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

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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 care 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 (≥24 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.
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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 Netherlands’ 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. 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%). 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. This trend is particularly pronounced among children under five years, who utilize
out-of-hours primary care the most.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{7} A three-minute whiteboard animation video was recently created for parents of children with AGE. However, results have not been published yet.\textsuperscript{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.

\textit{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.\textsuperscript{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.\textsuperscript{1} In contrast, healthcare professionals with knowledge of ORT effectiveness were more likely to ingrate ORT into their practices.\textsuperscript{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. 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. 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.

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. 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. 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. 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. 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. RCTs conducted in emergency departments showed that children who received ondansetron had higher ORT intake and improved tolerance. 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. Moreover, parents who observed the successful acceptance of ORT during the visit were more likely to continue ORT treatment at home. 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. 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. 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. 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. Moreover, introducing a placebo for a therapy that is already proven effective can raise ethical concerns. 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. 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. 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.
SUMMARY AND GENERAL DISCUSSION

Informed consent procedure
Early termination affects 40% of paediatric RCTs, with slow recruitment being the primary cause. 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. 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. 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. This means that participants can provide electronic consent for participation in WMO-obligated research. 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. 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. 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. 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. 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
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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.\textsuperscript{38} Despite rotavirus being associated with a more complicated clinical course and standing as the leading cause of referrals and hospitalizations,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{29,45} The introduction of a free rotavirus vaccine in Australia resulted in a 62\% reduction in hospital admission rates for children with AGE.\textsuperscript{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.\textsuperscript{47} In the Netherlands, rotavirus vaccination is scheduled for implementation in the national immunization program in 2024 without legislations mandating vaccination.\textsuperscript{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.\textsuperscript{49} Continuity of care is a vital element in fostering a strong GP-patient relationship and facilitating effective communication.\textsuperscript{50} Moreover, increased continuity in primary care is associated with lower hospitalization rates.\textsuperscript{51} Access to care is also important, with gatekeeping practices being linked to reduced healthcare utilizations and lower likelihood of hospitalizations.\textsuperscript{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.\textsuperscript{53} In Australia, despite 80\% of the patients reported having a regular GP,\textsuperscript{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.
REFERENCES


23. Geneesmiddel _ Ondansetron _ Kinderformulair [Internet]. Available from: https://www.kinderformulair.nl/geneesmiddel/30/ondansetron


SUMMARY AND GENERAL DISCUSSION


