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Acute Gastroenteritis Disease Burden in Infants With Medical Risk Conditions in the Netherlands

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Background: Infants with medical risk conditions are vulnerable to childhood infections including acute gastroenteritis (AGE). To guide prevention programs, we quantified AGE incidence, severity and virus prevalence among medical risk infants in the Netherlands.

Methods: This prospective cohort-study was part of the RIVAR-project recruiting infants with prematurity, low birth weight or severe congenital conditions in 13 hospitals. Follow-up included 18 monthly health questionnaires detailing AGE symptoms and healthcare usage. Parents were also instructed to notify when an infant developed AGE, to collect a stool sample and complete a daily severity score (Modified Vesikari Severity). Stool samples were analyzed by real-time polymerase chain reaction for rotavirus, norovirus, adenovirus and astrovirus.

Results: Between November 2014 and October 2017, 631 infants participated during 9125 person-months of observation. In total, 559 episodes were identified. The mean AGE incidence rate was 73.5 per 100 person-years (PY) (95% confidence interval: 67.6–79.9) and increased with age [incidence rate: 48.3 (39.8–58.3) vs. 80.2 (73.0–88.1)/100 PY for ages 1–5 vs. 6–18 months, respectively]. Healthcare was attended for 38.1% (213/559) and 26.8% (68/254) were classified as severe based on the Modified Vesikari Severity. Stool samples were obtained from 254 AGE episodes. Norovirus was identified in 65 (25.6%) and rotavirus in 44 (17.7%). Adenovirus and astrovirus together accounted for 8.3% (N = 21). Severe AGE occurred most frequently in rotavirus positive episodes.

Conclusion: The observed AGE incidence, severity and healthcare usage among medical risk infants confirms substantial disease burden. Norovirus and rotavirus are the dominant pathogens and severe episodes occurred most frequently in children with rotavirus infection. AGE prevention in medical risk infants should be prioritized.

Key Words: gastroenteritis, burden of disease, rotavirus, medical risk infants

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Acute gastroenteritis (AGE) is a common infection with the highest incidence in young children.[1,2] The large majority of childhood AGE episodes are caused by enteric viruses, with rotavirus and norovirus being the dominant pathogens.[1,3] Premature birth (<36 weeks of gestation), low birthweight (<2500 g) and/or the presence of a congenital disorder are known risk factors for severe and complicated AGE, which is reflected in increased hospitalization rates, prolonged hospital stay and mortality compared with healthy infants.[4–8]

As AGE is mainly a self-limiting disease, the majority of episodes occur outside of the hospital setting.[9] To quantify the disease burden in the community, several observational studies in Europe have evaluated AGE incidence and healthcare attendance among healthy children, adults or elderly and estimated the contribution of various enteric pathogens.[10,11] There is a reason to assume that the community AGE burden is increased among infants with medical risk conditions, similar to what is observed for AGE hospitalizations. However, no studies have specifically addressed community AGE among medical risk infants. Such data on specific risk-groups are valuable to prioritize target-groups for preventive interventions and assess the cost-effectiveness of various vaccination strategies against rotavirus and, possibly in the future, norovirus.[12,13]

Our aim is to quantify the all-cause AGE and virus-specific community burden of disease in medical risk infants in the Netherlands, and to identify infants most at risk of severe disease.

MATERIALS AND METHODS

Study Design

The Netherlands has not yet implemented rotavirus vaccination in the infant national immunization program. Uptake of rotavirus vaccine in the private market is less than 1%.[14]

This prospective cohort study is part of the *R*isk group *I*nfant *V*accination *A*gainst *R*otavirus (RIVAR) project. In brief, RIVAR pilots the implementation of a selective rotavirus vaccination program for medical risk infants organized in secondary pediatric care. Thirteen Dutch hospitals that host a Neonatal Intensive Care Unit or a neonatal post High/Intensive Care ward participated in the pilot and implemented rotavirus vaccination between May 2016 and October 2017. Implementation was combined with a before-after cohort study. All cohort participants were followed for the occurrence of AGE from enrollment between 6 and 14 weeks until 18 months of age. The current study uses data from the

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J.A.P.D. designed the study, collected data, carried out the initial analysis and drafted the initial manuscript. E.R. assisted in data collection and study setup and reviewed the manuscript. R.S. was responsible for all laboratory analyses and reviewed the manuscript. M.B. assisted in conceptualizing the study, reviewed and revised the manuscript. P.B.-V. conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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pre-implementation cohort only, recruitment ran from November 2014 to October 2017, when rotavirus vaccination was not yet routinely available in the hospitals.

Eligibility

All infants hospitalized in a participating hospital and less than 14 weeks of age were screened for eligibility, which includes infants with one of the following diagnoses (ie, medical risk conditions): preterm birth [gestational age < 36 weeks; low birthweight < 2500 g; the presence of a severe congenital disorder (see Figure, Supplemental Digital Content 1, http://links.lww.com/INF/E227 and Supplemental Digital Content 2, http://links.lww.com/INF/E228) receiving care in a participating hospital between 6 and 14 weeks of postnatal age. Parents of eligible infants were approached for participation in the cohort study, and asked for informed consent (see Figure, Supplemental Digital Content 2, http://links.lww.com/INF/E228).

Data Collection

For all eligible children, irrespective of cohort participation, we collected the following data: date of birth, gender, gestational age, birthweight, presence of congenital disorder and any contraindications for rotavirus vaccination.[15] This allowed us to evaluate differences between participants and nonparticipants. Medical risk conditions were classified into premature, small for gestational age (based on the 10th percentile cutoff for Dutch boys and girls[16,17]) and congenital disorder. Low, intermediate and high socioeconomic status were based on the highest family educational level.[18] Ethnicity was defined by parental background and divided into 3 categories, European, non-European and mixed.[19] Single parent households are combined in either of the first 2 categories.

A baseline parental questionnaire detailed socio-economic status, ethnicity, household composition, pregnancy and labor, and was filled upon enrollment. Thereafter, parents received a monthly questionnaire until the end of follow up, at 18 months of age (see Figure, Supplemental Digital Content 2, http://links.lww.com/INF/E228). The monthly questionnaire contained the following items: occurrence of gastrointestinal and respiratory symptoms during the previous month, any doctor's visit or hospitalization, administration of vaccinations and occurrence of adverse events, type of feeding and daycare attendance.

For all cohort participants, medical charts were reviewed for additional data on hospitalizations, diagnoses, medication and other supportive therapy at 6 weeks, 5 months and 18 months of age.

Follow-up for AGE

AGE was defined as acute watery or looser than normal stools, more than 3 times within in a 24-hour period, and/or acute forceful vomiting.[20] At enrollment, parents received verbal instructions concerning these AGE criteria, and on a plasticized instruction card. Parents of participants were instructed to instantly report if their child developed symptoms of AGE during the follow-up period. For each AGE episode, parents kept a standardized symptom 7-day diary, based on the Modified Vesikari Severity (MVS) scale[21,22] (see Table, Supplemental Digital Content 3, http://links.lww.com/INF/E229). Parents were requested to collect a fecal sample, as soon as possible after AGE onset. Fecal samples were packed in biosafety envelopes and send by regular mail to the central laboratory for PCR testing (see Methods, Supplemental Digital Content 4, http://links.lww.com/INF/E230). On day 14 after AGE onset, an additional questionnaire was filled by parents detailing healthcare usage, medication, total days with symptoms, lost parental work-days and daycare absenteeism. All monthly questionnaires and medical records were additionally checked for AGE symptoms that had not been reported to the study team. And identified as AGE episode if they met the AGE definition and no other cause for symptoms was provided. In this way, we were able to retrieve additional AGE episodes that had not been actively reported by parents. However, these episodes were incomplete on pathogen and MVS severity information.

Outcomes

The primary aim was to quantify the AGE burden of disease in rotavirus unvaccinated medical risk infants until 18 months of age. This was based on (1) the incidence rate (IR) of all-cause and virus specific AGE; (2) the AGE-related healthcare usage; and (3) the severity of AGE episodes, scored by the MVS scale (see more details on outcome measures, Methods, Supplemental Digital Content 4, http://links.lww.com/INF/E230).

A secondary aim of our study was the societal burden, expressed as daycare absenteeism and parental work loss as well as secondary cases that occurred within the household. For these analyses, we used data from the 14-day AGE questionnaire.

To evaluate possible risk factors for severe AGE occurrence, we compared patient and household characteristics between infants with at least one AGE episode to those without any AGE during follow-up.

Statistical Analysis

Descriptive statistics were performed using χ^2 or Fisher exact test for categorical data, t-tests for normally distributed continuous data and nonparametric test (Mann–Whitney U) for non-normally distributed continuous data. A P value <0.05 was considered statistically significant.

The AGE IRs were calculated by dividing all AGE episodes by the total person time of observation and corresponding 95% confidence intervals (95% CI) were computed using the Fisher exact method. For virus-specific IRs, estimates were adjusted for the proportion of AGE episodes for which no fecal sample was obtained. We used multiple imputation, by chained equations, for missing virus status of episodes without a stool sample collected (see Methods, Supplemental Digital Content 4, http://links.lww.com/INF/E230).

To further explore potential risk factors for severe AGE, we modeled the association between time to first severe AGE with baseline factors and AGE occurrence in seasonal months of known highest circulation of norovirus and rotavirus in the Netherlands (October–April).[23] We used a Cox regression model with age as time axis. All potential covariates were tested univariate; those with a significant effect were used for the multivariate model. Model selection was based on the likelihood ratio test. Proportional hazard assumption was checked using the Schoenfelds' residuals. We applied multiple imputation to account for missings, as described in Supplemental Digital Content 4, http://links.lww.com/INF/E230 (Methods).

As statistical software we used: SPSS IBM version 25, http://openepi.com and RStudio version 1.1.456.

Ethical Approval

This study was reviewed by the Institutional Review Board of the University Medical Center Utrecht, which has declared it does not involve the Medical Research Involving Human Subjects Act.

RESULTS

Between November 2014 and October 2017, 2500 medical risk infants met the RIVAR inclusion criteria across 13 participating hospitals (Fig. 1). Mean gestational age was 33 weeks (SD ± 4 weeks), 475 (19%) had a congenital disorder (cardiovascular 129, pulmonal 21, central nerve system 49, chromosomal 90, perinatal 70 and 199 other disorders) and 684 infants (27%) were small for gestational age.

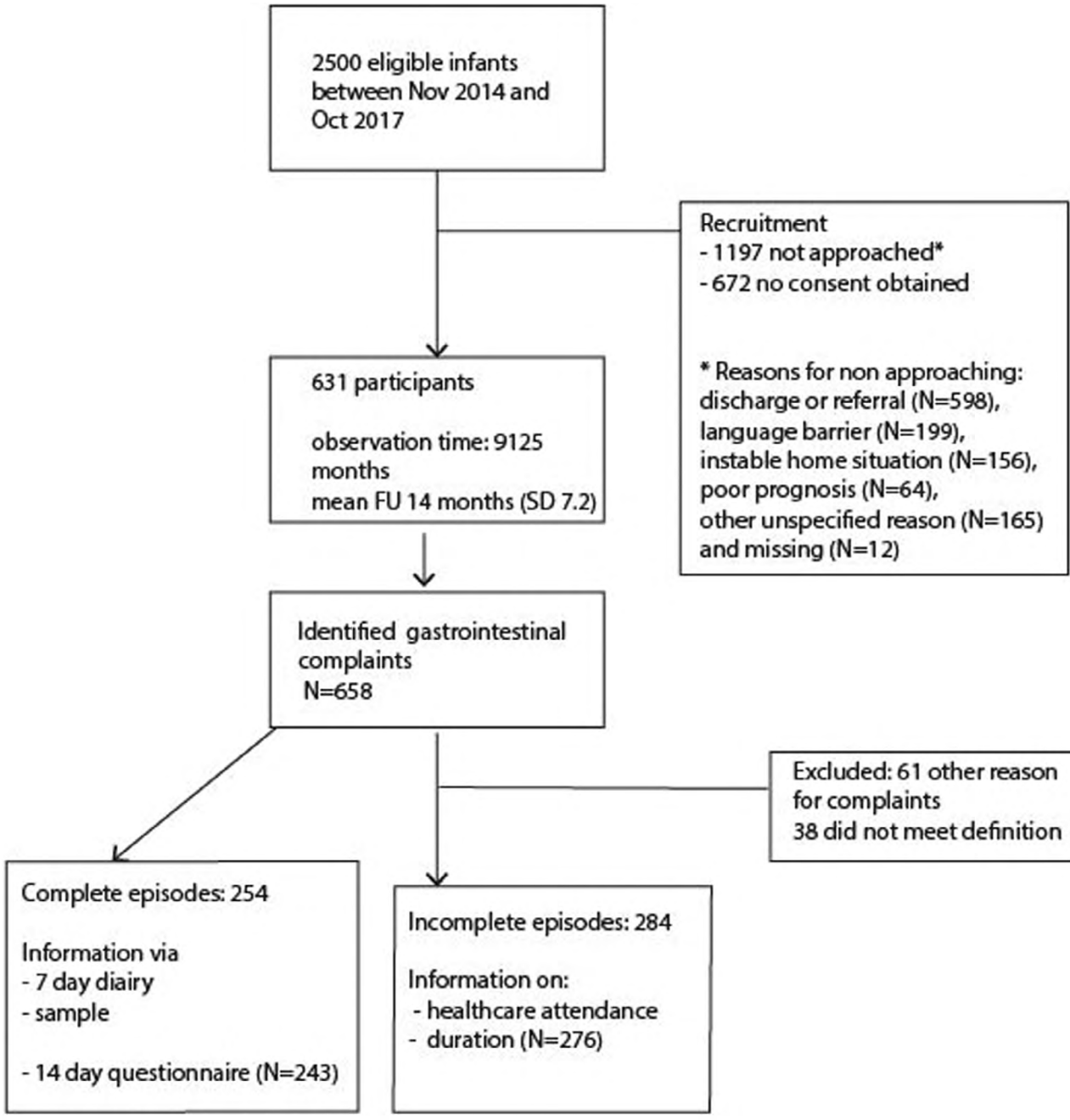

FIGURE 1. Study flowchart of eligible and participating infants.

Descriptive Statistics

In total, 631 parents of medical risk infants consented to participate. Baseline characteristics of participants and non-participants were comparable (see Table, Supplemental Digital Content 5, http://links.lww.com/INF/E231). Follow-up until 18 months of age was complete for 421 (67%) infants. Reasons for incomplete follow-up were dropped out (n = 50), deceased (n = 3) or loss to follow-up (n = 157) before 18 months of age. During participant follow-up, 559 AGE episodes occurred. In total, 275 episodes were reported by parents, and complete information was available for 254 of those, and an additional 284 AGE episodes were retrieved from monthly questionnaires and medical records (Fig. 1).

Pathogen Distribution

Of 254 AGE episodes, a fecal sample was collected within 14 days of symptom onset. Of these, 65 (25.6%) tested positive for norovirus and 44 (17.7%) for rotavirus. Coinfections for norovirus and rotavirus were present in 4 AGE episodes, 21 samples were adenovirus and/or astrovirus positive (8.3%). AGE episodes with a stool sample collected had a longer duration but less frequent healthcare attendance compared with those without a stool sample

(see Table, Supplemental Digital Content 6, http://links.lww.com/INF/E232).

AGE Disease Burden

The IR for all-cause AGE up to 18 months of age was 73.5 per 100 person-years (PY), IR increased with older age from 48.3 per 100 PY <6 months of age to 80.2 per 100 PY for infants 6–18 months of age (Table 1). No differences were observed in IRs between subgroups of medical risk infants. The AGE IR demonstrated a clear seasonal pattern with highest rates in months January to April and October to December (see Figure, Supplemental Digital Content 7, http://links.lww.com/INF/E233). Comparing the seasonal months to out-of-season months, the mean incidence was higher during seasonal months. After multiple imputation, the estimated IR for norovirus and rotavirus positive episodes was not significantly different.

Healthcare was attended for 213 of 559 of AGE episodes (38.1%, 95% CI 34%–43%), 42 infants were admitted to the hospital for their AGE episode (7.5%). The proportion of episodes requiring healthcare was twice as high for rotavirus and norovirus positive episodes compared with pan negative episodes, *P* value 0.00 (see Table 2). Nosocomial infections (based on acquiring infection during hospital stay) occurred in 6 patients.

Of 254 AGE episodes with an MVS-score available, 68 were classified as severe (26.8%, 95% CI 22%–33%). Rotavirus and norovirus positive infections were severe in 18 of 43 (41.9%) and 17 of 65 (26.2%) of cases, respectively. Differences for infections per pathogen are listed in Table 2; this information was only available for complete episodes.

Secondary Outcomes

Any paid parental work loss due to illness of the infant was reported in 73 of 244 AGE episodes, with a median duration of 1.75 days [interquartile range (IQR) 0.75–2.75]. Daycare absenteeism was reported for 67 of 236 AGE episodes, with a median of 1.5 days (IQR 0.5–2.5). In 32.8%–49.2% of AGE episodes, families were unable to proceed with regular activities, like grocery shopping, cleaning or leisure activities (Table 2).

Risk Factors for (Severe) AGE

Three hundred twelve participants (49%) had at least 1 AGE episode during follow-up and multiple episodes (varying from 2 to 7) were reported in 88 infants (14%), and differences in their characteristics are shown in Supplemental Digital Content 8, http://links.lww.com/INF/E234 (Table). The most important differences between the groups were more frequent daycare attendance and higher family education among infants with at least 1 AGE episode. Infants with severe AGE did not differ from those with nonsevere AGE.

Mean age for the first severe AGE episode was 8.3 months (95% CI 7.2–9.5) and 14.2 months (95% CI 13.5–14.8) for nonsevere AGE. The multivariate Cox regression analysis resulted in a final model with only seasonal months and daycare attendance statistically significantly associated with severity (Table 3).

Because of potential nonrandom missing information of risk factors, we compared complete cases versus those with at least 1 missing covariate, and found that complete cases were more frequently older at AGE episode or when censored. They less often had an older sibling in their household, attended daycare from six months onwards and had an episode in season (see Table, Supplemental Digital Content 9, http://links.lww.com/INF/E235). The estimates after multiple imputation account for the missing not at random.

TABLE 1. Community AGE Incidence for Medical Risk Infants

AGE	Subgroup	IR (per 100 PY)	95% CI	*P*
All cause		73.5	67.6–79.9	—
Age	<6 months	48.3	39.8–58.3	—
	6–12 months	85.7	75.3–97.1	0.00
	>12 months	79.3	68.4–90.1	0.43
Medical risk type	Preterm (GA < 36 weeks)	75.9	68.0–84.6	—
	Preterm and SGA	64.0	52.4–77.2	0.13
	Presence of congenital disorder	66.9	51.5–86.8	0.44
Season	January–October	94.5	85.6–104.1	—
	May–September	45.0	38.0–53.0	0.00
Pathogen*	Rotavirus	14.6	12.1–17.1	—
	Norovirus	14.2	11.7–16.7	0.89
	Pan negative	31.7	28.6–34.8	0.00

*Estimated with correction for pathogen under detection based on multiple imputation for missing AGE samples.

GA indicates gestational age; SGA, small for gestational age.

DISCUSSION

In this prospective cohort study, we quantified the AGE disease burden among infants with medical risk conditions on several items; incidence, severity, healthcare attendance and family impact. For community AGE we found an IR of 73.5 per 100 PY, translating to at least 1 AGE episode in the first 18 months of life in medical risk infants. One in 3 AGE episodes required a doctor visit and 1 in 13 required hospitalization. One-third of episodes were classified as severe. In addition to the AGE disease burden incurred by the infant, we observed substantial societal burden. In 30% parents and ill infants were absent from paid work or daycare, respectively, in 40% families could not fulfill their normal activities. Rotavirus and norovirus accounted for one-third of all AGE episodes and rotavirus positive AGE was associated with more severe disease. In line with this, AGE episodes occurring during seasonally active months for rotavirus and norovirus were associated with more severe disease.

We hypothesized that the burden of disease of AGE in medical risk infants is higher compared with healthy infants, because it is suggested that severe childhood infections are more prevalent[24,25] and harm these infants more.[26] However, the overall AGE IR found in our study is in line with reported IRs for healthy infant populations in the Netherlands. De Wit and colleagues found an IR of 74 per 100 PY in a population based setting for 0–1 year olds, and of 90 per 100 PY for 1–4 year olds.[27] Another Dutch community study (RotaFam) even found a 3 times higher all-cause AGE IR (301/100 PY in children up to 2 years of age),[28] but this study was conducted during the high epidemic months only (January–May). In our study, the incidence of AGE was also twice higher during the seasonal months compared with the off-season months. Furthermore, the RotaFam study used an interactive mobile application to monitor real-time AGE symptoms, which may have yielded higher case-ascertainment than in our study which relied on active reporting by parents and recording on monthly questionnaires. These IR comparisons suggest that medical risk infants do not have higher IRs compared with healthy infants.

Compared with studies among healthy infants, we found that AGE healthcare attendance and severity appear to be increased among medical risk infants. In our study, 51% of infants required healthcare related to AGE, whereas this proportion was only 18% in a Dutch community study among 1523 healthy infants.[10] Moreover, 7.5% of AGE episodes among medical risk infants required hospitalization in our study, compared with 3.4% and 1.6%, respectively, in British and Dutch studies among healthy infants with AGE.[10,29] Similarly, our findings suggest increased severity and prolonged duration of symptoms among medical risk infants with 27% of episodes classifying

TABLE 2. Severity and Social Impact per Pathogen

AGE Episodes	Severe	MVS	Duration	Healthcare Attended	Hospitalization	Parental Work Loss	Daycare Absenteeism	Transmission Within Household	Secondary Household Member(s)
All cause	68 (27%)	8 (3–13)	5 (1–9)	213 (38%)	42 (7.5%)	73 (30%)	67 (28%)	107 (44%)	2 (1–3)
Pan negative	26 (22%)	8 (4–12)	5 (2–8)	20 (18%)	4 (4%)	9 (7%)	15 (13%)	30 (26%)	2 (1–3)
Norovirus positive	17 (27%)	8 (3–13)	5 (2–8)	23 (40%)	4 (7%)	25 (40%)	19 (29%)	39 (67%)	2 (1–3)
Rotavirus positive	18 (43%)	10 (6–14)	5 (3–7)	17 (42%)	2 (10%)	17 (38%)	20 (44%)	27 (68%)	2 (1–3)
Adenovirus positive	8 (32%)	9 (3–15)	5 (0–10)	12 (48%)	1 (4%)	9 (36%)	10 (40%)	11 (44%)	1 (0–2)
Astrovirus positive	6 (40%)	10 (5–15)	7 (3–11)	4 (27%)	0	5 (33%)	6 (40%)	8 (53%)	1 (1–1)

Denominator changes for all variables and all groups of AGE episodes, because of missing data. Percentages are given for episodes with complete information. For continuous variables medians with IQRs are shown.

TABLE 3. Risk Factors Associated With Time to First Severe AGE Episode

Risk Factor	Univariate HR	Multivariate HR*	95% CI	Adjusted HR after MI*	95% CI
Seasonal months (October–April)	27.01	27.12	(10.60–69.39)	27.24	(12.96–57.26)
Sibling	0.77	0.42	(0.17–1.02)	0.76	(0.41–1.41)
Breast-fed	2.55	1.28	(0.46–3.56)	2.25	(1.18–4.30)
Born in seasonal months	0.92	0.62	(0.28–1.42)	0.82	(0.43–1.48)
Daycare	5.72	4.05	(1.35–12.17)	1.24	(0.43–3.55)

*Adjusted for seasonal months, siblings, breast-fed, born in seasonal months and daycare attendance.
HR indicates hazard ratio; MI, multiple imputation; RV, rotavirus.

as severe compared with 8% in healthy infants and a median symptom duration of 5 days vs. 3–4 days in healthy infants.[28,30,31] These findings are in contrast with the statement recently published by the European Academy of Pediatrics,[32] suggesting no accountable evidence on increased severity in specific risk groups. Based on our study, we conclude that the disease burden of AGE among medical risk infants is substantially increased relative to healthy infants.

In the absence of therapeutic interventions for AGE, prevention is the approach to decrease the burden of disease in this vulnerable patient population. In the Netherlands, a targeted rotavirus vaccination for medical risk infants only was suggested to be cost-effective in 2 previous studies.[5,14] However, due to changing epidemiology,[33,34] the effectiveness of a selected vaccine strategy might be modified. Most other European countries have implemented universal infant rotavirus vaccination, which has the added value of creating some herd immunity (indirect protection).[35,36] Our study results suggest that infants with medical risk conditions would certainly benefit from AGE prevention, which could be achieved by individual vaccination and by herd-immunity from universal rotavirus vaccination

As strengths, this study covers the full burden of disease by combining incidence rate, severity, healthcare attendance and family impact of AGE in infants with medical risk conditions. Furthermore, this vulnerable patient population is generally not studied. Therefore, this study provides unique information on community disease burden of AGE. By comparing participants and nonparticipants, it appeared that the study population is representable for the group of infants with medical risk conditions in the Netherlands.

This study has several limitations. First, data on pathogen and MVS scale were missing for about half of the AGE episodes, because parents failed to take a stool sample and complete the diaries. To reduce bias, we used multiple imputation in calculating pathogen-specific IRs and in the analysis on risk factors for severe AGE. While this method accounts nonrandom missing data and thereby adjusts for bias by complete case analysis, it also has limitations by assuming (too much) variance in outcome variables based on the imputation procedure.[37,38] However, with multiple imputation, the sample size is maintained and it yields unbiased standard errors.[37,38] With correct specified imputation procedures, estimates obtained will be less biased than by complete case analysis, which holds even with a high proportion of missing data.[39]

Furthermore, we checked for differential missingness and showed the results of complete case and imputed data analyses together. The high rate of missing data in community studies on AGE could be overcome by using modern interactive technologies to monitor participants.[28] In the RotaFam study, symptom data were in 97% complete and stool samples were obtained from 87% of AGE episodes, compared with 45% in our study.

Second, in our study 33% of participants were lost to follow up before 18 months of age. Possibly, because parents taking care of a child with special medical needs were overburdened and thereby limited in their capacity to adhere to study procedures, illustrated by the median days of hospitalization (35 days, range 3–439). Still, the mean follow-up was 14 months. In addition, the survival analysis is used to consider loss to follow up and observation time.[40]

In conclusion, the observed AGE incidence, severity and healthcare usage among medical risk infants confirms substantial disease burden with increased severity and healthcare usage compared with what has been observed in healthy infants. Norovirus and rotavirus are the dominant pathogens and rotavirus is most frequently severe. AGE prevention in medical risk infants should be prioritized.

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