to the hospital each year.[2,3] However, it is thought that many of these referrals and admissions can be avoided.[4]

International guidelines recommend care as usual (CAU) with oral rehydration therapy (ORT) to prevent and treat dehydration in children.[5] It has been shown that prescribing ORT with education can reduce hospital admission by up to 45%,[4,6–8] yet it is still underused in primary care; indeed, only 4% of all children overall with AGE received ORT through their GP.[9,10] A suggested reason for this underuse is that 70% of these children present with vomiting as the predominant symptom.[9] National paediatrics guidelines mention persistent vomiting as a predictor of ORT failure in children who are dehydrated;[11] as such, most GPs are less likely to prescribe ORT when the child predominantly presents with vomiting.[12]

Ondansetron has been reported to be safe and effective at stopping vomiting, increasing ORT success, and reducing hospitalisation rates among children presenting with AGE in secondary care;[13] however, the practical value of ondansetron for treating children with AGE in primary care is unknown. The authors aimed to conduct a pragmatic randomised controlled trial (RCT) to investigate the effect of ondansetron: added to CAU; compared with CAU alone; and on vomiting in children aged 6 months–6 years with AGE consulting out-of-hours primary care (OOH-PC) services.

METHODS

Study design

Participants were enrolled from December 2015 until January 2018 at three OOH-PC centres in the north of the Netherlands: one in Groningen, one in Zwolle, and one in Assen. A detailed description of the study design, recruitment strategy, outcomes, and discussion of the informed consent procedure are described elsewhere.[14] This study started with a pilot (Dutch Trial Register reference number: NL4700) undertaken from December 2015 until October 2016 but, as a result of the low inclusion rate, the primary outcome was changed from 'referrals' to 'vomiting'. In agreement with the Medical Ethics Review Committee of the University Medical Centre Groningen, children included from the pilot were also included in the new trial and the RCT was approved.

Inclusion and exclusion criteria

Children considered to be at increased risk of dehydration[15] were included if they met the following inclusion criteria:

- aged 6 months–6 years;
- diagnosis of AGE confirmed by a GP at the OOH-PC centre;
- ≥4 reported episodes of vomiting 24 hours prior to presentation; and
- ≥1 reported episode of vomiting 4 hours prior to presentation.

Children who met the following criteria were excluded:

- used, or prescribed, antiemetics in the previous 6 hours;
- known renal failure or hypoalbuminemia;
- known diabetes mellitus or inflammatory bowel disease;
- history of abdominal surgery that could explain the current symptoms (according to the GP);
- known sensitivity to 5-HT3 receptor antagonists;
- known prolonged QT interval, or current use of QT-prolonging medication; and
- previous enrolment in the study.

Additionally excluded were those children for whom no extended written informed consent of the second parent was received. Exclusion on this basis was performed after randomisation because of protocol violation as set by the university's Medical Ethics Review Committee.

Randomisation and blinding

Randomisation occurred after written informed consent was obtained from the consulting parent plus verbal informed consent from the second parent (in most cases they were at home).

After consent was gained, children were randomly allocated to one of two intervention groups at a ratio of 1:1. An online randomisation tool was used to generate the allocation sequence in direct response to participant inclusion by the research assistant; concealment was not an issue because allocation was only generated after randomisation. The allocation sequence was stratified by age (6–24 months or >24 months) and severity of dehydration ('at risk' for no alarm symptom or 'dehydrated' for ≥1 alarm symptom). Comparisons between groups were adjusted for these stratification factors.

Participants, parents, GPs, and research assistants were not blinded to the allocated treatment. Ondansetron has already been proven effective at reducing vomiting in blinded RCTs.[16,17] In this pragmatic RCT, the authors specifically aimed to investigate the potential effect of implementing ondansetron in routine primary care; blinding participants would, in this case, result in outcomes not translatable to daily practice. The statistician performing the analyses was blinded to the treatment allocation by an independent researcher. The primary outcome was not known by parents and GPs.

Interventions

Control group: CAU

CAU comprised instructions to buy oral rehydration solution and how to use it, as described in the acute diarrhoea guideline of the Dutch College of General Practitioners:[15] 10 ml/kg compensation when at risk of dehydration (that is, all children) and 15 ml/kg for 4 hours if a GP assessed the patient as being dehydrated. The research assistant provided the parents the instructions with a patient folder containing the same information, discussed alarm symptoms, and advised them to contact the GP if there was no improvement or symptoms worsened.[15]

The intervention: CAU plus ondansetron

Children allocated to the intervention group received the CAU described above plus a single weight-based dose of oral ondansetron syrup (0.1 mg/kg), in accordance with the Dutch Pediatrics Formulary.[18] If the child vomited within 15 min of administration, the same dose was repeated once, but a third dose was not given.

Outcomes

Parents completed diaries for 7 days. For the first 4 hours after presentation, they reported hourly; thereafter, they reported daily until 7 days after presentation. If parents did not return the diary after multiple requests, information about the primary outcome was collected by telephone.

Primary outcome

The primary outcome was the proportion of children who continued vomiting in the first 4 hours after randomisation. This evaluation point was chosen because the circulating concentration of ondansetron is expected to reach 50% of its maximum serum level at 3

hours after oral dosing, meaning that direct effects on vomiting are unlikely beyond 4 hours.[18] In addition, national guidelines recommend that GPs evaluate the effect of treatment on symptoms and assess the indications for referral in children with AGE by 4 hours after initial presentation.[8,11,15]

Secondary outcomes

The following outcomes were assessed up to 4 hours after randomisation:

- number of vomiting episodes per child;
- ORT intake (ml) per participant; and
- proportion of children who experienced ≥1 adverse event(s) related to ondansetron.

The following outcomes were assessed up to 7 days after randomisation:

- proportion of children referred to specialist care; and
- proportion of children admitted to hospital.

Finally, parental satisfaction with ondansetron therapy was assessed using a five-point Likert scale.

Statistical methods

Sample size

Based on a systematic review,[13] it was estimated that 85% of children in the CAU group and 64% of children in the intervention group would continue vomiting within 4 hours. It was calculated that 100 children per group were needed to achieve an alpha of 0.05 and a power of 0.90. To compensate for an expected loss to follow-up of 10%, the authors aimed to include 220 children.[19,20] For the intention-to-treat (ITT) analysis, the authors were able to include 88 and 87 children in the intervention and control groups, respectively; therewith, the power remained >80% (sample size n = 166).

Handling of missing data

Using logistic regression, the authors explored whether baseline characteristics were related to missing values relating to their outcomes. For all single outcomes, further inspection of frequencies and distribution of values gave no indication that the missing values were related to the true values themselves (that is, values were distributed as theoretically expected). In addition, Little's[21] Missing Completely at Random test was not statistically significant (P-value $\chi 2$ 0.76); thus, it was assumed that the missing data were missing at random. Appendix 1 gives an overview of the baseline characteristics of complete cases versus participants with missing values.

All available participant data were entered as predictors in multiple imputation: baseline characteristics, outcomes, and any available variables potentially related to outcomes. After analyses on 20 separate multiple imputed datasets, the results were pooled. In line with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and Consolidated Standards of Reporting Trials (CONSORT) guidelines, all analyses were also performed on cases with complete data only.

Main analyses

Data were analysed on both an ITT and a per protocol (PP) basis. In addition, analyses were performed on both multiple imputed data and complete cases. It was assumed that the pooled estimates of ITT analyses on the multiple imputed data would be most reliable and, as such, these were considered the main analyses. All analyses were performed using IBM SPSS Statistics (version 25).

The ITT population consisted of all patients randomly allocated to one of the two treatment groups, regardless of whether they received, or adhered to, the allocated intervention. The only excluded participants were those who did not meet the inclusion criteria or met the exclusion criteria (that is, no informed consent of the second parent or retraction of informed consent).

The PP population consisted of the ITT population, but also excluded participants if they did not receive treatment, deviated from the protocol, or withdrew from the study.

Primary and secondary outcome analyses

In all analyses, the treatment (intervention) group was the independent predictor. The primary outcome (continued vomiting) was evaluated by logistic regression, and because all included participants vomited at baseline, analyses were not adjusted for baseline status. The secondary outcome of the number of vomiting episodes was analysed with a log-linear negative binomial model. The secondary outcomes of summed millilitres of ORT intake and parental satisfaction were analysed with a Mann–Whitney U test. Other secondary outcomes — 'referred', 'admitted', and 'adverse events' — were evaluated with logistic regression.

Sensitivity analyses

Sensitivity analyses were performed on the pre-specified primary and secondary outcome of number of vomiting episodes, excluding the first hour (that is, from 2–4 hours only).

RESULTS

Study participants

In total, 1061 participants aged 6 months–6 years who presented with vomiting at one of the three participating primary care OOH-PC centres were screened. Of these, 867 children were excluded: no diagnosis of AGE (n = 227) and not eligible because the intention was to include children at increased risk of dehydration (n = 395) were the most common reasons for exclusion. Of the remainder, 194 children were included and randomised, 97 of these each formed the CAU and intervention groups (Figure 1).

Sixteen cases were excluded because parents did not return their written informed consent forms, despite initially giving their oral informed consent, and three parents withdrew informed consent after randomisation. As such, data for 175 participants were available for ITT analysis. Seventeen children did not receive the allocated intervention and six were lost to follow-up, resulting in 152 participants available for the PP analyses (Figure 1).

Included participants had a median age of 1.5 years (range: 6 months–6 years), 50.3% were female, the median duration of vomiting before presentation was 2 days (range 0.8–9.0 days), and 71.3% had diarrhoea. There were no statistical differences in baseline characteristics between the CAU and the intervention groups in either the ITT (Table 1) or the PP (Appendix 2) populations.

The most common risk factor was fever (24.9%) and the most common alarm symptom was no urine output for 24 hours (14.3%) (data not shown).

There was a wide range of missing data for the variables used in the composite measures (12%–49%); in total, 154 participants (88.0% of the 175 included children) provided all data needed for the primary outcome measure (Table 2).

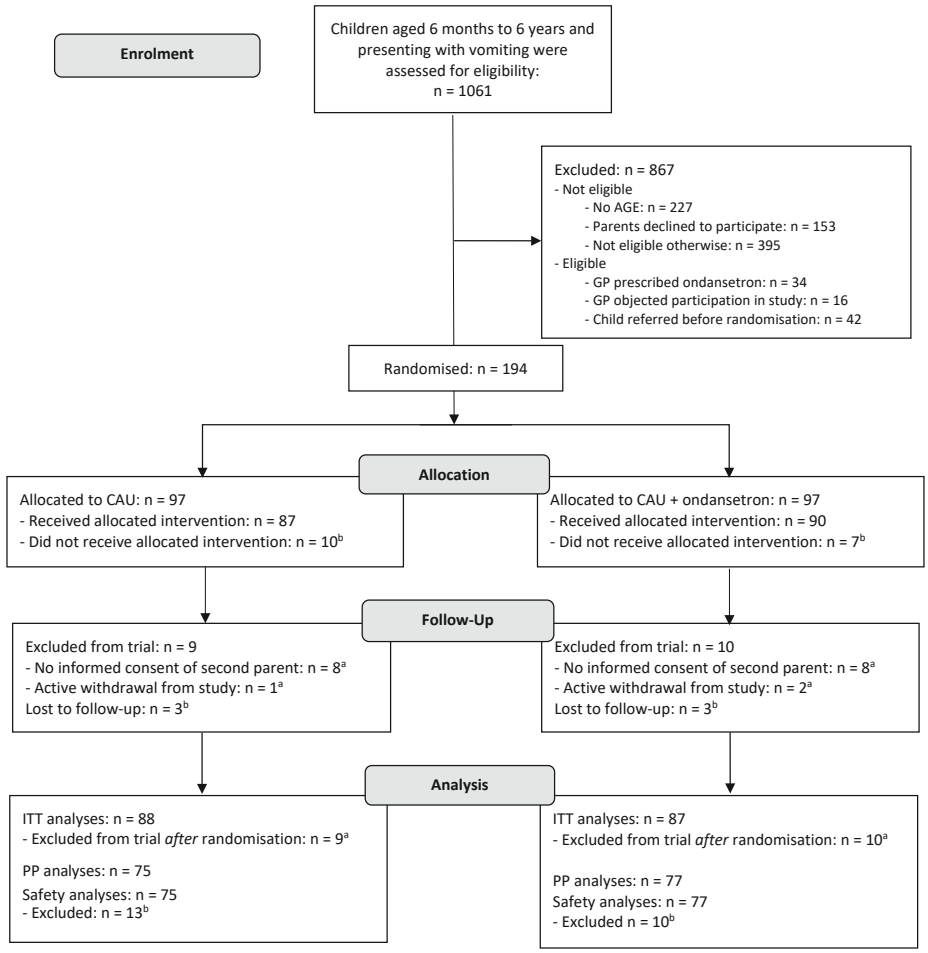

Figure 1. Participant pathway

[a]Excluded from trial because of no informed consent of second parent or active withdrawal from study (retracted informed consent). [b]Excluded from PP and safety analyses because participants did not receive the allocated intervention or data were lost to follow-up. Abbreviations: AGE = acute gastroenteritis. CAU = care as usual. GP = general practitioner. ITT = intention to treat. PP = per protocol.

Table 1. Baseline characteristics of the intention-to-treat population

Baseline characteristics	Valid n	Participants (n = 175)	Valid n	CAU (n = 88)	Valid n	Intervention (n = 87)
Age in years, median (IQR)	175	1.5 (0.9–2.1)	88	1.5 (0.9–2.0)	87	1.5 (0.9–2.2)
Females, n (%)	175	88 (50.3)	88	50 (56.8)	87	38 (43.7)
Weight in kg, median (IQR)	169	11.0 (9.5–14.0)	86	11.0 (9.4–14.0)	83	12.0 (9.5–14.3)
Duration of vomiting prior to presentation in days, median (IQR)	174	2.0 (1.0–3.0)	87	1.2 (1.0–2.0)	87	2.0 (1.0–3.0)
Frequency of vomiting in past 24 hours, median (IQR)	171	5.0 (4.0–10.0)	86	5.0 (4.0–10.0)	85	6.0 (4.0–10.0)
Diarrhoea present, n (%)	174	124 (71.3)	87	66 (75.9)	87	58 (66.7)
Duration of diarrhoea prior to presentation in days[a], median (IQR)	124	2.0 (1.0–3.0)	66	1.0 (0.4– 2.0)	58	1.0 (0.0–3.0)
Frequency of diarrhoea in past 24 hours[a], median (IQR)	123	3.0 (2.0–5.0)	66	2.0 (1.0–5.0)	57	1.5 (0.0–4.0)
Dehydration assessed at 0-100% by GP, median (IQR)	170	20.0 (10.0–40.0)	85	20.0 (6.0–40.0)	85	20.0 (10.0–40.0)
Use of concomitant medication, n (%)	175	65 (37.1)	88	31 (35.2)	87	34 (39.1)
Additional risk factors of dehydration, n (%)[b]						
1	175	63 (36.0)	88	33 (37.5)	87	30 (34.5)
≥2	175	18 (10.3)	88	10 (11.3)	87	8 (9.2)
Alarm symptoms of severe dehydration, n (%)[c]						
1	175	32 (18.3)	88	15 (17.0)	87	17 (19.5)
≥2	175	2 (1.1)	88	1 (1.1)	87	1 (1.1)

[a]Numbers only presented for those participants with diarrhoea. [b]Risk factors assessed at baseline were: ≥ 6 watery stools or diarrhoea, fever, reduced intake.[c]Alarm symptoms assessed at baseline were: confused or decreased consciousness, bradycardia, weak peripheral heartbeat pulsations, capillary refill >4 s, extremities cold/marbled, and no urine output for 24 hours. Abbreviations: CAU = care as usual; GP = general practitioner. IQR = interquartile range.

Outcomes

The effect of ondansetron on continued vomiting and vomiting episodes

The pooled estimates of ITT analyses on the multiple imputed data were considered as the main analyses. Ondansetron decreased the proportion of children who continued vomiting within the first 4 hours after randomisation from 42.9% to 19.5% (Table 2). This corresponded with a relative risk of 0.60 (95% confidence interval [CI] = 0.45 to 0.81) and number needed to treat of four (odds ratio [OR] 0.37, 95% CI = 0.20 to 0.72). In the intervention group, children had fewer vomiting episodes within the 4 hours after randomisation when compared with the CAU group; the incidence rate ratio (IRR) was 0.51 (95% CI = 0.29 to 0.88) (Table 2). Similar estimates were found when repeating the analysis in the PP population (Appendix 3).

The effect of ondansetron on ORT intake, referrals, and hospital admissions

Intake of ORT, number of referrals, and number of hospital admissions did not statistically significantly differ between treatment groups. In both treatment groups, the median ORT intake within 4 hours was 10 ml, referral occurred for 19.4% of all children, and most referred children (74.0%) were admitted to hospital (data not shown). Of all included children, 14.4% were admitted to hospital (Table 2).

Associated adverse events and parental satisfaction with ondansetron

Ondansetron did not increase the occurrence of adverse events. The median parental satisfaction with treatment after 1 week was statistically significantly higher in the intervention group 4.0 (interquartile range [IQR] 4.0–5.0) than in the CAU group 4.0 (IQR 3.0–4.0), respectively (P = 0.027) (Table 2).

Sensitivity analyses

In the sensitivity analysis, the effect of ondansetron on continued vomiting during the first 4 hours after randomisation remained statistically significant (OR 0.44, 95% CI = 0.23 to 0.87), but the number of vomiting episodes did not differ between treatment groups (IRR 0.62, 95% CI = 0.34 to 1.13) (data not shown).

Table 2. The effect of ondansetron on primary and secondary outcomes of the intention to treat population

The effect of ondansetron on primary and secondary outcomes	Valid n	Participants (n = 175)	Valid n	CAU (n = 88)	Valid n	Intervention (n = 87)	Valid n	Imputed cases, OR [95% CI]	Non-imputed cases, OR [95% CI]
Continued vomiting, hours 1-4, n (%)	154	48 (31.2)	77	33 (42.9)	77	15 (19.5)	154	**0.37 [0.20, 0.72]**	**0.32 [0.16, 0.66]**
Vomiting episodes, hours 1–4, median (range)[a]	137	0.0 (0.0–6.0)	67	0.0 (0.0–6.0)	70	0.0 (0.0–5.0)	137	**IRR 0.51 [0.29, 0.88]**	IRR 0.46 [0.21, 1.03]
Intake ORT, ml, median (IQR)	88	10.0 (0.0–100.0)	46	0.0 (0.0–72.0)	42	35.0 (0.0–180.0)	88	*P* = 0.522[b]	*P* = 0.093[b]
Referrals, n (%)	144	28 (19.4)	73	14 (19.2)	71	14 (19.7)	144	1.19 [0.60, 2.36]	1.04 [0.45, 2.36]
Hospital admissions, n (%)	132	19 (14.4)	73	10 (13.7)	59	9 (15.3)	132	1.80 [0.91, 3.55]	1.13 [0.43, 3.00]
Adverse events, n (%)[c]	96	30 (31.3)	48	19 (39.6)	48	11 (22.9)	96	0.63 [0.34, 1.17]	0.45 [0.19, 1.10]
Serious adverse events, n (%)[d]	91	6 (6.6)	46	4 (8.7)	45	2 (4.4)	91	0.83 [0.45, 1.54]	0.49 [0.09, 2.81]
Parental satisfaction, median (IQR)	107	4.0 (3.0–4.0)	53	4.0 (3.0–4.0)	54	4.0 (4.0–5.0)	107	***P* = 0.027**[b]	***P* = 0.013**[b]

Bold *= statistically significant difference. [a]Complete range provided instead of IQR because data are heavily skewed (IQR = 0–0). [b]Mann–Whitney U test. [c]Adverse events: erythema, hic-ups, and headache. [d]Serious adverse events: spasms/convulsions, breathing problems. [#]Odds ratio [95% confidence interval] [##]Incident rate ratio [95% confidence interval] [###]P-value of the. Abbreviations: CAU = Care as usual. IQR = interquartile range. IRR = incidence rate ratio. OR = odds ratio. ORT = Oral rehydration therapy.*

DISCUSSION

Summary

One dose of ondansetron given in an OOH-PC setting decreased the proportion of participants with AGE who had persistent vomiting by 54.5% (decreased from 42.9% [n = 33/88] to 19.5% [n = 15/87] = 54.5% reduction). Overall, ORT intake was low (10 ml/4 hours) and referral rates were high (19% in comparison with a mean referral rate of 8.1%).3 Ondansetron use did not appear to increase ORT intake or lead to fewer hospital referrals or admissions; nevertheless, parents were more satisfied with the addition of ondansetron compared with ORT alone.

Strengths and limitations

The authors are aware of no other studies investigating the practical effectiveness of ondansetron on vomiting and other important treatment goals in children with AGE, when parents consult in an OOH-PC setting. Other strengths of this study are that nearly 600 GPs collaborated over a period of >2 years, and that it was possible to gather data about the reasons for exclusion. From these data, it becomes clear that the intention to select the subgroup of children who, at presentation, frequently vomited was fulfilled. In addition, the use of an hourly diary for the first 4 hours provided detailed and reliable data on the primary outcome.

Limitations of the study were that there was a wide range of missing values measures. Although no association was found between missing values and either treatment, the findings based on these secondary outcome measures should be interpreted with caution. It could also be seen as a limitation that participants — that is, parents and GPs — were not blinded for the intervention. Although it is disputable whether this would have been desirable in a pragmatic trial, the authors believe it did not influence the primary outcome measurement as the aim was to investigate the potential effect of implementing ondansetron in routine primary care and the outcome assessors were blinded.

Comparison with existing literature

The finding that oral ondansetron reduces the incidence of vomiting and the proportion of vomiting episodes within 4 hours after presentation at an OOH-PC centre is consistent with results of other studies.[13,22] The findings presented here also indicate that this effect of ondansetron on vomiting persisted over a 4-hour period.

In addition, the results indicate that a 0.1 mg/kg dose of ondansetron in primary care is at least comparably effective at inducing vomiting cessation as a higher dose given in the emergency department.[13] Despite ORTs being prescribed for all children included by research assistants, the reported ORT intake was low in both treatment groups for the current study. Studies from emergency department settings indicate that ORT can have

a success rate of 100% when prepared and administered by qualified and trained nurses directly after giving a dose of ondansetron.[23]

It would be interesting to study alternatives to ORT that children can better tolerate or accept at home, such as diluted apple juice.[24] However, for the CAU group, the guideline of the Dutch College of General Practitioners was followed,[15] which does not include the use of apple juice.

There could be several reasons for the high referral rate among children with AGE and frequent vomiting; a plausible explanation may be that it reflects a lack of success with ORT at home. In the current study, the median intake of oral rehydration solution of 10 ml in 4 hours was considered ineffective for children at any age. Finding ways to improve ORT success at home seems to be key to rectifying this issue. In addition, because vomiting cessation did not lower referral rates, the decision to refer a child with AGE may have been influenced by considerations other than risk factors for dehydration and hydration status.

Such factors may include how parents interpret and communicate symptoms of dehydration, the related healthcare-seeking behaviour of parents, and how exactly GPs follow up on their paediatric patients after discharge from the OOH-PC setting.[25]

Treatment groups had comparable rates of adverse events consistent with the findings of a systematic review and meta-analysis,[17] which showed that the number and type of adverse events was comparable between oral ondansetron and placebo groups, with no serious adverse events. Although the use of ondansetron in primary care seems safe, further monitoring and reporting for potential side-effects is still indicated when it is prescribed.

Implications for practice and research

In this study, ondansetron use was found to be effective, safe, and positively evaluated by parents when used to stop vomiting among children aged 6 months–6 years presenting in primary care with AGE and vomiting.

As such, the authors advocate that ondansetron be considered an add-on treatment for use by GPs when managing dehydration due to AGE and frequent vomiting in primary care. However, the findings also show that ondansetron alone will not substantially affect ORT intake or reduce the high referral rate to specialised care.

Future research should aim to disentangle the key factors leading to hospital referral for children with AGE. Research should also consider ways to administer ORT more effectively in primary care or at home, such as direct administration by nurses, better parental education, and the use of alternatives for ORT.

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Appendix 1. Baseline characteristics and the effect of ondansetron on primary and secondary outcomes of the per protocol population

Baseline characteristics	Valid n	Participants (n = 152)	Valid n	CAU (n = 75)	Valid n	Intervention (n = 77)
Age in years, median (IQR)	152	1.5 (0.9–2.2)	75	1.4 (0.9–2.0)	77	1.5 (0.8–2.2)
Females, n (%)	152	69 (45.4)	75	38 (50.7)	77	31 (40.3)
Weight in kg, median (IQR)	148	11.0 (9.5–14.0)	73	11.0 (9.3–14.0)	75	11.7 (9.5–14.0)
Duration of vomiting prior to presentation in days, median (IQR)	152	2.0 (1.0–3.0)	75	2.0 (1.0–3.0)	77	2.0 (1.0–3.0)
Frequency of vomiting in past 24 hours, median (IQR)	149	5.0 (4.0–9.5)	73	5.0 (3.5– 9.0)	76	5.5 (4.0–9.8)
Diarrhoea present, n (%)	151	111 (73.5)	74	58 (78.3)	77	53 (68.8)
Duration of diarrhoea prior to presentation in days[a], median (IQR)	111	1.0 (0.0–2.0)	58	1.0 (0.2–2.0)	53	1.0 (0.0–3.0)
Frequency of diarrhoea in past 24 hours[a], median (IQR)	111	2.0 (0.0–4.0)	58	2.0 (1.0–5.0)	53	1.5 (0.0–4.0)
Dehydration assessed at 0-100% by GP, median (IQR)	147	20.0 (5.0–40.0)	72	17.5 (4.0–40.0)	75	20.0 (10.0–36.0)
Use of concomitant medication, n (%)	152	57 (37.5)	75	27 (36.0)	77	30 (39.0)
Additional risk factors of dehydration[b]						
1, n (%)	152	55 (36.2)	75	29 (38.7)	77	26 (33.8)
≥2, n (%)	152	14 (9.3)	75	8 (10.6)	77	6 (7.8)
Alarm symptoms of severe dehydration[c]						
1, n (%)	152	27 (17.8)	75	15 (20.0)	77	12 (15.6)
≥2, n (%)	152	2 (1.3)	75	1 (1.3)	77	1 (1.3)

Per protocol population is defined as the intention to treat population minus participants who did not receive allocated intervention and lost to follow-up (figure 1). [a]Numbers only presented for those participants with diarrhoea. [b]Risk factors assessed at baseline were: ≥ 6 watery stools or diarrhoea, fever, reduced intake. [c]Alarm symptoms assessed at baseline were: confused or decreased consciousness, bradycardia, weak peripheral heartbeat pulsations, capillary refill > 4 seconds, extremities cold/marbled and no urine output in the last 24 hours. Abbreviations: CAU = Care as usual. GP = general practitioner. IQR = Interquartile range.

Appendix 2. Baseline characteristics of participants with by those with complete data and missing values

	Participants who returned the diary with all data complete	Participants who returned the diary with ≥1 missing value	Participants who only gave outcome data by telephone on vomiting, referral, and admission	Participants with no follow-up data at all
	(n = 60)	(n = 63)	(n = 46)	(n = 6)
Characteristics				
Age in years, median (IQR)	1.1 (0.8–2.0)	1.6 (0.9–2.2)	2.0 (1.0–3.0)	1.8 (0.8–2.2)
Females, n (%)	29 (48.3)	27 (42.9)	26 (56.5)	6 (100)
Weight in kg, median (IQR)	10.4 (9.0–13.0)	11.7 (10.0–15.0)	12.0 (9.9–15.0)	10.5 (9.6–16.0)
Duration of vomiting prior to presentation in days, median (IQR)	2.0 (1.0 -2.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	0.5 (0.4–3.0)
Frequency of vomiting in past 24 hours, median (IQR)	5.0 (4.0–8.3)	6.0 (4.0–10.0)	5.0 (4.0–10.0)	6.5 (4.8–12.5)
Diarrhoea present, n (%)	49 (81.7)	39 (61.9)	34 (73.9)	2 (33.3)
Duration of diarrhoea prior to presentation in days[a], median (IQR)	1.0 (0.0–2.0)	1.0 (0.4-2.0)	1.0 (0.0-3.0)	1.0 (0.0-2.0)
Frequency of diarrhoea in past 24 hours[a], median (IQR)	2.0 (0.0–4.0)	2.0 (1.0-4.0)	1.5 (0.0-4.0)	2.0 (0.0-3.0)
Dehydration assessed at 0-100% by GP, median (IQR)	20.0 (9.0–40.0)	20.0 (5.0–40.0)	21.0 (10.0–40.0)	16.0 (8.0–38.0)
Use of concomitant medication, n (%)	26 (43.3)	21 (33.3)	18 (39.1)	0 (0.0)
Additional risk factors of dehydration[b]				
1, N (%)	21 (35.0)	20 (31.7)	19 (41.3%)	3 (50.0)
≥2, N (%)	7 (11.7)	7 (11.1)	3 (6.5%)	1 (16.7)
Alarm symptoms of severe dehydration[c]				
1, N (%)	13 (21.7)	10 (15.9)	8 (17.4)	1 (16.7)
≥2, N (%)	1 (1.7)	0 (0.0)	1 (2.2)	0 (0.0)

[a]Numbers only presented for those participants with diarrhoea. [b]Risk factors assessed at baseline were: ≥ 6 watery stools or diarrhoea, fever, reduced intake .[c]Alarm symptoms assessed at baseline were: confused or decreased consciousness, bradycardia, weak peripheral heartbeat pulsations, capillary refill >4 s, extremities cold/marbled, and no urine output in the last 24 hours. Abbreviation: GP = general practitioner. IQR = Interquartile range.

Appendix 3. The effect of ondansetron on primary and secondary outcomes of the per protocol population

	Valid n	Participants (n = 152)	Valid n	CAU (n = 75)	Valid n	Intervention (n = 77)	Valid n	Imputed cases, OR [95% CI]	Non-imputed cases, OR [95% CI]
Continued vomiting, hours 1–4, n (%)	137	40 (29.2)	67	29 (43.3)	70	11 (15.7)	137	**0.28 [0.14, 0.59]**	**0.24 [0.11, 0.55]**
Vomiting episodes hours 1–4, median (range)[a]	123	0.0 (0.0–5.0)	58	0.0 (0.0–5.0)	65	0.0 (0.0–5.0)	123	**IRR 0.45 [0.24, 0.85]**	IRR 0.48 [0.20, 1.14]
Intake ORT in ml, median (IQR)	80	10.0 (0.0–100.0)	39	0.0 (0.0–65.0)	41	50.0 (0.0–180.0)	80	*P* = 0.626[b]	***P* = 0.031**[b]
Referrals, n (%)	130	18 (13.8)	65	8 (12.3)	65	10 (15.4)	130	1.43 [0.63, 3.24]	1.30 [0.48, 3.52]
Hospital admissions, n (%)	121	15 (12.4)	66	7 (10.6)	55	8 (14.5)	121	2.29 [1.04, 5.04]	1.44 [0.49, 4.24]
Adverse events, n (%)	88	27 (30.7)	41	16 (39.0)	47	11 (23.4)	88	0.54 [0.28, 1.04]	0.48 [0.19, 1.20]
Serious adverse events, n (%)[c]	83	4 (4.8)	39	2 (5.1)	44	2 (4.5)	83	0.71 [0.36, 1.39]	0.88 [0.12, 6.57]
Parental satisfaction, median (IQR)	99	4.0 (3.0–5.0)	46	4.0 (3.0–4.0)	53	4.0 (4.0–5.0)	99	***P* = 0.031**[b]	***P* = 0.016**[b]

Per protocol population is defined as the intention to treat population minus participants who did not receive allocated intervention and lost to follow-up (figure 1). ***Bold*** *= statistically significant difference. [a]Complete range provided instead of IQR because data are heavily skewed (IQR = 0–0). [b]Adverse events: erythema, hic-ups, headache. [c]Serious adverse events: spasms/convulsions, problems with breathing. Abbreviations: CAU = Care as usual. IQR = Interquartile Range. IRR = incidence rate ratio. ORT = Oral rehydration therapy.*

CHAPTER 8

Cost-effectiveness of oral ondansetron for children with acute gastroenteritis in primary care: a randomised controlled trial

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ABSTRACT

Background

Acute gastroenteritis is a common childhood condition with substantial medical and indirect costs, mostly because of referral, hospitalisation, and parental absence from work.

Aim

To determine the cost-effectiveness of adding oral ondansetron to care as usual (CAU) for children with acute gastroenteritis presenting to out-of-hours primary care (OOH-PC).

Design and setting

A pragmatic randomised controlled trial from December 2015 to January 2018, at three OOHPC centres in the north of the Netherlands (Groningen, Zwolle, and Assen) with a follow-up of 7 days.

Method

Children were recruited at the OOH-PC and parents kept a parental diary. Inclusion criteria were: aged 6 months–6 years; diagnosis of acute gastroenteritis; at least four reported episodes of vomiting 24 hours before presentation, at least one of which was in the 4 hours before presentation; and written informed consent from both parents. Children were randomly allocated at a 1:1 ratio to either CAU (oral rehydration therapy) or CAU plus one dose of 0.1 mg/kg oral ondansetron.

Results

In total, 194 children were included for randomisation. One dose of oral ondansetron decreased the proportion of children who continued vomiting within the first 4 hours from 42.9% to 19.5%, (a decrease of 54.5%), with an odds ratio of 0.4 (95% confidence interval [CI] = 0.2 to 0.7; number needed to treat: four). Total mean costs in the ondansetron group were 31.2% lower (€488 [£420] versus €709 [£610]), and the total incremental mean costs for an additional child free of vomiting in the first 4 hours was −€9 (£8) (95% CI = −€41 [£35] to €3 [£3]).

Conclusion

A single oral dose of ondansetron for children with acute gastroenteritis, given in OOH-PC settings, is both clinically beneficial and cost-effective.

INTRODUCTION

The high incidence of acute gastroenteritis among children aged <5 years in the Netherlands (609 per 1000 person–years) is associated with substantial medical and indirect costs.[1,2] The total costs in this age group are estimated at €77.28 million (£66.5 million) per year.[3] Referral to specialist care — and hospitalisation in particular — are the main drivers of high medical costs,[4] but hospitalisation results in parents missing work, which also contributes to high indirect costs.[5]

Acute gastroenteritis usually has a self-limiting course in children.[1] Oral rehydration therapy (ORT) is recommended for mild-to-moderate dehydration, but it remains underused.[2,6] Excessive vomiting during acute gastroenteritis can cause ORT failure, which in turn, can be responsible for referral and hospitalisation.[7] Symptomatic treatment of vomiting may, therefore, prevent ORT failure, reduce referral rates to emergency departments, and decrease medical and indirect costs.[8–11] The most widely used antiemetics to date — domperidon and metoclopramide — are not recommended overall because of a lack of evidence of their effectiveness and the risk of severe side-effects;[6,12] the Dutch Paediatric Formulary recommends oral ondansetron for children with acute gastroenteritis, vomiting, and dehydration.[13] Ondansetron, a 5-HT3 serotonin antagonist with a central antiemetic effect, has not only been shown to decrease vomiting rates by 54.5% among children at increased risk of dehydration in out-of-hours primary care (OOH-PC) settings, it also seems to be safe and positively evaluated by parents.[14] Its use reduces immediate hospitalisation rates and the need for intravenous rehydration therapy, while enhancing compliance with ORT;[7,15] in addition, no serious adverse events have been reported to date.[15,16]

Despite the available data in support of the clinical efficacy of ondansetron, data are lacking about the cost-effectiveness of adding ondansetron to care as usual (CAU) in OOH-PC settings. Cost-effective data are used, in addition to clinical evidence, in decision making by policymakers and guideline developers. Therefore, the aim was to assess the cost-effectiveness of adding oral ondansetron to CAU in children aged 6 months–6 years with acute gastroenteritis in OOH-PC settings.

METHODS

Design and setting

The cost-effectiveness of adding oral ondansetron to CAU was studied alongside a randomised controlled trial (RCT) on the effectiveness of this approach. The RCT started with a pilot study (NL4700) (https://www.trialregister.nl/trial/4700) that was carried out from December 2015 until October 2016, and then extended with the final trial until January 2018; it was conducted at three OOH-PC centres in the north of the Netherlands (Groningen, Zwolle, and Assen). The design, recruitment strategy, outcomes, and informed-consent procedure of the RCT are reported elsewhere.[17] In agreement with the Medical Ethics Review Committee of the University Medical Centre Groningen, the primary outcome changed from referral to vomiting to guarantee an outcome that was more relevant to patients. The researchers were allowed to include children from the pilot study in the final trial (NL5830) (https://www.trialregister.nl/trial/5830).

Participants

Children aged 6 months–6 years with a diagnosis of acute gastroenteritis who were considered to be at increased risk of dehydration were included,[12] based on the following inclusion criteria:

- at least four episodes of vomiting 24 hours before presenting to the OOH-PC centre;
- at least one episode of vomiting in the 4 hours before presenting to the OOH-PC centre; and
- written informed consent of both parents.

The age range of 6 months–6 years was chosen for two reasons: the known incidence of acute gastroenteritis and related dehydration is highest in children aged <6 years old;[9] and, as an age of <6 months is seen as an additional risk factor for ORT failure at home, Dutch paediatric and GP guidelines recommend low-threshold referral in children aged <6 months and at risk of dehydration.[12,18]

The exclusion criteria were as follows:

- antiemetic use or prescription in the 6 hours before presentation;
- known renal failure or hypoalbuminemia;
- known diabetes mellitus or inflammatory bowel disease;
- history of abdominal surgery explaining current symptoms according to the GP;
- known sensitivity to 5-HT3 receptor antagonists;
- known prolonged QT interval or current use of QT-prolonging medication; and
- previous enrolment in the study.

Randomisation and blinding

Children were randomly allocated to one of two intervention groups at a 1:1 ratio. An online randomisation tool generated the allocation sequence in direct response to participant inclusion by the research assistant. Allocation was not generated before inclusion to ensure concealment, and the allocation sequence was stratified by age (6–24 months or >24 months) and dehydration severity ('at risk', meaning no alarm symptoms; or 'dehydrated', meaning at least one alarm symptom). Risk factors assessed at baseline were: ≥6 watery stools or diarrhoea, fever, and reduced intake. The following alarm symptoms were assessed at baseline:

- confused or decreased consciousness;
- bradycardia;
- weak peripheral pulses;
- capillary-refill time of >4 seconds;
- skin-pinch test of >4 seconds;
- cold or marbled extremities; and
- no urine output for 24 hours.

This study was designed as a pragmatic RCT with emphasis on the potential implementation of ondansetron in primary care, so participants, parents, GPs, and research assistants were deliberately not blinded to treatment allocation. In this case, blinding participants would result in outcomes that could not be translated to daily practice. The statistician, who performed the statistical analyses was blinded to treatment allocation; an independent statistician performed this blinding. The primary outcome was not known by participants, parents, or GPs.

Interventions

Control group, CAU

CAU involved giving instruction on the use of ORT, as described in the guideline for acute diarrhoea by the Dutch College of GPs.[12] This included advice to buy an oral rehydration solution, together with the following instructions on how to use it: 10 mL/kg compensation for diarrhoea when at risk (that is, all children) and 15 mL/kg for 4 hours if assessed as dehydrated by the GP. The research assistant provided the instructions, together with a patient folder in which the information was repeated. In addition, the research assistant discussed alarm symptoms and advised parents to contact the GP if there was either no improvement or a worsening of symptoms 4 hours after presentation.

ORT had to be bought by parents at the pharmacy or over the counter, and was initiated at home. If children were referred to the hospital within 1 hour after randomisation, the CAU was considered as not received and were removed from the per protocol analysis in the effectiveness outcome.

Intervention: CAU plus ondansetron

Children allocated to the intervention group received a single weight-based dose of oral ondansetron syrup (0.1 mg/kg body weight) in accordance with the *Dutch Paediatric Formulary*.[13] If the child vomited within 15 minutes after administration, this dose was repeated once.

Ondansetron therapy was considered 'received' if one adequate dose had been successfully administered within 1 hour after randomisation. So if children were referred within 1 hour, it was noted as 'not received'.

Follow-up

Parents were asked to complete a diary for 7 days. In the first 4 hours, they were asked to report on their child's progress each hour; thereafter, they reported once daily until 7 days after presentation.

The primary outcome was assessed on return of the diary or by telephone if parents had not returned the diary after three requests.

Outcomes

Primary outcome

The efficacy of the study medication, assessed as the proportion of children who continued vomiting in the first 4 hours after randomisation (that is, at least one episode), has been reported previously.[14] The fourth hour was considered based on two criteria: national guidelines, which state that GPs should re-evaluate dehydrated children after 4 hours;[11] and the circulating concentration of ondansetron, which is expected to reach 50% of its maximum serum level at 3 hours after oral ingestion[19] (the half-life of ondansetron is 3 hours, which is used to examine the effect).

Costs

Costs were grouped into healthcare and indirect costs (see Appendix 1). They were valued according to the cost manual of the National Health Care Institute of the Netherlands[20] and the standard prices of the medication.[21] Prices were indexed to the level of 2018 and are reported in euros. The measurements for the cost analyses were based on the details provided in the parental diaries.

Statistical analysis

The total mean cost and effectiveness per group were compared based on complete cases. To be eligible for analysis, each child needed complete data on cost and effect. Comparing the demographic characteristics of children with and without complete cost-and-effect pairs suggested data were missing at random. A cost-effectiveness analysis was then performed, in which the effect of ondansetron added to CAU was compared with CAU alone. The primary outcome measure (unit of health) was the number of children who continued to vomit within 4 hours; the time horizon for the analysis was 7 days.

Incremental costs and outcomes were assessed, and are expressed as an incremental cost-effectiveness ratio, representing the additional costs or savings per additional child free of vomiting. Any difference in effect, based on the primary outcome, was divided by the cost difference between interventions. Cost-and-effect pairs were bootstrapped (5000 replications) to calculate alternate confidence intervals (CIs) and plotted on a cost-effectiveness plane. In addition, a cost-effectiveness acceptability curve (CEAC) was plotted to evaluate the probability that adding a single dose of oral ondansetron to CAU is more cost-effective than CAU alone, over a range of different maximum values. This was used to reveal whether the intervention was cost-effective compared with CAU over a range of maximum monetary values that a decision maker may be willing to pay for an additional unit of health.[22]

RESULTS

Study sample

The study process is summarised in Figure 1. A total of 1061 children were screened for eligibility at the participating OOH-PC centres. Of the 867 children who were excluded, 775 were ineligible. This was because they were assessed as not being at increased risk of dehydration (n = 395), did not have a diagnosis of acute gastroenteritis (n = 227), and the parents declined to participate (n = 153).

In total, 194 children were included, with 97 each allocated randomly to the control and intervention groups (Figure 1). Another 19 children were excluded after randomisation because no second written informed consent was obtained (n = 16) or they withdrew from the study (n = 3), (data not shown).

Data for 175 children (n = 88 CAU, n = 87 intervention) were then available for analysis of the primary efficacy outcome (Figure 1). Data for 109 children were available for the cost-effectiveness analysis (n = 51 control, n = 58 intervention).

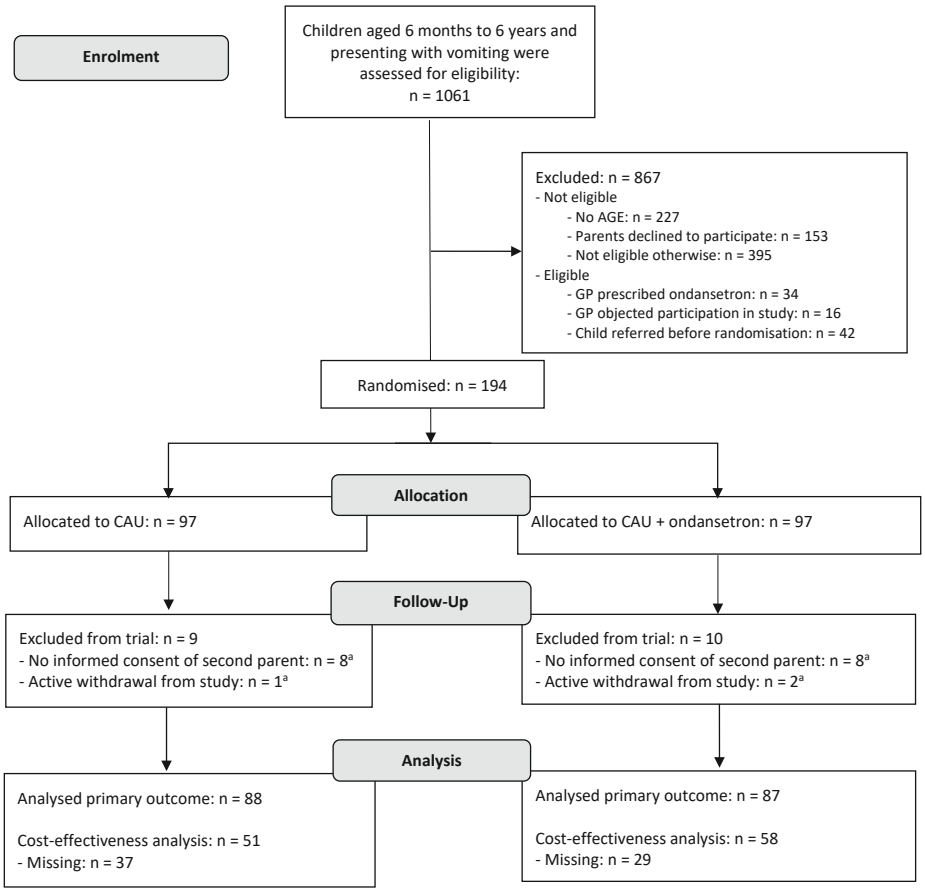

Figure 1. Study flow diagram

[a]Excluded from trial because of no informed consent of second parent or active withdrawal from study (retracted informed consent). Abbreviation: AGE = acute gastroenteritis. CAU = care as usual. GP = general practitioner.

Baseline characteristics of included participants

Of the included participants, the median age was 1.5 years (range: 6 months–6 years, medium IQR), 50.3% were female, the median duration of vomiting before presentation was 2 days (range: 0.8–9.0 days, medium IQR), and 71.3% experienced diarrhoea (n = 124).

There were no major differences in baseline characteristics between children in the control and intervention groups (Table 1).

Table 1. Baseline characteristics of the population

Baseline characteristics	Valid n	Participants (n = 175)	Valid n	CAU (n = 88)	Valid n	Intervention (n = 87)
Age in years, median (IQR)	175	1.5 (0.9–2.1)	88	1.5 (0.9–2.0)	87	1.5 (0.9–2.2)
Females, n (%)	175	88 (50.3)	88	50 (56.8)	87	38 (43.7)
Weight in kg, median (IQR)	169	11.0 (9.5–14.0)	86	11.0 (9.4–14.0)	83	12.0 (9.5–14.3)
Duration of vomiting prior to presentation in days, median (IQR)	174	2.0 (1.0–3.0)	87	1.2 (1.0–2.0)	87	2.0 (1.0–3.0)
Frequency of vomiting in past 24 hours, median (IQR)	171	5.0 (4.0–10.0)	86	5.0 (4.0–10.0)	85	6.0 (4.0–10.0)
Diarrhoea present, n (%)	174	124 (71.3)	87	66 (75.9)	87	58 (66.7)
Duration of diarrhoea prior to presentation in days[a], median (IQR)	124	2.0 (1.0–3.0)	66	1.0 (0.4– 2.0)	58	1.0 (0.0–3.0)
Frequency of diarrhoea in past 24 hours[a], median (IQR)	123	3.0 (2.0–5.0)	66	2.0 (1.0–5.0)	57	1.5 (0.0–4.0)
Dehydration assessed at 0-100% by GP, median (IQR)	170	20.0 (10.0–40.0)	85	20.0 (6.0–40.0)	85	20.0 (10.0–40.0)
Use of concomitant medication, n (%)	175	65 (37.1)	88	31 (35.2)	87	34 (39.1)
Additional risk factors of dehydration, n (%)[b]						
1	175	63 (36.0)	88	33 (37.5)	87	30 (34.5)
≥2	175	18 (10.3)	88	10 (11.3)	87	8 (9.2)
Alarm symptoms of severe dehydration, n (%)[c]						
1	175	32 (18.3)	88	15 (17.0)	87	17 (19.5)
≥2	175	2 (1.1)	88	1 (1.1)	87	1 (1.1)

[a]Numbers only presented for those participants with diarrhoea. [b]Risk factors assessed at baseline were: ≥ 6 watery stools or diarrhoea, fever, reduced intake.[c]Alarm symptoms assessed at baseline were: confused or decreased consciousness, bradycardia, weak peripheral heartbeat pulsations, capillary refill >4 s, extremities cold/marbled, and no urine output for 24 hours. Abbreviations: CAU = care as usual; GP = general practitioner. IQR = interquartile range.

Health outcomes

One dose of oral ondansetron decreased the proportion of children who continued vomiting within the first 4 hours from 42.9% (n = 33/77) to 19.5% (n = 15/77). The odds ratio for this association was 0.4 (95% CI = 0.2 to 0.7), giving a number needed to treat of four.[14]

Cost-effectiveness analysis

Costs for the control and intervention groups are outlined in Table 2. The total mean costs in the intervention group (€488 [£420]) were 31.2% lower (mean difference €221 [£190]) than in the CAU group (€709 [£610]). Total healthcare costs per patient were also lower in the intervention group, by €48 (£41), with hospital admission being the main driver. The costs for hospital admission were also calculated per day, meaning that children in the CAU group were admitted to hospital for longer. Indirect costs (that is, work absence of parents) accounted for 62.9% (€446 [£384]) of the total costs in the CAU group and 55.7% (€272 [£234]) in the intervention group, giving a reduction of €174 (£150).

Table 2. Total mean costs (€)

Types of costs	CAU	Intervention
	(n = 51)	(n = 58)
Health care costs		
General practitioner	54 (93)	40 (64)
Out-of-hours primary care	1 (5)	2 (8)
Referral to paediatrician	45 (72)	37 (74)
Hospital admission	162 (512)	134 (426)
Oral rehydration solution	2 (3)	3 (3)
Indirect costs		
Work absenteeism mother	287 (390)	151 (216)
Work absenteeism father	159 (258)	121 (274)
Total costs all sectors	709 (839)	488 (638)

Total mean costs were only calculated for 109 participants. Results are shown as mean (standard deviation). Abbreviation: CAU = care-as-usual.

The total incremental mean cost per child free of vomiting within 4 hours of assessment was −€9 (£8) (95% CI = −€41 to €3) The cost-effectiveness plane revealed 94.0% of the bootstrap replicates to be in the bottom-right quadrant, indicating lower costs and better effectiveness with ondansetron (Figure 2). The CEAC indicated an almost 95% chance that the intervention was cost-effective without investing additional money; however, at an investment of approximately €1000, the chance of the intervention being cost-effective increased to 100% (Figure 3).

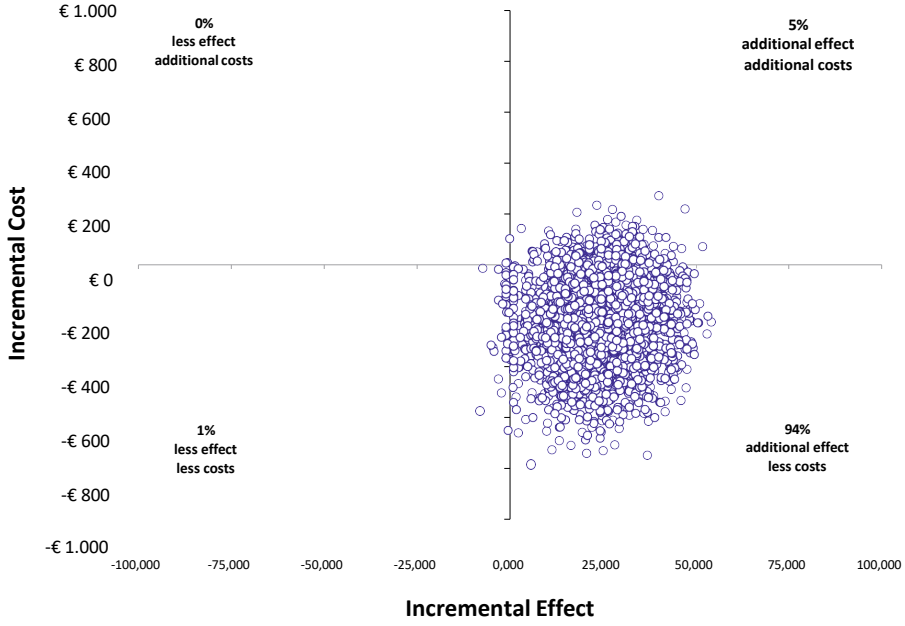

Figure 2. Cost-effectiveness plane

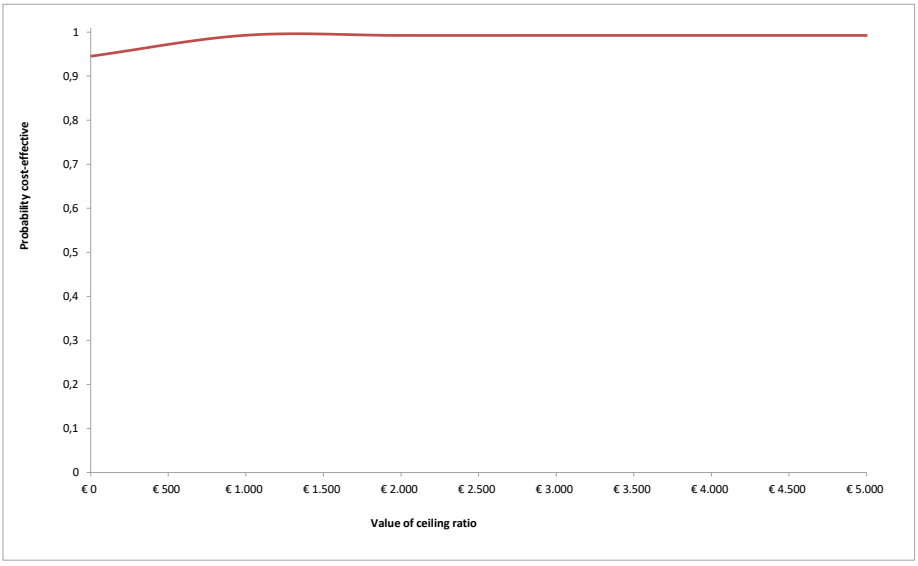

Figure 3. Cost-effectiveness acceptability curve

DISCUSSION

Summary

This RCT showed the cost-effectiveness of adding a single dose of oral ondansetron to CAU for children at increased risk of dehydration due to acute gastroenteritis in an OOH-PC setting. Specifically, one dose of ondansetron was associated with a decrease in the percentage of children with persistent vomiting due to acute gastroenteritis over the first 4 hours after assessment from 42.9% to 19.5%, saving an average of €9 (£8) per child who stopped vomiting. The total mean costs were 31.2% lower with the addition of ondansetron, making it a cost-effective treatment for children diagnosed with acute gastroenteritis in OOH-PC settings.

Strengths and limitations

This is the first study, to the authors' knowledge, to evaluate the cost-effectiveness of adding oral ondansetron to CAU when managing acute gastroenteritis among children in OOH-PC centres. Nearly 600 GPs collaborated and nearly all children aged6 months–6 years who presented with vomiting at three OOH-PCs in the north of the Netherlands over a period exceeding 2 years were screened. As such, the sample is highly representative of children presenting to OOH-PC centres at increased risk of dehydration. Patients seen in the three centres were representative of the general population. Moreover, the use of an hourly diary for the first 4 hours, and a daily dairy for another 7 days, provided important follow-up data. Another strength is that the findings were based on estimated healthcare utilisation and associated costs from the National Health Care Institute of the Netherlands[20] and the standard prices of the medication costs,[21] indexed to 2018; these ensure the data are representative and applicable for decision makers overall.

This study also has some limitations. Data were available for 109 participants (62.3% of included children) only, when calculating the total mean costs; however, bootstrapping (5000 replications) meant that accounting for the missing data did not alter the findings. Participants, parents, GPs, and research assistants were not blinded to the intervention but, given the pragmatic design, it is contentious whether this would have been desirable. Ondansetron has already been proven effective at reducing vomiting in blinded RCTs in specialist care[23,24] and, aside from the research assistants, the groups were unaware of the primary outcome. Parents were informed about ondansetron and that the course of acute gastroenteritis was being investigated but, as no information was given regarding a specific focus on vomiting, the authors do not think the lack of blinding affected the study's outcomes.

Another limitation is that only work absence by parents was considered in the indirect costs, with other non-medical costs — such as consumption of special food, extra diaper use, and travel costs — excluded. This choice was deliberate to avoid burdening the parents of sick children with excessive information requests; however, absence from work

is known to be the largest contributor to indirect costs when managing children with acute gastroenteritis.[3,5] The costs of oral ondansetron were also not included; this was because these are extremely low (€0.25–€0.37 [per dose]).

Comparison with existing literature

The study presented here showed that an average of €9 (£8) could be saved for every additional child who did not vomit in the first 4 hours after being given a single dose of ondansetron. With an incidence of 1.96 episodes/person–years and an average annual cost of €88.57 (£76) per child aged <5 years, oral ondansetron could lead to significant cost reductions.[3]

The main cost drivers in the study presented here — hospitalisation and work absence — were comparable with those reported in another study.[3] The differences in costs between groups can be explained by the reductions in health care and indirect costs with ondansetron use, resulting in fewer referrals to a paediatrician and fewer hospital admissions, which typically drive costs, as stated by Elliott.[25]

Paediatrician referrals were made for 19% of children in the present study, far higher than the previously reported rate of 8%,[26] but these almost certainly resulted from the deliberate inclusion of children at increased risk of dehydration; supporting this, the degree of dehydration is known to be among the main reasons for referral and hospitalisation.[27]

The costs for hospital admission were also calculated per day, so the results showed that children in the control group were admitted to hospital for longer. Furthermore, costs for a GP visit were lower in the intervention group, indicating that these children were less likely to require a repeat visit to the GP. These results imply that adding oral ondansetron to CAU could reduce the considerable burden that acute gastroenteritis places on the healthcare system in the Netherlands.[2]

Differences in indirect costs were attributable to fewer work absences in the intervention group. This was particularly evident for mothers of children not receiving ondansetron, among whom productivity losses are typically double those of fathers, and consistent with evidence that mothers stay at home more often than fathers to take care of sick children.[28] In the US, 80% of non-medical costs per case of acute gastroenteritis in children were shown to be attributable to parents missing work.[29] In the CAU group in the study presented here, parental work absence accounted for 62.9% of the total costs compared to 55.7% in the ondansetron group. Work absence also tends to increase with the severity of acute gastroenteritis (that is, degree of dehydration);[30] the parents of children who received ondansetron required less time off work because of their sick child and, as a consequence, had lower indirect costs.

Implications for practice

A single dose of oral ondansetron is cost-effective for children who are at increased risk of dehydration and present to OOH-PC with vomiting due to acute gastroenteritis. Multiple studies have proven the efficacy and safety of oral ondansetron in emergency departments. The authors recommend advocating oral ondansetron use in primary care guidance on the management of vomiting in children with acute gastroenteritis who are at increased risk of dehydration; this could reduce both the burden of the disease for children and the costs to the healthcare system and wider society.

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Appendix 1. Costs applied in the cost-effectiveness analysis

Types of costs	Costs (€)
Health care costs	
General practitioner	33.76 per visit
Out-of-hours primary care	110.50 per visit
Referral to paediatrician	103.34 per visit
Hospital admission	487.02 per day
Oral rehydration solution	0.18 per 25 mL
Indirect costs	
Work absence of mother	35.50 per day
Work absence of father	35.50 per day

CHAPTER 9

Comparing healthcare systems between the Netherlands and Australia in management for children with acute gastroenteritis

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Submitted.

ABSTRACT

Background

Acute gastroenteritis is a highly contagious disease demanding effective public health and clinical care systems for prevention and early intervention to avoid outbreaks and symptom deterioration. The Netherlands and Australia are both top-performing, high-income countries where general practitioners (GPs) act as healthcare gatekeepers, but differences in gastroenteritis incidence rates and costs per episode exist. This study aims to compare public health and clinical care for children with acute gastroenteritis in both countries.

Methods

A cross-country expert study was conducted for the Netherlands and Australia. Using the Health System Performance Assessment framework and discussions within the research group, two questionnaires (public health and clinical care) were developed. Questionnaires were delivered to local experts in the Netherlands and the state of Victoria, Australia. Data synthesis employed a narrative approach with constant comparison.

Results

In Australia, rotavirus vaccination is implemented in the national program with immunisation requirements and legislations for prevention, whereas this is not the case in the Netherlands. Access to care differs, as Dutch children must visit their regular GP before the hospital, while in Australia, children have multiple options and can go directly to hospital. Funding varies, with the Netherlands providing fully funded healthcare for children, whilst in Australia it depends on which GP (bulk-billing or not) and hospital (public or private) they visit. Additionally, the guideline-recommended dosage of ondansetron is lower in the Netherlands.

Conclusions

Healthcare approaches for managing childhood gastroenteritis differ between the Netherlands and Australia. The lower annual incidence and per-case costs for childhood gastroenteritis in Australia cannot solely be explained by the differences in healthcare system functions. Nevertheless, Australia's robust public health system, characterized by legislations for vaccinations and quarantine, and the Netherland's well-established clinical care system, featuring fully funded continuity of care and lower ondansetron dosages, offer opportunities for enhancing healthcare in both countries.

INTRODUCTION

Acute gastroenteritis is a highly contagious disease that leads to significant morbidity, especially among young children.[1] Although the disease is self-limiting, its associated social and economic burdens are substantial.[2,3] For children with acute gastroenteritis, a good public health and clinical care system is required for prevention and early intervention to avoid outbreaks and symptom deterioration.[4] The Netherlands and Australia are both ranked in the top-performing health systems amongst other high-income countries, and both have general practitioners (GPs) as key components of the healthcare system.[5,6] Despite this, there are differences in the functions of these healthcare systems, which may affect the actual provision of care.

Differences in the annual incidence of acute gastroenteritis episodes per child under five years are evident between the two countries, with 1.96 episodes per child per year in the Netherlands compared to 1.58 episodes per child per year in Australia.[7,8] The incidence rate of a communicable disease can serve as an indicator of the effectiveness of the public health system, encompassing health promotion, vaccination programs, and infectious disease prevention.[9] Besides the variation in incidence, the costs per episode also vary significantly across these countries. The estimated medical costs per episode for children under five years of age in the Netherlands is €55.68 (AUD$ 81.29) compared to €14.37 (AUD$ 20.98) per episode in Australia in 2016.[7,8] These costs primarily encompass expenses related to GP visits, referrals, and hospitalizations.

Comparative research in these two countries can contribute to healthcare system strengthening by understanding and acknowledging best practices and learning from these best practices.[10] Therefore, this study aimed to compare the public health (outbreak management) and clinical daily care for children with acute gastroenteritis in the Netherlands and Australia.

MATERIALS AND METHODS

A cross-country expert study was conducted, among experts from the Netherlands and Australia aiming to compare the public health (outbreak management) and clinical daily care for children with acute gastroenteritis. Study methods and findings are reported in accordance with the Consolidated Criteria for Reporting Qualitative Research.[11] Ethical approval was obtained from the Ethics Committee of the University Medical Centre Groningen (METc 2023/134) and University of Melbourne (2023-26907-39606-3). Informed consent was obtained from participating experts.

Health System Performance Assessment framework

Study-designed questionnaires were based on the Health System Performance Assessment (HSPA) for Universal Health Coverage framework.[12] The European Observatory on Health Systems and Policies (hosted by the World Health Organization (WHO) Regional Office for Europe) has established the HSPA framework to be able to understand, describe, and compare the functioning of health systems (Figure 1). This framework provides a foundation for policy makers for evaluating health systems by linking their functions to intermediate objectives and final health system goals. Four health system functions have been created to describe the working of the healthcare system: governance; financing; resource generation; and service delivery (see below). Optimizing these functions can improve the intermediate objectives which will lead to better final health system goals.[12]

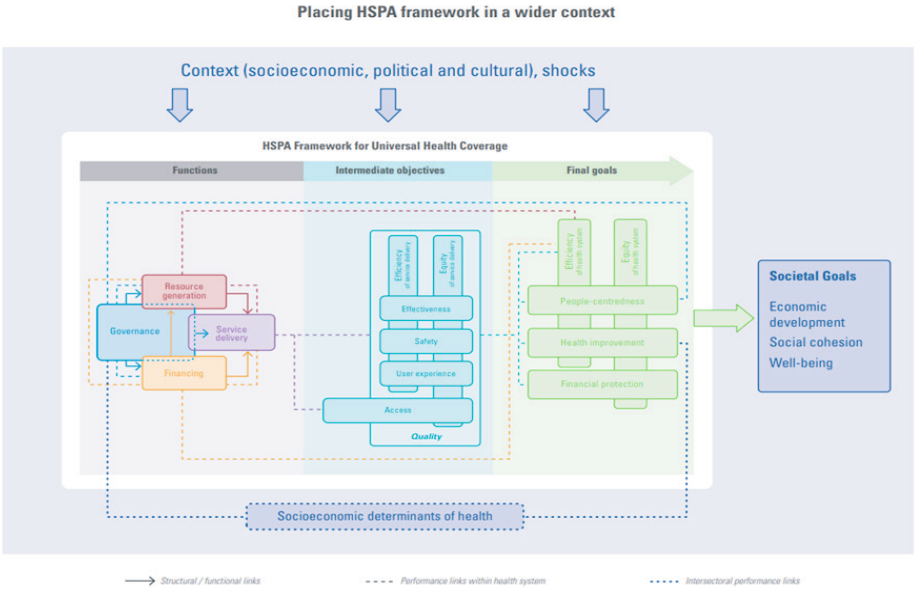

Figure 1. Health System Performance Assessment Framework – an overview

Source: World Health Organization, Papanicolas I, Rajan D, Karanikolos M, Soucat A, Figueras J. Health System Performance Assessment: A Framework for Policy Analysis. 2022.

Governance is a core health system function, shaping how the other functions are managed and operate. Governance determines the oversight, regulation and policies to effectively address the needs of the country. Financing is vital for sustaining the healthcare system by providing the necessary monetary resources for care implementation. Resource generation is essential for equipping the healthcare system with essential input, including human resource; infrastructure and medical equipment; and pharmaceuticals and other consumables. Service delivery is a function influenced by the performance of governance, financing and resource generation. It has direct impact on the intermediate objectives, such as access, quality and safety of care.

Questionnaire

Based on the HSPA framework and discussions within the research group, we developed two questionnaires (Appendix 1). One questionnaire focussed on the functioning of the public health system for children with gastroenteritis. The other questionnaire addressed clinical daily care for treating children with gastroenteritis. Public health includes the effective outbreak management and prevention of this highly contagious disease. Clinical daily care encompasses the healthcare pathway from the initial onset of gastroenteritis until fully recovered. The questionnaires were piloted among experts and were adjusted if needed. For the experts in the Netherlands, the questionnaires were translated into Dutch.

Data Collection

Questionnaires were delivered online to local experts in the Netherlands and the state of Victoria, for the Australian context, in April and May 2023. As these questionnaires aimed to understand the accepted guidelines and regulatory parameters for public health and clinical care system responses only, we considered two experts per category, per country as an adequate sample size. Opinions on the healthcare system were not requested. Public health questionnaires were provided to experts specializing in the public health of outbreak management of infectious diseases. The clinical care questionnaires were distributed among general practitioners, paediatricians and guideline developers. Input from their organizational group or team was welcome.

Data Synthesis

A narrative approach was employed to synthesize the data obtained from the questionnaires, including data from guidelines and other relevant sources provided by the experts. Through the synthesis, a constant comparison was made between data from the Netherlands and Australia. Unless specified, the description of the system for Victoria is the same for all of Australia.

RESULTS

Participants

In the Netherlands, two physicians from the National Institute for Public Health and the Environment answered the public health questionnaire. In Australia, an infectious disease physician and a manager responsible for communicable disease prevention and control, both working for the government of Victoria, provided information for the public health questionnaire. The clinical care questionnaire in the Netherlands was completed by a GP, a staff member from the Dutch College of GPs, and a pharmacist. Responses pertaining to clinical care practices in Australia were obtained from a GP specializing in child health and a paediatrician. The experts, on average, had over 15 years of experience in their professional field.

Governance

Table 1 gives a comprehensive overview of the government and legislations applicable for children with acute gastroenteritis for both the Netherlands and Australia.

Table 1. Government and legislations

Netherlands		Australia	
Ministry of Health, Welfare and Sport (VWS)	Government department responsible for public health, welfare, and sports policy.	**Department of Health**	Government department responsible for the administration and oversight of healthcare, public health and related services.
Health and Youth Care Inspectorate (IGJ)	Governmental agency responsible for monitoring and regulating healthcare and youth care.	**Safer Care Victoria**	Governmental agency responsible for driving improvements in the quality and safety of healthcare services.
Dutch Medical Treatment Contracts Act (WGBO)	Legislation that governs the relationship between healthcare professionals and patients.	**Health Services Act**	Legislation that governs various aspects of healthcare services and facilities.

Table 1. Government and legislations (continued)

Netherlands		Australia	
Healthcare Professionals Act (Wet BIG)	Legislation that regulates the practice of healthcare professionals.	**Health Practitioner Regulation National Law Act**	Legislation that governs the registration, regulation, and professional conduct of healthcare professionals.
Healthcare Insurance Act (Zvw)	Legislation that governs the mandatory health insurance system.	**Health Insurance Act (Australia)**	Legislation that establishes the legal framework for the country's public health insurance system known as Medicare.
General Data Protection Regulation	Data protections and privacy regulation implemented by the European Union.	**Privacy and Data Protection Act**	Legislation that governs the protection of personal information, including health-related data.
Medicines Act	Legislation that regulates the production, distribution, sale, and use of medicinal products.	**Pharmacy Regulation Act**	Legislation that regulates the practice of pharmacy.
Public Health Act (Wpg)	Legislation that governs the public health policy and public health interventions.	**Public Health and Wellbeing Act**	Legislation that establishes the framework for public health and wellbeing measures.

Public health

Outbreak management is achieved through the implementation of a systematic approach aimed at rapidly gaining insight into the outbreak. Both countries adopt a multisectoral approach to outbreak management. In the Netherlands, there is no legislation specifically aimed at prevention. The inclusion of the rotavirus vaccine in the National Immunisation Program is planned for 2024, and participation in the program is voluntary. In Australia, children are required to stay at home for 48 hours in an outbreak setting. The rotavirus vaccine has been included in the National Immunisation Program in Australia since 1st July 2007. To encourage the number of children fully immunised in line with the National Immunisation Program, the Australian Government initiated two policies. To access family assistance payments, children must meet immunisation requirements under the No Jab No Pay scheme. Children attending childcare in Australia are required to meet the National

Immunisation Program under the No Jab No Play legislation 2016, unless there is a medical exception.

Clinical care

Residents of Australia are not required to register with a regular GP. The Netherlands follows a system where patients must be registered with a GP practice to access their services and are not allowed to register with more than one GP. This ensures access to a GP when needed, allows for after-hours primary care, and facilitates the continuity of healthcare and monitoring of health status. In Australia, patients have the flexibility to book appointments with their preferred GP, sometimes even consulting multiple GPs on a single day.

Financing

The financing of the Dutch healthcare system is based on social health insurance and managed competition. Dutch citizens are required to obtain health insurance that covers a standard basic benefits package. Insurance premiums are determined by individual insurers. In Australia, the healthcare system is financed through Medicare which is the government-funded healthcare system in Australia. Medicare is accessible to all Australian citizens. Citizens can choose to purchase extra private health insurance to access additional healthcare services (largely hospital care) and benefits not covered by Medicare.

Public health

Both countries fully cover the expenses associated with rotavirus vaccinations through their Public Health Services.

Clinical care

In the Netherlands, Dutch GPs receive a fixed annual fee for each registered patient in their practice along with a small fee for each visit. The fixed fee is determined based on factors like the patient's age, gender, and health status. It is adjusted annually to account for inflation and changes in the practice's patient demographics. In Australia, the payment structure for GPs is primarily based on a fee-for-service model. GPs charge a fee for each service provided to patients. Patients typically pay the GP directly and then claim a rebate from Medicare. However, GP remuneration is not adjusted for inflation and rising costs, often leading GPs to charge higher fees, resulting in out-of-pocket expenses for patients. Some GPs offer 'bulk-billing', where Medicare covers the full consultation cost, and GPs bill Medicare directly instead of patients.

In the Netherlands, children under 18 years are automatically covered by their caregivers' insurance and clinical care for children with acute gastroenteritis is therefore fully funded through government contribution from taxes, meaning no out-of-pocket costs for patients. This includes prescription of medication (i.e., ondansetron). Over-the-counter medications (i.e., oral rehydration solution, paracetamol) are paid for by caregivers. In Australia, the costs for primary care for caregivers of children with acute gastroenteritis depend on the choice

of GP (bulk-billing or not). Medication prescribed in general practice is typically issued as a private prescription, and the caregivers are responsible for the costs. The Pharmaceutical Benefits Scheme helps cover the costs of a wide range of prescribed medication (i.e., paracetamol, oral rehydration solution, ondansetron), making them more affordable.

Hospital care for children with acute gastroenteritis in the Netherlands is fully covered. In Australia, it depends on whether caregivers choose public or private hospitals. Care provided in public emergency departments and hospitals is fully covered by state and federal governments. Medication prescribed in the public hospital is included in the hospital visit. For private hospital care, state and federal governments covers 75% of the hospital and medical fees. The remaining fees are billed to the caregivers, and depending on their private health insurance, certain fees might be covered.

Resource generation

Health workforce

Organizations and professionals involved in the health workforce of infectious gastroenteritis outbreaks in children in both countries include: the institution where the outbreak occurred (i.e., schools and child day-care centres), public health services (infectious disease control doctors and nurses, infection prevention experts, youth health care doctors), laboratories (medical microbiology doctors), GPs, and paediatricians. In both countries, management of acute gastroenteritis, particularly dehydration in children, is covered in medical school and training for GPs and paediatricians.

Infrastructure and medical equipment

In the event of an outbreak, both countries offer stool testing to identify the infectious agent causing the gastroenteritis outbreak. For clinical care, the availability of medical equipment for the management of childhood gastroenteritis in primary care is minimal in both countries. Emergency departments and paediatricians in-hospital in both countries have access to a wide range of additional diagnostics, including point-of-care blood testing.

Pharmaceuticals and other consumables

For public health, both countries offer access to the rotavirus vaccine. However, in the Netherlands the rotavirus vaccine is not included in the National Immunisation Program whereas in Australia it is included. For the clinical care in both countries, over-the-counter options (i.e., paracetamol, ibuprofen/naproxen, oral rehydration solutions) are available through pharmacies, drugstores or supermarkets. Prescribed ondansetron is available through pharmacies in syrup (Netherlands) or wafer form (Australia).

Service delivery

Public health

For the prevention of rotavirus gastroenteritis, in Australia it is recommended to receive the first dose by 14 weeks of age followed by a second dose by 24 weeks of age.
Both countries have established national guidelines for managing infectious gastroenteritis outbreaks in children which outline a step-by-step plan:[13,14] surveillance and detection, reporting to Public Health Service, investigation and epidemiological analysis, control measures, communication and education strategies, and follow-up and evaluation.

Clinical care

In both countries, access to clinical daily care for children with acute gastroenteritis is initiated by caregivers. During working hours, the first point of contact is typically the GP. In the Netherlands, caregivers usually reach out to the child's regular GP, who has knowledge of the child's medical history. In Australia, while 80% of patients are said to have a regular GP,[15] caregivers have multiple avenues for seeking care, including booking an appointment with any GP, contacting a telephone nurse for basic advice, scheduling virtual emergency department consultations through telehealth services, or visiting the emergency department to see a clinician. After working hours, in the Netherlands caregivers of children with acute gastroenteritis can contact GP out-of-hours facilities operated by larger cooperatives of GPs, where locum GPs are available for (telephonic) consultations. In Australia, limited GP practices are open after-hours and clinical care can be provided by locum GPs or through the options mentioned earlier. In the Netherlands, the practice of visiting the emergency department directly is not customary. Instead, referrals to emergency care follow mostly after telephonic consultation between the GP and the on-duty paediatrician in the local hospital.

Guidelines for GPs and paediatricians are available online in both countries.[16–19] These guidelines cover acute gastroenteritis background, assessment and management.

In both countries, the primary recommendation for the clinical care for children with acute gastroenteritis is to prioritize rehydration as the initial treatment approach, primarily through oral rehydration solutions. The use of antibiotics and antidiarrheal medications are not recommended for the treatment of children with acute viral gastroenteritis in both countries. As of December 2022, the Netherlands introduced a recommendation for a single dose of oral ondansetron syrup (0.1 mg/kg) for primary care management of gastroenteritis, whereas it previously was only advised in secondary care provided by paediatricians. In Australia, ondansetron is recommended in a higher weight base dose (8-15 kg 2mg; 15-30kg 4mg; >30kg 6-8mg) in the form of a wafer. After triage in emergency departments, there is early access to oral rehydration and ondansetron. Hospital management by a paediatrician is in both countries based on the severity of dehydration (mild, moderate or severe). For children with mild to moderate dehydration enteral rehydration is preferred. Intravenous

dehydration is recommended for severely dehydrated children or children who cannot tolerate enteral rehydration.[18,19]

Both countries offer online information for caregivers of children with acute gastroenteritis encompassing information about aetiology, symptoms, treatment advice, when to seek medical assistance, and preventive measures.[20,21] In the Dutch resource, written information is supported with a video. Australian guidelines recommend that children should not refrain from eating for more than 24 hours, while Dutch guidelines state that a few days without or with reduced food intake does not significantly affect the child.

DISCUSSION

A comparative synthesis of healthcare systems of two top-performing, high-income countries, the Netherlands and Australia, with the focus on public health (outbreak management) and clinical daily care for children with acute gastroenteritis was performed. In Australia, rotavirus vaccination is implemented in the national program with immunisation requirements and legislations for prevention, whereas this is not the case in the Netherlands. Access to care differs, as Dutch children must visit their regular GP before the hospital, while in Australia, children have multiple options and can go directly to hospital. Funding varies, with the Netherlands providing fully funded healthcare for children, whilst in Australia it depends on which GP (bulk-billing or not) and hospital (public or private) they visit. Additionally, the guideline-recommended dosage of ondansetron is lower in the Netherlands.

Public health

While the Netherlands and Australia have similar goals and step-by-step outbreak management plans aiming to promptly address outbreaks, they diverge in their strategies regarding vaccination and legislation for disease prevention. Rotavirus is the most common cause of severe gastroenteritis in young children and is a primary pathogen among hospitalized children with gastroenteritis.[2,22] In Australia, the introduction of a free rotavirus vaccine into the National Immunisation Program in 2007 resulted in a significant reduction in rotavirus-positive tests.[23] Moreover, the hospital admission rate showed a 62% reduction after the free rotavirus vaccine was implemented in Australia.[24] With the implementation of the 'No Jab No Pay' and 'No Jab No Play' legislations, an increase in full vaccination coverage among children in Australia was seen.[25] In contrast, the Netherlands does not include the rotavirus vaccine in its National Immunisation Program and lacks legislation restricting non-vaccinated children. It is plausible to hypothesize that thanks to effective immunisation and improved adherence to the immunisation program in Australia, there may less severe rotavirus cases, potentially leading to fewer hospital admissions and reduced healthcare costs. One can assume that it will have the same benefits in the Netherlands, but the question remains if these legislations will be tolerated by Dutch society.

Clinical care

In both countries, the primary goal in managing childhood gastroenteritis is rehydration. Oral rehydration solutions are recommended, while antibiotics and antidiarrheal medications are discouraged, aligning with international guidelines.[26] In the Netherlands, the recommended single dose of oral ondansetron is 0.1 mg/kg, while Australia advises a higher single dosage regimen (8-15kg 2mg; 15-30kg 4mg; >30kg 6-8mg)[17,27] consistent with previous research.[28,29] The lower dosage strategy in the Netherlands is based on a more recent randomised controlled trial that found (cost-)effectiveness at a lower dosage.[30,31] Furthermore, another study has revealed that children with acute gastroenteritis who received higher doses of ondansetron did not experience a greater reduction in vomiting, nor did they require less intravenous rehydration or hospitalizations compared to children who received lower doses.[32] As there seems no added benefit for higher single doses of oral ondansetron and emphasizing the importance of minimizing the risk of side effects, it could be advisable for Australia to consider adopting a lower single dose of ondansetron in their clinical guidelines.

Continuity of care

Effective management of childhood gastroenteritis requires safety netting advice, including dehydration and alarm symptom recognition, along with guidance on help-seeking.[33] The quality of safety netting relies on the GP-patient relationship, and a lack of care continuity hampers its provision.[33,34] Research also highlights the benefits of maintaining continuity in general practice and accessing the preferred GP can reduce emergency admissions.[35] Additionally, gatekeeping practices are associated with reduced healthcare utilizations and the likelihood of fewer hospitalizations.36 In the Netherlands, the predominant pathway for children with gastroenteritis involves initially consulting their familiar, fully funded GP before entering the hospital. However, gastroenteritis ranks among the top five diagnoses for children seeking out-of-hours primary care centres in the Netherlands, where multiple GPs work in shifts to provide care outside regular working hours.[37] In Australia, although it is reported that 80% of the patients have a regular GP,[15] this is not obligatory and parents have diverse care-seeking options. Therefore, both countries should be aware on optimizing care continuity, focusing on the establishing GP-patient relationships, as this could affect the actual care delivery for children with gastroenteritis.

Strengths and limitations

Strengths of this study were that we used the HSPA framework established by the WHO, which gave us a full understanding of the health system functioning in both countries and we placed emphasis on the public health, including outbreak management, as well as clinical daily care. Moreover, the research team responsible for the formulation and evaluation of the questionnaire comprised researchers from both participating countries, thereby enriching the depth of knowledge and expertise applied in the study. Nonetheless, a limitation of this study could be that we only surveyed two experts per category per country. We decided this was an adequate sample size as we aimed to understand the National published guidelines and regulatory parameters and opinions were not requested.

We selected experts who possessed considerable experience (on average >15 years) in the field of public health or clinical care and input of their organization was welcome. Lastly, it is worth noting that we used Victoria for the Australian context. However, the measures described here are national and not varying by state in Australia.

Conclusions

Healthcare approaches for organizing and providing healthcare for children with acute gastroenteritis varies between the Netherlands and Australia. The lower annual incidence and per-case costs for childhood gastroenteritis in Australia cannot solely be explained by the differences in healthcare system functions. Nevertheless, Australia's robust public health system, characterized by legislations for vaccinations and quarantine, and the Netherland's well-established clinical care system, featuring fully funded continuity of care and lower ondansetron dosages, offer opportunities for enhancing healthcare in both countries.

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Appendix 1a. Public health questionnaire

Governance

Policy and vision

- What is the public health policy[a] and vision of the State of Victoria for management of acute gastroenteritis outbreaks in children with goals and targets? Can you provide documents or websites?
- Does the public health policy of the State of Victoria include a multisectoral approach[b] for acute gastroenteritis outbreaks in children? If yes, how?
- Are there recommendations and transmural agreements for acute gastroenteritis outbreaks in the State of Victoria (across different health units and providers)? If yes, can you explain this?

Stakeholder voice

- Who is responsible for the development and review of the public health policy for management of acute gastroenteritis outbreaks in children?
- Do/have stakeholders participate(d) in the development and review of the public health policy for the management of acute gastroenteritis outbreaks in children? If yes, which stakeholders are/were involved and in which way?
- What mechanisms or rules are in place to ensure involvement of stakeholders in the development and review of this public health policy?

Information and intelligence

- Is there a regular monitoring and evaluation for acute gastroenteritis outbreaks in children in the State of Victoria? If yes, how?
- What data on acute gastroenteritis outbreaks is the government of the State of Victoria committed to collect for decision-making?
- Are relevant databases available for acute gastroenteritis outbreaks (i.e., registration, health insurance, pharmaceutical databases, health facility reporting and resource tracking systems)? If yes, how are these connected and can you provide documents or websites?
- How is data sharing regarding acute gastroenteritis outbreaks arranged between various layers of government and stakeholders?

Legislation and regulation

- Which legislation is applicable for acute gastroenteritis outbreaks in children?
- Are existing health laws aligned with the public health policy for acute gastroenteritis outbreaks? If yes, can you explain this and provide documents or websites?
- Is there a legislation that affects the prevention of children with acute gastroenteritis (i.e., vaccination, staying at home)? If yes, can you explain this and provide documents or websites?

Resource generation

Health workforce

- Which organizations and healthcare professionals are involved in the implementation of the public health policy regarding acute gastroenteritis outbreaks?
- Are there enough healthcare professionals available for the workforce in acute gastroenteritis outbreaks? Can you provide evidence for this?
- Do healthcare professionals receive specific training for the management of acute gastroenteritis outbreaks (i.e., medicine study, outbreak strategies)? If yes, what training is offered? Can you provide specific websites or documents about this training?
- Infrastructure and medical equipment
- What basic infrastructure and medical equipment is available for acute gastroenteritis outbreaks (i.e., health facilities, information systems, electronic files, additional testing)? Can you provide evidence about the quality and quantity of it?
- How is the infrastructure and medical equipment distributed across different types of care for acute gastroenteritis outbreaks (i.e., primary, secondary)? And in different sectors (i.e., private, public)?

Pharmaceuticals and other consumables

- Which pharmaceuticals and other consumables are available for acute gastroenteritis outbreaks (i.e., vaccines, oral rehydration solutions, antibiotics, anti-emetics, antipyretics)? Can you comment on the quantity and/or availability of it?
- Who is responsible for providing these pharmaceuticals and other consumables to healthcare professionals?
- How are pharmaceuticals distributed across different types of care for acute gastroenteritis outbreaks (i.e., primary, secondary)? And in different sectors (i.e., private, public)?

Financing

- How is the management of acute gastroenteritis outbreaks, including vaccination, financed?
- How are the pharmaceuticals and other consumables for acute gastroenteritis outbreaks financed (i.e., government, health insurers, consumers)?

Service delivery

- Which healthcare professionals are involved in the management of acute gastroenteritis outbreaks (i.e., infectious disease physicians, nurses, general practitioners, triage specialists, paediatricians)?
- Could you describe how the access to care in acute gastroenteritis outbreaks is organized (i.e., telephonic contact, home visit, regular hours, out-of-hours, emergency, primary and secondary care)?
- How is the service delivery arranged in acute gastroenteritis outbreaks (i.e., information, prescription of pharmaceuticals, referrals, vaccination)?

[a]Public health policy plays an essential role in defining a country's vision, policy directions and strategies for ensuring the health of its population (WHO).
[b]Multisectoal approach refers to deliberate collaboration among various stakeholder groups (e.g., government, civil society, and private sector) and sectors (e.g., health, environment, and economy) to jointly achieve a policy outcome. (Salunke, et al. Multi sectoral approach for promoting public health).

Appendix 1b. Clinical care questionnaire

Clinical care

- Could you describe how the clinical care for children with acute gastroenteritis is organized in the State of Victoria (i.e., telephonic contact, home visit, emergency, primary and secondary care)?
- Could you describe how the access to care for children with acute gastroenteritis is organized in the State of Victoria (i.e., regular hours, out-of-hours, primary and secondary care)?
- Which healthcare professionals are involved in the clinical care for children with acute gastroenteritis (e.g., triage specialists, nurses, general practitioners, paediatricians)?
- Who is responsible for delivering services and/or pharmaceuticals to children with acute gastroenteritis (e.g., advice, information, referrals, admission, additional testing)?

Resources

Infrastructure and medical equipment

- What basic infrastructure is available for the clinical care of children with acute gastroenteritis (i.e., health facilities)? Can you comment on the quantity and/or availability of it?
- What medical equipment is available for the clinical care of children with acute gastroenteritis (i.e., electronic files, additional testing)? Can you comment on the quantity and/or availability of it?
- How is the infrastructure and medical equipment distributed across different types of care for children with acute gastroenteritis (i.e., primary, secondary)? And in different sectors (i.e., private, public)?

Pharmaceuticals and other consumables

- Which pharmaceuticals and other consumables are available for the clinical care in children with acute gastroenteritis (i.e., apple juice, oral rehydration solutions, antibiotics, anti-emetics, antipyretics)? Can you comment on the quantity and/or availability of it?
- Who is responsible for providing these pharmaceuticals and other consumables to healthcare professionals?

- How are pharmaceuticals distributed across different types of care for the clinical care in children with acute gastroenteritis (i.e., primary, secondary)? And in different sectors (i.e., private, public)?

Human resources

- Do healthcare professionals receive specific training for the clinical care of children with acute gastroenteritis (i.e., medicine study, primary care course, triage course)? If yes, what training and can you provide specific websites or documents about this training?
- Are there enough healthcare professionals available for the workforce in the clinical care of children with acute gastroenteritis? Can you provide evidence for this?

Information

- Is there a guideline for healthcare professionals for the clinical care in children with acute gastroenteritis? If yes, can you provide documents or websites?
- Who is responsible for the development and review of this guideline?
- Is there any information/education available for parents of children with acute gastroenteritis? If yes, can you provide documents or websites?

Financing

- How are healthcare providers paid for delivering services to children with acute gastroenteritis?
- How is the clinical care of children with acute gastroenteritis financed (i.e., patients, health insurers, national funds/government)?
- How are the pharmaceuticals and other consumables for the clinical care in children with acute gastroenteritis financed?
- Is there an authority overseeing the financing for delivering the clinical care in children with acute gastroenteritis?

Government

- What is the role of the government in the clinical care for children with acute gastroenteritis (i.e., development and implementation)?
- Which ministries are involved in the clinical care for children with acute gastroenteritis?
- Who is responsible for overseeing the standard of clinical care of healthcare professionals involved in the clinical care of children with acute gastroenteritis?
- Which legislation is applicable for the clinical care in children with acute gastroenteritis?

CHAPTER 10

Summary and general discussion

SUMMARY

With this thesis we aimed to optimize the management of children with acute gastroenteritis (AGE) at home and in primary care, as it is assumed that too many children with AGE at low dehydration risk are referred, or even admitted, to the hospital and receive unnecessary medical interventions. This thesis encompasses the results of eight articles, including two cohort studies, a systematic review, qualitative research among 14 parents, a randomised controlled trial (RCT) involving nearly 600 GPs over a period of more than two years, and a cross-country expert study.

In **chapter 2** we investigated the healthcare trends for children with AGE at the out-of-hours primary care in the Netherlands from 2007 to 2014 through a retrospective cohort study. Data of 12,455 children (median age 20.2 months) who were diagnosed with AGE were included. The incidence rate for AGE decreased significantly over the seven-year period, while the face-to-face contact rate increased significantly (both, P <0.01). The median referral rate remained at 8.1%, with no significant change over time (P = 0.82). Less than 20% of the children received oral rehydration therapy (ORT) advice or prescription. Subgroup analysis for age categories (6 to 12 months and 1 to 6 years) showed a rise in face-to-face contact rate for older children. Overall, these findings serve as a valuable reference for assessing the potential impact of new interventions for children with AGE.

In **chapter 3** we performed a systematic review to identify facilitators and barriers to home management for children with AGE from the perspectives of healthcare professionals and parents. Out of 4,476 screened studies, 16 met the inclusion criteria. Facilitators for healthcare professionals encompassed knowledge of guidelines, enhanced skills, and the use of clinical decision support systems. For parents, lack of knowledge created a barrier to home management, while access to information resources, positive emotions and belief in their own capabilities served as facilitators. Consequently, optimizing home management should involve implementing comprehensive changes for healthcare professionals, focusing on increasing knowledge, enhancing skills and integrating clinical decision support systems. For parents, the emphasis should be on knowledge enhancement, educational resources, and reassurance. Addressing these aspects holds the potential to formulate an effective strategy, potentially enabling more children to be treated at home.

In **chapter 4** we conducted 14 interviews with parents of children with AGE who contacted the out-of-hours primary care, aiming to explore their motivations, expectations and experiences. Parents initiated contact when their sick child exhibited unusual behaviour, experienced absent micturition, or had ongoing vomiting and/or diarrhoea, coupled with reduced or no fluid intake. They contacted the out-of-hours primary care to prevent symptom deterioration and to seek reassurance from a general practitioner (GP). They expected a thorough physical examination, information, and follow-up plans from the GP. Parental dissatisfaction arose when they felt unheard, misunderstood, or not taken seriously,

increasing the likelihood of seeking another consultation. GPs did not always meet parental expectations. Thus, various factors influence parents' decision to contact the out-of-hours primary for children with AGE and there is a mismatch between parental expectations and GP actions. Awareness of parental feelings and understanding their expectations can guide GPs in their interactions with parents, potentially improving satisfaction with primary health care and out-of-hours primary care specifically.

In **chapter 5** we performed a seven-day prospective follow-up study involving children with uncomplicated AGE and visited the out-of-hours primary care. The objective was to describe the course of symptoms and risk of clinical deterioration. Utilizing data from the RCT, explained below, and the parallel cohort study alongside the RCT, we conducted subgroup analyses for young children (≤ 12 months) and those with severe vomiting, as they are at increased risk of dehydration. Among the 359 children with uncomplicated AGE presented at the out-of-hours primary care, 31 (8.6%) developed a complicated illness necessitating referral of hospitalization. In the majority of cases (>90%), all symptoms decreased within five days. Rapid reductions in vomiting and fever were observed, while diarrhoea decreased at a somewhat slower rate, especially among children aged 6–12 months. Children who deteriorated during follow-up were characterized by a higher frequency of vomiting at the initial presentation and continued to have higher frequencies of vomiting and fever during follow-up. Hence, the frequency of vomiting, rather than its duration, appears to be a more important predictor of clinical deterioration. Healthcare professionals should remain vigilant for children presenting with a higher frequency of vomiting, both initially and during follow-up, as they are more susceptible to clinical deterioration.

In **chapter 6** we outline the design of the pragmatic RCT aimed at evaluating the (cost-) effectiveness of adding oral ondansetron to standard care for children with AGE at increased risk of dehydration due to vomiting in primary care. This chapter also delves into the challenges encountered during research in children in primary care, utilizing data of the RCT and the parallel cohort study. Children aged 6 months to 6 years, diagnosed with AGE by a GP, with increased risk of dehydration due to vomiting (≥4 reported episodes of vomiting in the 24 hours before presentation and ≥1 reported episode of vomiting in the four hours before presentation), and with written informed consent from both parents were included in the RCT. For children who did not meet the excessive vomiting criteria, a parallel cohort study was offered, where consent was required from one parent. The inclusion rate of the RCT was affected by the informed consent procedure, as 39.0% of children were accompanied by only one parent. Furthermore, GPs prescribed ondansetron off-protocol to 34 children of which 19 were eligible for the RCT. RCT-eligible children included in the parallel cohort study had fewer risk factors for dehydration compared to children in the RCT, but the GP-assessed dehydration level did not differ. Consequently, the informed consent procedure and off-protocol use of study medication affected the inclusion rate but had little impact on the selection. Employing a parallel cohort study alongside an RCT can assist in evaluating selection bias, while a pilot study can reveal potential barriers to inclusion.

In **chapter 7** we present the outcomes of the effectiveness of the RCT. Children were randomly allocated to either the control group receiving standard care, consisting of ORT, or the intervention group receiving the same care along with one dose of oral ondansetron (0.1 mg/kg). Among 1,061 screened children, 194 were included for randomisation. One dose of oral ondansetron significantly reduced the proportion of children who continued vomiting within four hours from 42.9% to 19.5% (OR 0.37; 95%-CI = 0.20 to 0.72; NNT 4). Ondansetron also decreased the number of vomiting episodes within four hours (IRR 0.51; 95%-CI = 0.29 to 0.88) and improved overall parental satisfaction with treatment (*P* = 0.027). Ondansetron use did not lead to increased ORT intake, fewer referrals, or hospitalizations. In conclusion, children with AGE at increased risk of dehydration due to vomiting can be effectively and safely treated with ondansetron in primary care to stop vomiting more quickly and increase parental satisfaction with treatment.

In **chapter 8** we assessed the cost-effectiveness of this RCT. The total mean costs in the ondansetron group were 31.2% lower (€488 versus €709), and the total incremental mean costs for achieving an additional child free of vomiting in the first four hours was -€9 (95%-CI = -€41 to €3). The cost-effectiveness plane revealed that 94.0% of the bootstrap replicates fell into the bottom right quadrant, indicating reduced costs and increased effectiveness with ondansetron use. The cost-effectiveness acceptability curve indicated an almost 95% chance that ondansetron was cost-effective without investing additional money. Therefore, providing one dose of oral ondansetron to children with AGE at increased risk of dehydration due to vomiting given in primary care is not only clinically beneficial but also cost-effective.

Lastly, in **chapter 9** we conducted a cross-country expert study comparing the public health and clinical care for children with AGE in the Netherlands and Australia. Both countries are top-performing, high-income countries where GPs act as healthcare gatekeepers, but differences in the functions of these healthcare systems exist. Australia has implemented rotavirus vaccination within its national immunisation program, supported by immunisation requirements and legislations for prevention. In contrast, the Netherlands lacks comprehensive vaccination legislation. Access to care also differs, as Dutch children are required to consult their regular GP before being referred to the hospital, whereas Australian children have multiple options and can directly seek care at the hospital. Funding mechanisms vary, as the Netherlands offers fully funded healthcare for children, while in Australia, it depends on the GP and hospital visited. Additionally, the guideline-recommended dosage of ondansetron is lower in the Netherlands. Consequently, Australia's robust public health system, characterized by legislations for vaccination and quarantine, and the Netherland's well-established clinical care system, featuring fully funded continuity of care and lower ondansetron dosages, present opportunities for improving healthcare for children with AGE in both countries.

GENERAL DISCUSSION

With this thesis we aimed to optimize the management of children with acute gastroenteritis (AGE), both at home and in primary care. In the first part of this discussion, we will discuss our main findings, address the identified barriers, and explore potential strategies to optimize the management of children with AGE based on the findings of this thesis. Following this, we will delve into the methodological considerations, including the rationale behind selecting a pragmatic trial without a placebo. Subsequently, we will focus on the clinical implications of this thesis, followed by the strategies for implementation. Hereafter, we will broaden our perspective to the healthcare system and prevention. Finally, we will present a comprehensive conclusion of this thesis.

Management of acute gastroenteritis and chances for improvement

This thesis highlights the (cost-)effectiveness of adding oral ondansetron into standard care for children with AGE at increased risk of dehydration due to vomiting in primary care. One dose of oral ondansetron significantly reduced the proportion of children who continued vomiting within four hours from 42.9% to 19.5%, decreased the number of vomiting episodes within four hours, improved overall parental satisfaction with treatment, and reduced costs with 31.2% over a seven-day follow-up period.[1,2] However, ondansetron had no impact on oral rehydration therapy (ORT) intake, referral, or hospitalization rates. The rationale behind administering ondansetron was that by reducing vomiting, children might be more inclined to accept ORT, potentially influencing referrals and hospitalizations. The ORT intake was remarkably low (median 10 ml/4 hours) and the referral rate was more than twice as high as the median referral rate in the overall population of children with AGE (19.4% versus 8.1%).[1,3] This discrepancy in referral rate is attributable to our deliberate inclusion of children at increased risk of dehydration due to excessive vomiting, those who would benefit the most from ondansetron.

Throughout this thesis, it became evident that optimizing the management of children with AGE is a complex interplay of clinical and nonclinical factors, involving both parents and healthcare professionals. We identified several barriers in the management of children with AGE, including a lack of parental knowledge about AGE, symptoms and management, lack of knowledge among healthcare professionals about guidelines, clinical benefits and side effects of ORT and ondansetron, and suboptimal communication between general practitioners (GPs) and parents in primary care. We proposed strategies to enhance the prescription and utilization of ORT. In the subsequent discussion, we will delve into these barriers and potential strategies based on the findings of this thesis.

Knowledge of parents

Finding solutions to limit face-to-face contacts at the out-of-hours primary care for children with AGE is necessary, as this rate increased significantly for these children the past couple of years.[3] This trend is particularly pronounced among children under five years, who utilize

out-of-hours primary care the most.[4] A lack of parental knowledge about the disease, symptoms and management, including the importance of ORT and fluid intake, acted as a barrier to manage children with AGE at home.[5] This lack of knowledge led to negative emotions among parents, such as stress, worry, uncertainty, and helplessness, prompting them to contact the out-of-hours primary care.[5,6] Conversely, well-informed parents were more likely to confidently manage their child at home, responding promptly and ensuring timely fluid and ORT administration. Parents with more experience and disease-related knowledge felt more confident in managing their child with AGE at home.[5] This underscores the need for a stronger focus on educating parents in the management of children with AGE.

Regarding resources for educating parents, our systematic review results indicated that video discharge instructions enhanced parents' knowledge but had no impact on revisit rates. Information sheets provided by healthcare professionals guided parents through necessary steps and aided in identifying signs of dehydration. Although perceived as valuable by parents, expressing intentions to review them in future cases, the actual impact on revisit rates was not tested.[5] A French trial evaluating patient information leaflets for parents of children with AGE demonstrated increased parental knowledge, improved adherence to guideline-recommended behaviours, and a reduction in consultations deemed unnecessary.[7] A three-minute whiteboard animation video was recently created for parents of children with AGE. However, results have not been published yet.[8] It would be beneficial to explore the most effective parental education tools (e.g., online videos, information sheet) and their impact on face-to-face contact and referral rates, as these tools could improve knowledge and potentially allow more children to be treated at home.

Knowledge of healthcare professional

Inadequate knowledge among healthcare professionals regarding guidelines and the clinical benefits of ORT and ondansetron emerged as a barrier to management for children with AGE. This knowledge deficit led to increased use of non-recommended interventions while reducing the initiation of both ORT and ondansetron.[5] Misconceptions among healthcare professionals about the consequences of ORT, such as potential prolonged emergency stays, further diminished the likelihood of its initiation. This is concerning, as we found that the past couple of years, less than 20% of the children presenting to out-of-hours primary care received a prescription for ORT.[3] In contrast, healthcare professionals with knowledge of ORT effectiveness were more likely to ingrate ORT into their practices.[5] Concerning ondansetron, it is crucial that not every child with AGE receives a prescription, but only those at an increased risk of dehydration i.e. due to excessive vomiting. This highlights the imperative to educate healthcare professionals concurrently with the implementation of ondansetron in primary care. Furthermore, in the process of educating healthcare professionals, it is essential to emphasize the importance and effectiveness of ORT alongside ondansetron, while dispelling misconceptions about ORT.

Communication in primary care

The actions and attitudes of GPs played a crucial role for parents of children with AGE when contacting the out-of-hours primary care. Interviews with parents revealed that while not all children were severely sick or dehydrated, parents were concerned and wanted to prevent severe illness. Parents reported feeling unheard, misunderstood, or not taken seriously, which resulted in a more negative experience, thereby increasing the likelihood of seeking contact with another GP.[6] Effective communication emerged as a key factor in addressing parental concerns and understanding their underlying causes. Research indicates that when GPs prioritize open communication, parents are more likely to accept GPs' advice and decision, even if it deviates from their initial expectations.[9] This need for effective communication is even more pronounced in the out-of-hours primary care setting, where no established relationship exists between GPs and patients, making trust, treatment acceptance and satisfaction more challenging.[10]

When parents received information and advice on improving fluid intake, recognizing alarm symptoms, understanding the course of the disease, and knowing when to call again, they were more satisfied with the contact.[6] Regarding the uncomplicated course of AGE, we found that symptoms such as vomiting, diarrhoea, and fever generally resolve within five days after presentation. For children aged 6-12 months, diarrhoea may persist up to seven days.[11] This information could serve as a helpful supplement to the information provided to the parents. Parents emphasized the importance of receiving practical advice about AGE and dehydration, as this could not only assist them in managing current illness but also potentially prevent the need for future contact in primary care.[6] Therefore, fostering open communication, aligning expectations, and providing practical information can enhance the parental experience with out-of-hours primary care.

Strategies for improving oral rehydration therapy

An editorial discussing our randomised controlled trial (RCT) underscored the need of broadening the focus beyond ondansetron and emphasized the importance of developing strategies to improve ORT intake.[12] In our RCT, the ORT intake was remarkably low, 10 ml over four hours, and ondansetron did not impact this. Given the median weight of the children, they should have received at least 110 ml (10 ml/kg) or 165 ml (15 ml/kg) over four hours, depending on their hydration status.[1] RCTs conducted in emergency departments showed that children who received ondansetron had higher ORT intake and improved tolerance.[13–15] In our RCT, parents were instructed on the procurement and administration of ORT, while in the emergency department studies, ORT was directly administered to the child. In our systematic review, we found that providing ORT during a face-to-face visit increased its average use and success rate.[5] Moreover, parents who observed the successful acceptance of ORT during the visit were more likely to continue ORT treatment at home.[5] To enhance ORT utilization, a potential strategy could involve administering ORT during primary care visits instead of solely prescribing it.

In our systematic review, we found that implementing a combination of process changes aimed at increasing skills, knowledge, and regulating the behaviour of healthcare professionals optimized management. This resulted in increased ORT utilization along with a 45% reduction in hospitalizations for children with AGE.[5] Among these process changes, offering free ORT during visits was impactful, as was the establishment of a protocol for ORT administration and a clinical decision tool. Notably, single process changes effectively increased both ORT and ondansetron administration when directly administered to the child, but they did not affect return visit or hospitalization rates.[5] This highlights the importance of not relying solely on ondansetron administration but simultaneously implementing tools to enhance skill and knowledge of healthcare professionals, along with the provision of ORT.

Methodological considerations of the trial

Pragmatic trial

When designing the RCT, we had a choice between adopting an explanatory or pragmatic design. Explanatory RCTs focus on evaluating the efficacy of an intervention under optimal, tightly controlled conditions. In contrast, pragmatic RCTs are designed to assess how an intervention performs in a broader, more real-world setting.[16,17] The use of placebos in RCTs for blinding purposes can significantly deviate from standard clinical practice and may not align with the objectives of a pragmatic RCT.[18] Moreover, introducing a placebo for a therapy that is already proven effective can raise ethical concerns.[19] For oral ondansetron, its efficacy has been established in four RCTs conducted in emergency departments for children with AGE. These RCTs provided evidence that ondansetron effectively reduced vomiting, decreased hospitalization rates, lowered the need for intravenous rehydration therapy, and improved the feasibility of ORT compared to placebo.[13–15,20] In conducting our RCT, our aim was to evaluate the real-world (cost-)effectiveness of adding oral ondansetron in comparison to standard care in routine primary care. Therefore, taking all these factors into consideration, we deliberately chose a pragmatic RCT design that omitted the use of a placebo.

Primary outcome

The primary outcome of our RCT was the proportion of children who continued vomiting within the first four hours after randomisation. This four-hour evaluation point was selected in accordance with guidelines that recommend re-evaluating children at increased risk of dehydration after four hours.[21,22] If there is no clinical improvement at this point, the GP is recommended to conduct a reassessment whether there is an indication for referral to emergency department or if the current therapy can be safely continued at home. Additionally, the elimination half-life of ondansetron in children is approximately three hours, meaning direct effects on vomiting are unlikely beyond four hours.[23]

Informed consent procedure

Early termination affects 40% of paediatric RCTs, with slow recruitment being the primary cause.[24] During our RCT, we encountered an important recruitment challenge related to the informed consent procedure. Initially, we required written informed consent from both parents. However, in 39% of cases, only one parent was present with their child with AGE at the out-of-hours primary care.[25] This procedure would have made recruitment not feasible and therefore was later modified, with agreement of the medical ethics committee, to immediate written consent by one parent plus immediate verbal consent from the other, followed by written consent by the second parent at a later stage. This modification increased the inclusion rate from seven to 10 cases per month.[25] Despite repeated calls, we did not receive a second written informed consent of 16 children of which eight received the study medication. These children were excluded due to protocol deviation, raising ethical concerns, as they had completed study activities and received the study medication. Since July 1st 2022, the use of eConsent in WMO-obligated research has been legally permitted.[26] This means that participants can provide electronic consent for participation in WMO-obligated research.[27] In our RCT, this would have meant that one parent provided immediate written informed consent, followed by immediate eConsent from the second parent at home simultaneously. If this approach had been implemented in our RCT, it could have improved inclusion rate at that time and reduced the exclusion of children.

Clinical implications of oral ondansetron in primary care

The finding that oral ondansetron added to standard care is (cost)-effective in primary care opens up opportunities for structural integration. The initial step of integration is to include it into the primary care guideline. Indeed, the Dutch College of General Practitioners has updated its treatment guideline for "Nausea and Vomiting" recommending oral ondansetron as a new treatment option for children with AGE in primary care.[21] For the effectiveness of ondansetron, they relied on a systematic review aimed at meta-analysing evidence regarding the efficacy and safety of a single dose ondansetron in children at emergency departments.[28] We understand this decision but we are puzzled that they used the findings of our RCT for the feasibility of oral ondansetron in primary care. Demonstrating feasibility was not our goal, as it requires a different study design, and we did not show this. We believe that the significance of our trial is herewith underestimated. Our pragmatic RCT demonstrated that ondansetron is cost-effective in a primary care setting despite all the barriers related to the management of children with AGE. With a cost-effectiveness analysis, we showed that an average of € 9 could be saved for every child who did not vomit in the first four hours after administration of one dose of oral ondansetron.[2] With an incidence of 1.96 episodes per child-year and an average annual cost of € 88,57 per child under five years, oral ondansetron could lead to significant cost-reduction.[29] Additionally, our cost-effectiveness acceptability curve indicated an almost 95% chance that ondansetron is cost-effective without any additional investment. The decision to use our trial for feasibility highlights the misunderstanding about the value and significance of pragmatic trials. As researchers, we could have presented these findings together to reduce the chance of the

misunderstanding. Nevertheless, the guideline embraced our lower weight-based dose (0.1 mg/kg) as opposed to the higher dose used in the systematic review (0.15-0.3 mg/kg) and they endorsed the recommendation to administer ondansetron only as additional treatment to standard care in children with increased risk of dehydration due to vomiting.

When integrating a medication, it is important to consider potential side effects. Some evidence suggests that ondansetron might increase diarrhoea, although findings are inconclusive.[28] In the Dutch Pharmacotherapeutic Compass, diarrhoea is classified as a rare side effect (0.01-0.1%).[30] Our seven-day prospective cohort study found no association between a single dose of ondansetron (0.1 mg/kg) and an increase in diarrhoea episodes.[11] Several RCTs offer insight into this side effect. An RCT by Rang et al. comparing intravenous ondansetron (single bolus of 0.2 mg/kg) with placebo, reported no difference in diarrhoea frequency.[31] An RCT by Hagbom et al. involving a single dose of oral ondansetron (0.15 mg/kg), demonstrated even a reduction in diarrhoea episodes compared to placebo.[32] In contrast, an RCT by Ramsook et al. administering oral ondansetron every eight hours (1.6-4.0 mg depending on age), reported more diarrhoea after 48 hours compared to those who received placebo.[20] Still, they revealed clinical benefits as ondansetron reduced vomiting, decreased the length of stay in the emergency department, hospitalization rates, and the likelihood of intravenous rehydration.[20] Overall, we recommend a single 0.1 mg/kg dose of oral ondansetron, and we believe that the potential risk of diarrhoea does not outweigh the substantial clinical benefits.

Currently, over 300 medications, including ondansetron, are associated with a QT-prolongation.[33] The Food and Drug Administration cautions that a single intravenous dose of 32 mg may lead to QT-prolongation, potentially resulting in Torsade de Pointes, a life-threatening heart rhythm.[34] A recent retrospective study involving 32,737 adults who received a 4 mg intravenous dose of ondansetron found no episodes of Torsade de Pointes.[35] In paediatric studies among children with AGE, using intravenous ondansetron (0.15 mg/kg) or a single oral dose (mean dose 0.18 ± 0.04 mg/kg) showed no evidence for QT-prolongation.[36,37] We recommend a single dose of 0.1 mg/kg ondansetron and there are no reported clinical examples of QT-prolongation at this dosage. It is imperative for every healthcare professional, especially when prescribing new medication, to possess comprehensive knowledge about the indications, potential side effects, and contraindications. The Dutch Pharmacotherapeutic Compass emphasizes caution with ondansetron for patients with congenital long QT-interval syndrome.[30] In cases where a child is known to have a congenital long QT-interval syndrome, collaboration between the pharmacist, paediatrician, GP and parents is essential to discuss the decision of whether to administer ondansetron or not.

Implementation strategies

Embedding oral ondansetron in the guideline for "Nausea and Vomiting" by the Dutch College of General Practitioners is a step forward, but it does not guarantee that ondansetron will be prescribed as intended: in the correct dosage, to the right children, and in combination with ORT in the appropriate manner. Throughout this thesis several barriers have been identified, including a lack of parental knowledge about AGE, symptoms and management, as well as lack of knowledge among healthcare professionals about guidelines, clinical benefits and side effects of ORT and ondansetron. Additionally, structural implementation of ondansetron in primary care faces obstacles such as the absence of practical infrastructure for integration, along with collaboration among healthcare professionals.

Building upon the findings of this thesis, a funding proposal was submitted and approved by ZonMw (GO-KIDS: gepast gebruik ondansetron bij kinderen in de huisartsenpraktijk; translated as appropriate use of ondansetron in children in primary care). This implementation project focuses on developing three key strategies to overcome barriers to implementation. Firstly, the existing online information for parents of children with AGE in the Netherlands will be evaluated. This evaluation will include multiple websites, such as thuisarts.nl 'My child has gastroenteritis', apotheek.nl and kijksluiter.nl, to assess how parents perceive this information, identify any missing information, and recommend adjustments if necessary.

Secondly, an e-learning module will be implemented for GPs and pharmacists to enhance their understanding of ondansetron's indications and effectiveness, its side effects, the importance of ORT use and fluid intake alongside ondansetron, the course of illness in children with AGE, follow-up recommendations, and communication with parents and other healthcare professionals.

Thirdly, a pharmacotherapeutic consultation module will be introduced to promote the appropriate use and prescription of ondansetron in primary care. This module is designed to facilitate local agreements between GPs, pharmacists, and paediatricians, utilizing the existing pharmacotherapeutic consultation groups that most GPs in the Netherlands are part of.

Finally, after the implementation project, further research is needed to determine if the implementation of oral ondansetron into primary care affects the ORT intake, referrals, and hospitalizations.

Healthcare system and prevention

Taking a comprehensive view of the healthcare system, it is evident that both an effective public health and clinical care system are essential for optimizing the management of children with AGE.

Prevention takes precedence over management and rotavirus emerges as the primary cause of AGE in children.[38] Despite rotavirus being associated with a more complicated clinical course and standing as the leading cause of referrals and hospitalizations,[39] an evaluation of stool samples from children included in the parallel cohort study alongside our RCT revealed no significant correlation between rotavirus, a complicated course, and increased referral rates. We attribute this discrepancy to the inclusion of lower-risk children in the cohort study, as opposed to the high-risk children included in the RCT.[40]

The World Health Organization advocates for the integration of rotavirus vaccines into all national immunization programs, recommending administration of the first dose as soon as possible after six weeks of age.[41] A Cochrane review of high-income countries demonstrated that the two rotavirus vaccines used in Europe, Rotarix and Rotateq, successfully prevented 93% and 97% of severe rotavirus cases.[42]

Australia and the Netherlands, both top-performing high-income countries with GPs playing a pivotal role, exhibit variations in the incidence rates and costs per episode for children under five with AGE (Australia: 1.58 annual episodes; €14,37 per episode | the Netherlands: 1.96 annual episodes; €55,68 per episode).[29,45] The introduction of a free rotavirus vaccine in Australia resulted in a 62% reduction in hospital admission rates for children with AGE.[46] Legislations such as 'No Jab No Pay' and 'No Jab No Play' in Australia contributed to an increased rate of full vaccination coverage among children.[47] In the Netherlands, rotavirus vaccination is scheduled for implementation in the national immunization program in 2024 without legislations mandating vaccination.[48] While effective immunization and enhanced adherence to the immunization program could lead to a decrease in severe rotavirus cases and subsequent reductions in hospitalizations and healthcare costs in Australia, the question remains whether such legislation will be accepted by Dutch society.

The differences between Australia and the Netherlands extend beyond vaccination policies, encompassing crucial aspects such as continuity and access to care.[49] Continuity of care is a vital element in fostering a strong GP-patient relationship and facilitating effective communication.[50] Moreover, increased continuity in primary care is associated with lower hospitalization rates.[51] Access to care is also important, with gatekeeping practices being linked to reduced healthcare utilizations and lower likelihood of hospitalizations.[52] In the Netherlands, the pathway for children with AGE involves initiating contact with their familiar, fully funded GP before proceeding to the hospital. However, there is an increasing trend in face-to-face contact rates with the out-of-hours primary care for children with AGE, where the GP is unfamiliar with the child.[53] In Australia, despite 80% of the patients reported having a regular GP,[54] it is not obligatory, and parents have a range of care-seeking options. One option is the ability to directly access the hospital, thus bypassing the gatekeeping role of the GP. Furthermore, public hospitals are fully funded, whereas this is not the case for all primary care practices. As a result, a situation may arise in which more children are treated in the hospital who could have been adequately treated by in primary care, or even at home.

We highlight the importance of the gatekeeping function of the GP but also recommend for both countries to be aware of optimizing care continuity, focusing on establishing GP-patient relationships, as this could affect the actual care delivery for children with AGE.

Overall conclusion

Optimizing management of children with AGE is a complex process of clinical and nonclinical factors, involving both parents and healthcare professionals. Oral ondansetron is a (cost-) effective option in primary care as additional treatment for children with AGE at increased risk of dehydration due to vomiting. However, to increase the ORT use and subsequently affect the referral and hospitalization rates more barriers need to be broken through. Overall, parents would benefit from increased knowledge and educational resources to enhance their understanding and increase reassurance. Healthcare professionals should engage open communication with parents and have more knowledge about guideline-based management, including the use of ORT and ondansetron. Administering ORT during primary care visits instead of solely prescribing it could enhance ORT utilizations. Further research is needed to assess parental education tools, the impact of rotavirus vaccination in the Netherlands, and evaluate the structural implementation of oral ondansetron in primary care.

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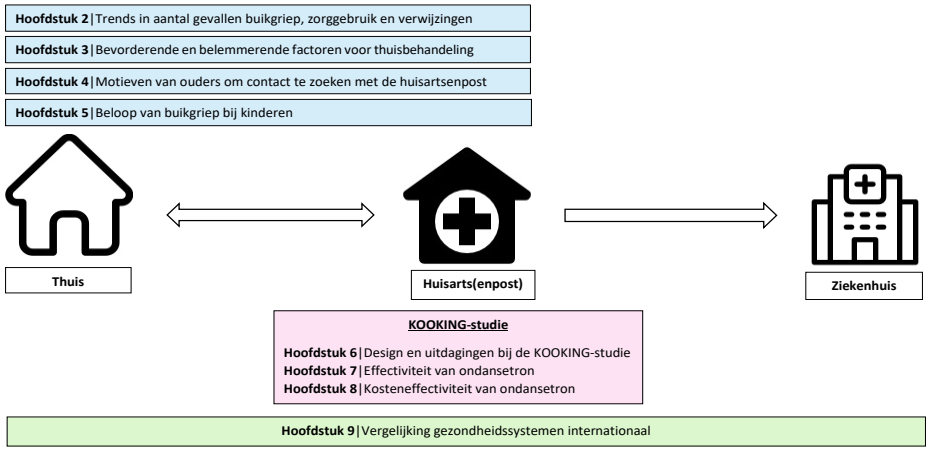
Nederlandse samenvatting

NEDERLANDSE SAMENVATTING

Het doel van dit proefschrift is om de behandeling van kinderen met buikgriep te verbeteren, zowel thuis als in de huisartsenpraktijk. Dit proefschrift omvat meerdere hoofdstukken, die allemaal vanuit verschillende perspectieven een bijdrage leveren aan dit doel (figuur 1). In dit hoofdstuk laten we een korte achtergrond van het probleem zien, beschrijven we de verschillende hoofdstukken en geven we een alomvattende conclusie.



Figuur 1. Overzicht van de hoofdstukken van dit proefschrift

Achtergrond

Buikgriep is één van de meest voorkomende infectieziekten bij kinderen onder de vijf jaar in Nederland. Meestal wordt buikgriep veroorzaakt door een virus, met name het rotavirus of norovirus. Hierdoor krijgen kinderen last van braken en/of diarree met soms koorts. Deze klachten gaan meestal vanzelf binnen een paar dagen over. Als de klachten erger worden, kunnen kinderen veel vocht verliezen en uitgedroogd raken. Uitdroging is de belangrijkste complicatie van buikgriep. Buikgriep is een veelvoorkomende reden voor ouders om contact op te nemen met de huisarts of huisartsenpost. Jaarlijks worden de kosten van buikgriep bij kinderen onder de vijf jaar in Nederland geschat op meer dan €77 miljoen. Deze hoge kosten komen vooral door verwijzingen naar het ziekenhuis, ziekenhuisopnames en werkverzuim van ouders. Om het vochttekort aan te vullen en de vochtbalans weer te herstellen, is het belangrijk om het kind voldoende vocht en ORS te geven, een drankje met suikers en zouten. In de dagelijkse praktijk blijkt ORS echter nauwelijks gebruikt te worden. Bovendien wordt gesuggereerd dat er te veel kinderen met buikgriep en een laag risico op uitdroging naar het ziekenhuis worden verwezen, of daar zelfs worden opgenomen.

Hoofdstukken

Allereerst wilden we een inzicht krijgen in het aantal gevallen buikgriep bij kinderen, het zorggebruik en het aantal verwijzingen in **hoofdstuk 2**. Hiervoor hebben we de gegevens van 12,455 kinderen met buikgriep op de huisartsenpost in Nederland over de periode van 2007 tot 2014 gebruikt. Gedurende deze zeven jaar was er een afname in het aantal gevallen buikgriep, terwijl het aantal fysieke contacten met de huisartsenpost juist toenam. Het percentage verwijzingen bleef over de zeven jaar stabiel rond de 8.1%. Opmerkelijk was dat minder dan 20% van de kinderen advies of een recept voor ORS kreeg. Daarnaast hebben we specifiek gekeken naar verschillende leeftijdscategorieën (zes tot twaalf maanden en één tot zes jaar). Hierbij was er een stijging te zien in het aantal fysieke contacten met de huisartsenpost voor de oudere kinderen. De resultaten van dit onderzoek dienen als een waardevolle referentie voor het beoordelen van de potentiële impact van nieuwe interventies voor kinderen met buikgriep.

Vervolgens hebben we in **hoofdstuk 3** een systematisch overzicht van de literatuur uitgevoerd om de bevorderende en belemmerende factoren voor de thuisbehandeling van kinderen met buikgriep te identificeren. Dit hebben we onderzocht vanuit het perspectief van zorgprofessionals en ouders. Van de 4,476 gescreende studies voldeden zestien studies aan de inclusiecriteria. Uit dit onderzoek kwam naar voren dat zorgprofessionals baat hebben bij kennis van richtlijnen en behandelingen. Het gebruik van systemen om het gedrag en de vaardigheden van zorgprofessionals te beïnvloeden, zoals ORS-toedieningsprotocollen of een systeem voor het beoordelen van uitdroging, werkte ook bevorderend voor de thuisbehandeling. Voor ouders vormde een gebrek aan kennis over de ziekte, symptomen en behandeling een belemmering voor de thuisbehandeling. Toegang tot informatiebronnen en het geloof in hun eigen kunnen, werkten juist als bevorderende factoren voor de thuisbehandeling. De resultaten van dit onderzoek suggereren dat voor het optimaliseren van de thuisbehandeling meerdere veranderingen nodig zijn bij zorgprofessionals, gericht op het vergroten van de kennis, verbeteren van de vaardigheden en integreren van ondersteunende systemen voor klinische besluitvorming. Voor ouders zou de nadruk moeten liggen op het vergroten van de kennis rondom de ziekte en behandeling, en het verstrekken van informatie om het vertrouwen in hun eigen kunnen te vergroten. Door dit aan te pakken, kunnen mogelijk meer kinderen met buikgriep succesvol thuis behandeld worden.

In **hoofdstuk 4** hebben we veertien ouders van kinderen met buikgriep die contact opnamen met de huisartsenpost geïnterviewd. Het doel van deze interviews was om inzicht te krijgen in de motivaties, verwachtingen en ervaringen van deze ouders. Ouders gaven aan dat ze bij de volgende symptomen contact opnamen met de huisartsenpost: wanneer hun zieke kind ongewoon gedrag vertoonde, niet plaste, voortdurend moest braken en/of diarree had, in combinatie met verminderde of geen vochtinname. De reden voor contact was het voorkomen van verslechtering van de symptomen en het krijgen van geruststelling van een huisarts. Ouders verwachtten een volledig lichamelijk onderzoek bij hun kind, informatie

en geruststelling van de huisarts. Ontevredenheid bij ouders ontstond wanneer ze zich niet gehoord voelden, verkeerd begrepen werden of niet serieus werden genomen, wat de kans vergrootte dat ze contact zochten met een andere huisarts. Uit de interviews bleek dat huisartsen niet altijd voldeden aan de verwachtingen van ouders. Hieruit concluderen we dat verschillende motieven de beslissing van ouders beïnvloeden om contact op te nemen met de huisartsenpost voor kinderen met buikgriep en dat er een mismatch is tussen de verwachtingen van ouders en het handelen van de huisarts. Bewustwording van de gevoelens van ouders en het begrijpen van hun verwachtingen kan huisartsen helpen in de interacties met ouders, waardoor de tevredenheid in de huisartsenpraktijk, en specifiek de huisartsenpost, kan vergroten.

In **hoofdstuk 5** hebben we onderzocht wat het beloop van symptomen (braken, diarree en koorts) en het risico op klinische verslechtering is bij kinderen die zich presenteren op de huisartsenpost met buikgriep. Hiermee hoopten we richtlijnen voor vangnetadvies aan ouders te kunnen ontwikkelen. Kinderen die direct verwezen werden naar het ziekenhuis werden niet meegenomen, aangezien deze ouders geen vangnetadvies krijgen van de huisarts. We hebben hiervoor gebruikgemaakt van de gegevens uit de KOOKING-studie, die hieronder wordt beschreven, en een cohortstudie naast de KOOKING-studie. We hebben aparte analyses uitgevoerd voor jonge kinderen (≤ twaalf maanden) en kinderen met ernstig braken, aangezien zij een verhoogd risico op uitdroging hebben. Van de 359 kinderen met buikgriep, werden 31 kinderen (8.6%) verwezen of opgenomen in het ziekenhuis tijdens de follow-up. In de meerderheid van de gevallen (>90%), waren de symptomen braken, diarree en koorts binnen vijf dagen over. De uitzondering hierbij was diarree bij kinderen ≤ twaalf maanden, wat over was binnen zeven dagen. Kinderen die werden verwezen of opgenomen tijdens de follow-up vertoonden een hogere frequentie van braken bij het eerste contact en bleven een hogere frequentie van braken en koorts hebben tijdens follow-up. Hieruit kunnen we concluderen dat de frequentie van braken, eerder dan de duur ervan, een belangrijkere voorspeller lijkt te zijn voor klinische achteruitgang. Zorgprofessionals en ouders moeten daarom waakzaam zijn bij kinderen met een hogere frequentie van braken, zowel bij het eerste contact als tijdens de follow-up, omdat zij vatbaarder zijn voor klinische verslechtering.

KOOKING-studie

Braken bij jonge kinderen met buikgriep is een belangrijke risicofactor voor uitdroging. Kinderen die in het ziekenhuis terecht komen vanwege buikgriep en veelvuldig braken krijgen daar ondansetron, een middel dat ervoor zorgt dat het braken stopt. Het idee is dat door het toedienen van ondansetron het kind stopt met braken, waardoor het kind weer vocht en ORS kan vasthouden en de vochtbalans zich kan herstellen. Uit eerder onderzoek is gebleken dat ondansetron, gegeven op de spoedeisende hulp, effectief het braken stopt, de inname van ORS verbetert en ziekenhuisopnames voorkomt. Er is nog geen onderzoek gedaan in de huisartsenpraktijk. Daarom is de KOOKING-studie (KOOKING: *Kosteneffectiviteit ondansetron bij kinderen met acute gastro-enteritis*) opgezet om te kijken naar de (kosten)

effectiviteit van het toevoegen één dosis ondansetron siroop aan de standaardzorg op het stoppen met braken bij kinderen met buikgriep met een verhoogd risico op uitdroging door braken op de huisartsenpost.

In **hoofdstuk 6** beschrijven we het design van de KOOKING-studie en gaan we in op de uitdagingen die zich voordoen bij onderzoek bij kinderen op de huisartsenpost, aan de hand van gegevens van zowel de KOOKING-studie als de parallelle cohortstudie. Kinderen in de leeftijd van zes maanden tot zes jaar, gediagnosticeerd met buikgriep door een huisarts, met een verhoogd risico op uitdroging door braken (≥ vier braakepisodes in de 24 uur voor presentatie en ≥ één braakepisode in de vier uur voor presentatie) en met schriftelijke toestemming van beide ouders werden geïncludeerd in de KOOKING-studie. Voor kinderen die niet voldeden aan de criteria van overmatig braken werd een parallel cohortonderzoek aangeboden, waarvoor schriftelijk toestemming van één ouder vereist was. De inclusiesnelheid van de KOOKING-studie werd beïnvloed door de toestemmingsprocedure. Van de kinderen werd 39.0% door slechts één ouder begeleid, terwijl van twee ouders schriftelijk toestemming nodig was. Bovendien schreven huisartsen ondansetron off-protocol voor aan 34 kinderen, waarvan er negentien in aanmerking kwamen voor de KOOKING-studie. Kinderen die aanmerking kwamen voor de KOOKING-studie, maar werden geïncludeerd in de parallelle cohortstudie hadden minder risicofactoren voor uitdroging in vergelijking met kinderen in de KOOKING-studie, maar het door de huisarts vastgestelde niveau van uitdroging verschilde niet. Hieruit kunnen we concluderen dat de toestemminsprocedure en het off-protocol gebruik van studiemedicatie de inclusie beïnvloedden, maar weinig invloed op de selectie hadden. Het gebruik van een parallel cohortonderzoek kan helpen bij het evalueren van de selectiebias, terwijl een pilotonderzoek potentiële barrières voor inclusie kan onthullen.

In **hoofdstuk 7** presenteren we de uitkomsten van de effectiviteit van de KOOKING-studie. Kinderen werden willekeurig toegewezen aan ofwel de controlegroep die de standaardzorg kreeg, bestaande uit ORS, of de interventiegroep die dezelfde zorg kreeg met één dosis ondansetron siroop (0.1 mg/kg). Van de 1,061 gescreende kinderen werden er 194 geïncludeerd voor randomisatie. Eén dosis ondansetron verminderde significant de proportie kinderen dat tijdens de daaropvolgende vier uur bleef braken van 42.9% naar 19.5% (OR 0.37; 95%-CI 0.20 - 0.72; NNT 4). Ondansetron verminderde ook het *aantal* braakepisodes binnen vier uur (IRR 0.51; 95%-CI 0.29 - 0.88) en verbeterde de tevredenheid van ouders over de behandeling ($P = 0.027$). Het gebruik van ondansetron leidde niet tot verhoogde ORS-inname, minder verwijzingen of ziekenhuisopnames. Concluderend kunnen kinderen met buikgriep met een verhoogd risico op uitdroging door braken veilig en effectief worden behandeld met ondansetron in de huisartsenpraktijk om het braken sneller te stoppen en de tevredenheid van ouders over de behandeling te verhogen.

In **hoofdstuk 8** hebben we de kosteneffectiviteit van de KOOKING-studie beoordeeld. De totale gemiddelde kosten voor kinderen die ondansetron kregen waren 31.2% lager (€488 versus €709). De grootste kostendrijvers, werkverzuim van ouders en ziekenhuisopnames, waren ook beide lager voor de kinderen die ondansetron kregen (werkverzuim ouders €272 versus €446; ziekenhuisopnames €134 versus €162). Voor een extra kind vrij van braken in de eerste vier uur kon €9 bespaard worden. Het kosteneffectiviteitsvlak toonde aan dat 94.0% van de bootstrap replicaties in het kwadrant rechtsonder vielen, wat duidt op lagere kosten en meer effectiviteit bij gebruik van ondansetron. De kosteneffectiviteitsacceptatiecurve liet een kans van bijna 95% zien dat ondansetron kosteneffectief was zonder extra geld te investeren. Daarom kunnen we concluderen dat het geven van één dosis ondansetron siroop aan kinderen met buikgriep en een verhoogd risico op uitdroging als gevolg van braken in de huisartsenpraktijk niet alleen klinisch effectief is, maar ook kosteneffectief.

Tot slot hebben we in **hoofdstuk 9** een internationaal expertonderzoek uitgevoerd waarin de publieke gezondheidszorg en de klinische zorg voor kinderen met buikgriep in Nederland en Australië met elkaar werden vergeleken. Beide landen zijn top presenterend in de gezondheidszorg, met een hoog inkomen, waarbij huisartsen een belangrijke rol in de gehele gezondheidszorg spelen. Er bestaan echter verschillen in de organisaties van deze gezondheidssystemen. We vonden dat in Australië rotavirusvaccinatie in het nationale immunisatieprogramma zit, met vaccinatiewetgevingen en wetgevingen voor preventie. In Nederland is vanaf 1 januari 2024 rotavirusvaccinatie opgenomen in het nationale immunisatieprogramma maar er ontbreekt een uitgebreide vaccinatiewetgeving. Ook verschilt de toegang tot zorg: Nederlandse kinderen moeten eerst hun huisarts raadplegen voordat ze naar het ziekenhuis gaan, terwijl Australische kinderen direct naar het ziekenhuis kunnen gaan. Financieringsmechanismen verschillen ook: Nederland biedt een volledig gefinancierde gezondheidszorg voor kinderen, terwijl het in Australië afhankelijk is van de huisarts en het bezochte ziekenhuis. Bovendien is de door richtlijnen aanbevolen dosering van ondansetron lager in Nederland. Het Australische publieke gezondheidssysteem, gekenmerkt door wetgeving voor vaccinatie en quarantaine, en het Nederlandse klinische zorgsysteem, met volledig gefinancierde zorg, continuïteit en lagere doseringen van ondansetron, bieden mogelijkheden voor het verbeteren van de gezondheidszorg voor kinderen met buikgriep in beide landen. Bovenkant formulier

Conclusie en aanbevelingen

Het optimaliseren van de behandeling van kinderen met buikgriep is een complex proces waarbij zowel ouders als zorgprofessionals betrokken zijn. Het gebruik van ondansetron in de huisartsenpraktijk blijkt een effectieve en kosteneffectieve optie te zijn als aanvullende behandeling voor kinderen met buikgriep met een verhoogd risico op uitdroging door veelvuldig braken. Echter, om het gebruik van ORS te verhogen en daarmee de verwijzingen en ziekenhuisopnames te beïnvloeden, moeten er meerdere barrières doorbroken worden. Ouders zouden meer baat hebben bij meer kennis en toegang tot informatiebronnen om hun begrip van de ziekte te vergroten en geruststelling te krijgen. Zorgprofessionals zouden open communicatie met ouders moeten aangaan en meer kennis moeten hebben van richtlijnen, inclusief het gebruik van ORS en ondansetron. Het toedienen van ORS tijdens het bezoek aan de huisarts, in plaats van het alleen voor te schrijven, zou het gebruik van ORS kunnen verbeteren. Verder onderzoek is nodig om informatiebronnen voor ouders te evalueren, de impact van rotavirusvaccinatie in Nederland te onderzoeken, en de structurele implementatie van juist gebruik van ondansetron in de huisartsenpraktijk te bevorderen en beoordelen.

Dankwoord

Curriculum Vitae

List of publications

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CURRICULUM VITAE

Anouk Weghorst was born on August 7th 1997 in Oldenzaal, the Netherlands. After completing secondary school (VWO) at the Twents Carmel College de Thij in 2015, she started her Bachelor of Medicine at the University of Groningen. During her Bachelor she worked as a research assistant for the KOOKING study which is part of this thesis. After finishing her Bachelor in 2018 she started her Master of Medicine with her research internship. During this research internship she applied and got accepted for the MD/PhD trajectory at the University of Groningen. With this trajectory she combined the Master program of Medicine with an additional two years of scientific research.

From 2019 till 2023 she performed this MD/PhD trajectory at the Department of General Practice at the University Medical Centre Groningen resulting in this thesis. She investigated the management of children with acute gastroenteritis at home and in primary care under supervision of Prof. dr. Marjolein Berger, dr. Gea Holtman, and dr. Irma Bonvanie. In February 2022 she graduated her Master of Medicine. Hereafter, she had a fellowship at the University of Melbourne and Murdoch Children's Research Institute in Melbourne, Australia, funded by a grant from the Ter Meulen Grant of the Royal Netherlands Academy of Arts and Sciences.

Anouk presented her work at various national and international conferences, was invited to talk in several podcasts and interviews about her research. During her research she obtained the SHARE PhD top publication award three times for the articles on the cost-effectiveness, effectiveness and qualitative research presented in this thesis. After finishing her MD/PhD trajectory in 2024, Anouk started to work as a medical doctor at the general surgery of the Medisch Spectrum Twente, Enschede.

LIST OF PUBLICATIONS

PUBLICATIONS IN PEER REVIEWED JOURNALS

International

1. **Weghorst AAH**, van den Brink MJ, Bonvanie IJ, Tuinstra J, Holtman GA, Landeweer EGM, Berger MY. Acute gastroenteritis: a qualitative study of parental motivations, expectations, and experiences during out-of-hours primary care. *Annals of Family Medicine*. 2023;21(5):432-439.
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1. **Weghorst AAH**, Sanci LA, Berger MY, Hiscock H, Jansen DEMC. Comparing healthcare systems between the Netherlands and Australia in management for children with acute gastroenteritis. *Submitted.*
2. **Weghorst AAH**, Lawrence J, Jansen DEMC, Holtman GA, Sanci LA, Berger MY, Hiscock H. Facilitators and barriers to home management for children with acute gastroenteritis: systematic review. *Submitted.*

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