Biennial Pattern of Rotavirus Gastroenteritis in The Netherlands and a Shifting Age Distribution Following a Low Rotavirus Season, 2010-2016

JANNEKE D.M. VERBERK*¹, MSC, ROAN PIJNACKER*¹,², MSC, PATRICIA BRUIJNING-VERHAGEN¹,³, MD, PhD, EELCO FRANZ¹, PhD, HARRY VENNEMA¹, PhD, MARIËTTE HOIVELD¹,⁴, PhD, SUSAN J.M. HAHNÉ¹, PhD, AND HESTER E. DE MELKER¹, PhD

1Centre for Infectious Disease Control, National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands
2European Programme for Intervention Epidemiology Training (EPIET), European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden
3Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht, the Netherlands
4NIVEL (Netherlands institute for health services research), Utrecht, the Netherlands

ABSTRACT
A hyper-endemic rotavirus season was expected after a low-endemic 2014 season in the Netherlands. Rotavirus detections were however similar in 2015 and lower in 2016 compared with 2010-2013. Gastroenteritis consultations rates were also similar in 2015, but the age-distribution shifted to older children due to an accumulation of non-infected children. Results indicate a possible shift to a biennial rotavirus pattern.

INTRODUCTION
An unexpected 58% decrease in rotavirus (RV) detections was observed in virological laboratory surveillance in the Netherlands during the 2014 RV epidemiological year (August 2013 to July 2014), while RV vaccination is not included in the National Immunization Programme. Similarly, gastroenteritis (GE) consultations of children younger than 5 years at general practitioners (GP) decreased by 36% in 2014 compared with previous years[1]. Moreover, the seasonal annual peak shifted from March to May. A concurrent decrease in RV incidence was reported in preschool children in day-care sampled at random and regardless of symptoms[2], providing evidence that the lower number of RV detections was caused by a genuine drop in RV circulation rather than altered pathogenicity of the
Material and Methods
We used anonymized weekly data of RV laboratory detections from August 2009-July 2016, reported by the Working Group for Clinical Virology: a sentinel network of laboratories serving primary and secondary care. Second, we used weekly all-cause gastroenteritis (GE) consultation rates in children younger than 5 years (International Classification of Primary Care - code D73) from 2010-2015. These data were collected by routine electronic health record extractions from GPs participating in NIVEL Primary Care Database (~7% national coverage). Weekly rates were calculated as the number of patients with one or more records for GE consultations, using the total number of patients enlisted in the practice as denominator (weekly prevalence rate). Weekly number of RV laboratory detections in the 2014, 2015- and 2016 RV epidemiologic years (August to July) were compared with those in 2010-2013. We calculated Incidence Rate Ratios (IRR) with corresponding 95% confidence intervals using negative binominal regression models.

The weekly GE consultation rate in those 5 years and younger in the 2014 and 2015 RV season were compared with the same time period in 2010-2013. Here, we defined a season as the period from January to June in order to minimize distortion by other GE-causing pathogens. We calculated IRRs using negative binomial regression models, with the weekly number of children younger than 5 years enlisted in GPs as offset variable. The same analyses were performed stratified by age (1, 2, 3- and 4-year-olds). Due to the incomplete registration of 0-year-olds during the study period, age-stratified analyses were not performed for this age group. Statistical analyses were performed with STATA (version 14.2), and statistical significance was set to p<0.05.

Results
Between August 2009 and June 2016, the mean annual number of RV laboratory detections during the RV epidemiologic years was 1,306 (range 551-2,227) and the mean annual number of GE consultations in children younger than 5 years was 4,182 during the RV seasons (range 2,991-5,017). Both show similar seasonal patterns with annual peaks in March and the beginning of April (Figure 1). Only in 2014 and 2016 (laboratory detections), the peak has shifted to May.

FIGURE 1
The weekly number of RV laboratory detections in the 2015 RV epidemiological year was similar (mean 27.0; IRR 0.86; 95%-CI 0.62-1.19) to those in 2010-2013 (mean 31.3; range 1-180). However, the weekly number of RV detections in 2014 and 2016 were significantly lower (mean 10.6; IRR 0.34; 95%-CI 0.25-0.47 and mean 12.7; IRR 0.41; 95%-CI 0.29-0.56, respectively) compared with 2010-2013. The weekly GE consultation rate in children younger than 5 years in the 2014 RV season was significantly lower (1.42/1,000 population; IRR 0.65; 95%CI 0.54-0.78) compared to 2010-2013 (range: 0.69 to 4.73/1,000 population, mean: 2.18/1,000 population). During the 2015 RV season, it did not differ from 2010-2013 (2.03/1,000 population; IRR 0.93; 95%CI 0.77-1.13). The GE consultation rate during the 2014 RV season was significantly lower in 1-, 2-, and 3-year-olds (IRR 0.59; 95%CI 0.49-0.72; IRR 0.67; 95%CI 0.55-0.82 and IRR 0.67; 95%CI 0.54-0.83, respectively) compared with 2010-2013. A non-significant decrease occurred in 4-year olds (IRR: 0.85; 95%CI 0.68-1.05). During the 2015 RV season, the GE consultation rate in 1- and 4-year-olds was similar to the rate in 2010-2013 (IRR: 0.9; 95%CI 0.72-1.11 and IRR: 1.07; 95%CI: 0.85-1.35, respectively). However, it was significantly higher in 2- and 3-year-olds (IRR 1.66; 95%CI 1.34-2.07 and IRR 1.52; 95%CI 1.21-1.90, respectively).

DISCUSSION
We observed in 2016 like in 2014 a significantly reduced RV activity, while the 2015 RV year was as usual. Observations were consistent between the two surveillance sources. Furthermore, the age-distribution of GE consultations during the 2015 RV season shifted after the low-endemic year 2014, affecting relatively more 2- and 3-year-olds.

The results in this study suggest a shift in the Netherlands from an annual to a biennial pattern. Preliminary observations of RV laboratory detections for 2017 show a continuing pattern. To our knowledge, a biennial RV pattern has not been observed before in a country without RV vaccination. A shift from annual to biennial seasons has been predicted after implementation of mass vaccination in mathematical transmission models[5] and has been reported in post-vaccination years in the United States and Belgium, countries with moderate to high vaccination coverage[6, 7]. The slower accumulation of unvaccinated susceptible children that is required to set off the seasonal epidemic, results in stronger RV seasons every other year, rather than every year. However, other vaccinating countries with high vaccination coverage have not reported a biennial pattern[8]. Belgium, England, Wales and Germany also observed a delay in the typical seasonal peak of RV in post-vaccination years as we observed in the low-endemic 2014 and 2016 RV years, while the start of the RV seasons were similar[6]. We speculate that the pattern observed in the Netherlands might be a herd effect from vaccinating surrounding countries (Belgium, West Germany and the UK) with high RV vaccination coverages. However, to our knowledge, this phenomenon has not been described before and the mechanisms that could explain this biennial pattern in the Netherlands have yet to be revealed.

In the Netherlands, G1P[8] was the most prevalent genotype until 2011. Since then, the contribution of G1P[8] has gradually decreased, while other strains such as G9P[8] and G4P[8]
have become more prevalent[3, 9]. Both in low-endemic years 2014 and 2016, G9P[8] was the dominant strain. Although some studies indicate that severity of disease is associated with rotavirus genotype, other studies were unable to confirm this[10, 11]. A day-care study in the Netherlands showed that symptomatic and asymptomatic RV infections were reduced in 2014[2], rendering reduced pathogenicity an unlikely explanation. Recent studies have provided new insights into human genetic susceptibility to various rotavirus strains. A sub-domain (VP8) of the human RV VP4 (P-genotype) surface protein interacts with components of the human to attach to intestinal cells[12]. Genetic polymorphisms in genes encoding histo-blood group antigens mediate host susceptibility to different RV P-genotypes and the expression differs between ethnic populations[13]. While the dominant P-genotypes circulating in the Netherlands have been relatively stable over the years, G-genotypes have differed to a much larger extent. Both in low-endemic years 2014 and 2016, G9P[8] was the dominant strain. Yet, variations in host-susceptibility to different G-genotypes has not been described so far, but forms an interesting hypothesis given the observed shift in G-strains and concurrent decline in RV disease in the Dutch population. In addition, we cannot confirm if the observed changes in dominant circulating genotypes are natural, or the result of vaccination in surrounding countries.

A plausible explanation for the significantly increased GE consultation rates in 2- and 3-years-olds in 2015 compared with 2010-2013 is that the preceding low-endemic 2014 RV season resulted in an accumulation of non-infected 2- and 3-year-old susceptible children in the 2015 season.

This study has some limitations. First, the laboratory data do not include information on the total number of RV tests performed. However, we believe that this has only minor impact, since there were no changes in diagnostic guidelines or reimbursements policies during the study period. Second, data on GE consultations in 2016 were not yet available, and due to incomplete registration we were unable to include 0-year-olds in age-stratified analyses. Third, distortion from other circulating enteric pathogens is possible, which was minimized by restricting our analyses of GE consultations to months of RV peak activity.

Whether the biennial pattern in the Netherlands could be driven by RV vaccination in neighboring countries, or the presence of other causes remains to be determined. A shift towards older children was observed in the year after a low-endemic RV season. Close monitoring of RV epidemiology is warranted to identify new or changing trends.

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Privacy
Dutch law allows the use of electronic health records for research purposes under certain conditions. According to this legislation, neither obtaining informed consent
from patients nor approval by a medical ethics committee is obligatory for this type of observational studies containing no directly identifiable data (Dutch Civil Law, Article 7:458)

This study has been approved by the applicable governance bodies of NIVEL Primary Care Database under nr NZR-00316.036.

REFERENCES
Figure 1. Weekly rotavirus laboratory detections and weekly all-cause gastroenteritis (GE) consultation rates in children younger than 5 years per 1,000 population, the Netherlands, August 2009 to July 2016.