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ORIGINAL PAPERS

Validity and reliability of the minimum basic data set in estimating nosocomial acute gastroenteritis caused by rotavirus

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ABSTRACT

Introduction: Rotavirus is the principal cause of nosocomial acute gastroenteritis (NAGE) under 5 years of age. The objective is to evaluate the validity and reliability of the minimum basic data set (MBDS) in estimating the NAGE caused by rotavirus (NAGER) and to analyze any changes during the three years that the Rotarix® and Rotateq® vaccines were used in Spain.

Material and methods: A descriptive, retrospective study was carried out in the University Hospital of Guadalajara (UHG) (Spain) between 2003-2009 using the MBDS, positive microbiological results for rotavirus (PMRs), and medical histories. Three methods of estimation were used: 1) An ICD-9-CM code 008.61 in the secondary diagnosis fields (DIAG2) of MBDS; 2) method 1 and/or PMRs with a current or recent hospitalization; and 3) the reference method or method 2 contrasted with patient medical histories. The validity of methods 1 and 2 was determined –sensitivity, specificity, predictive values and likelihood ratios (LRs)–, along with their agreement with method 3 (Kappa coefficient). In addition, the incidence rate ratio between the NAGER rate in 2007-2009 (commercialization period of both vaccines) was calculated with respect to 2003-2005 (pre-commercialization period).

Results: Method 1 identified 65 records with a DIAG2 of 008.61. Method 2 found 62 probable cases, and the reference method, 49 true cases. The sensitivity of the MBDS was 67 %, the positive predictive value was 51 %, and both negative LR (LR-) and reliability were moderate (LR- 0.33, Kappa coefficient 0.58). During 2007-2009, the NARGE decreased by 5 cases per 10^3 hospitalizations and by 9 per 10^4 days of hospitalization. Method 2 overestimated both the decline in incidence by 2 per 10^3 hospitalizations and the decreased risk per day of stay by 10 %. The MBDS found no differences between the two three-year periods, but, like method 2, showed an excellent level of diagnostic evidence (LR+ 67).

Conclusion: The MBDS taken together with microbiological results, is more exact, safer and more reliable than the MBDS alone in estimating NAGER; and more useful in ruling out it. Nevertheless, the MBDS alone may be used to estimate and compare such disease in contexts with different prevalences.

Key words: Rotavirus infections. Rotavirus vaccines. Gastroenteritis. Hospital infections. Medical registries. Spain.

ABBREVIATIONS

AGE: Acute gastroenteritis; NAGE: Nosocomial acute gastroenteritis; NAGER: Nosocomial acute gastroenteritis caused by rotavirus; MBDS: Minimum basic data set; DIAG2: Secondary diagnosis fields; DIAG1: Principal diagnosis fields; UHG: Hospital Universitario de Guadalajara (Spain); PMRs: positive microbiology results for rotavirus; 95 % CI: 95 % confidence interval; PPV: Positive predictive value; NPV: Negative predictive value; IR: Incidence rate; LR: Likelihood ratio; IRR: Incidence rate ratio; IQR: Interquartile range.

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INTRODUCTION

Nosocomial acute gastroenteritis (NAGE) caused by rotavirus (NAGER) occurs in 5 % in hospitalized children, leading to increased hospital stays and the use of extra hospital resources (1-3). Rotavirus is the main cause of NAGE in children under the age of 5 years (31-87 %) (4-7), with 70 % of cases occurring in children under 1 year of age (8). The seasonal pattern coincides with the winter peak of other pediatric viral infections (4), although this period is extended with respect to that of community-acquired rotavirus, starting in the autumn and finishing in the early spring (6).

NAGER becomes full blown after a 3-day incubation period (3). Twenty to forty percent of all cases are asymptomatic or subclinical (6), which, together with the great stability of rotavirus, contributes to contagion and the low efficacy of control measures (9). In Europe, nosocomial cases constitute 14-51 % of all rotavirus infections in children under 5, with an incidence of 0.1 to 2.8 per every 10^3 hospital admissions (newborns: 4-7.3 per 10^3). The additional costs for treating the infection can range from 367 to 1,837 euros per case (4-6,10-12). The differences in incidence between countries reflect the heterogeneity of studies conducted on this disease, making comparisons difficult (10,11,13,14). The same occurs between Spanish regions. Few studies have been carried out on NAGER in Spain (3,4,6,8). In Europe as a whole, the average incidence rate is around 4.6 per 10^4 days of hospitalization (range: 0.1-6.8 per 10^4), which lengthens the average hospital stay between 4 and 12 days (13). The attack rate of symptomatic rotavirus infection can reach up to 56 % in outbreak periods (14,15).

The Rotarix® and Rotateq® vaccines were first marketed in Spain in July, 2006, and February, 2007, respectively (4). At the time, they were not included in the Spanish vaccination schedule (16), nor were they added in 2013 (17) as they were not considered cost effective (18). However, given the morbidity of the disease and the increased burden on the healthcare system, vaccination is generally recommended (19). The new vaccines are considered safe, with a 5-10 times lower risk of intussusception (20) than that associated with Rotashield® in the past. With a universal vaccination program and assuming 90 % coverage, it is estimated that up to 58 % of NAGER cases in Spain could be avoided over a 5-year period (21).

The recording of rotavirus in hospital information systems has been described as highly deficient (5), partly due to the elevated incidence of asymptomatic cases of NAGER (22). Furthermore, the attack rate of the disease after discharge may be as high as 16 %, and if these cases are mild or asymptomatic, they generally remain unreported. Nevertheless, the minimum basic data set (MBDS) and other similar tools have been used to assess the incidence of NAGER (8,10). It is uncertain whether the secondary diagnoses fields (DIAG2) in the MBDS constitute a valid method for identifying the disease, as they give no information of the time between hospitalization and onset; moreover, some microbiological diagnostic results are administered after hospital discharge. In a similar vein, the MBDS contains cases categorized as the principal diagnosis field (DIAG1), which in reality correspond to infections acquired during a prior hospitalization. Likewise, the consistency of DIAG2 in always giving equivalent results (diagnostic agreement) has not been determined. Although the code system is well-established, variability still arises due to the different experience of those doing the actual coding and how the clinicians filled out medical histories at discharge.

The main objective of this study is to assess the validity and reliability of the DIAG2 of the MBDS in estimating NAGER. Also, to analyze any possible changes in incidence during the first three-year period that the new vaccines against rotavirus were commercially available in Spain.

MATERIAL AND METHODS

This is a descriptive, retrospective study carried out at the Hospital Universitario de Guadalajara (UHG, Spain) between 2003 and 2009. Three data sources were used:

1. *The MBDS of the UHG:* The mandatory registry for hospital discharges for any reason in the pediatric and neonatal wards.
2. *The computerized Modulab® registry of the Microbiology laboratory of the UHG:* Positive microbiology results for rotavirus (PMRs) found with a rapid and simultaneous detection immunochromatographic kit for rotavirus and adenovirus *(VIKIA Rota-Adeno®, bioMérieux)*. This method has a reproducibility of 100 %, a sensitivity of 92 % (95 % confidence interval (95 % CI) 84-99 %), and a specificity of 91 % (95% CI 78-100 %). Its positive predictive value (PPV) is 96 % (90-100 %) whereas its negative predictive value (NPV) is 83 % (67-98 %).
3. *Medical histories from the central archives of the UHG,* of the *probable and possible nosocomial cases* as defined below in methods 2 and 3, respectively.

This project was approved by the hospital's Ethics Committee for Clinical Research of Guadalajara (Spain).

Definition of the variable of interest and the estimation methods

NAGER was defined as "the development of symptoms 72 hours after hospital admission and up to 72 hours after discharge" (3). The estimation methods were defined according to the following data selection criteria:

1. *Method 1:* Registry entries with a code of The International Classification of Diseases, Ninth Revision,

Clinical Modification (ICD9-CM) 008.61 (rotavirus) in any of the DIAG2 of the MBDS, where the DIAG1 field was something other than 558.9 (unspecified AGE), 787.03 (vomiting), or 787.91 (diarrhea).

2. *Method 2:* Method 1 combined with PMRs coinciding with a current or recent hospitalization (within the last 3 days) according to the MBDS. The PMRs were joined with the MBDS, using the medical history numbers of patients as the crossover tool. We searched for codes of 008.61, 558.9, 787.03, 787.91, or 780.06 (fever) in the DIAG1 or the DIAG2 coinciding with a PMR.
   Probable nosocomial cases were defined as episodes (registry entries) in the MBDS with:
   – A DIAG1 other than 008.61 and a DIAG2 of 008.61 without PMR.
   – A DIAG1 other than 008.61 and a DIAG2 of 008.61, 558.9, 787.03, or 787.91 with PMR 72 hours after hospitalization or within the first 72 hours after discharge. Also, as an exception, newborns with PMR occurring ≤ 72 hours after hospitalization.
   – A DIAG1 of 008.61, 558.9, 787.03, or 787.91 and previous hospitalization with a DIAG1 other than 008.61 and a discharge within 72 hours preceding the second admission, besides a PMR from 72 hours after the first hospitalization or during the second.
3. *Method 3* (reference or "clinical method"): Method 2 contrasted with patient medical histories. To find *true nosocomial cases*, we reviewed not only the medical histories of those cases categorized by method 2 as *probable nosocomial cases,* but also those of the *possible nosocomial cases,* that is, registries with a DIAG1 of 008.61, 558.9, 787.3, or 787.91 and a prior hospitalization with a DIAG1 other than 008.61 without PMRs. A data collection sheet based on one used in a prior study on NAGER (6) was elaborated to this end.

Cases that were ruled out as being *true nosocomial cases* were categorized as *false nosocomial cases* or as community-acquired cases, both of which would be false positives according to method 2.

Statistical analysis

Frequency indicators were calculated for NAGER cases in the pediatric and neonatal wards, globally and by department, by age group, by year of study period, and by the two three-year periods (2003-2005 and 2007-2009), with their corresponding 95 % CI, with each method described. Prior to calculating incidence rates (IRs), lengths of hospital stays were previously estimated.

We then determined the sensitivity and specificity (internal validity) for methods 1 and 2, along with external validity: The PPVs and NPVs (performance or safety) and positive and negative LRs (LHR+ and LHR-) (plausibility). In addition, Chamberlain's percentage of positive agreement (% PA) was calculated (23). We lastly estimated the kappa index values to determine the *agreement* of methods 1 and 2 with regard to the clinical method, using the Altman scale (24) in interpreting the data thus obtained.

The seasonal pattern was described by means of the monthly distribution of the number of cases. To compare the prevalence of the disease among different pediatric age groups, three-year study periods, and estimation methods, the chi-square test was used. We compared the IR of NAGER in the three-year study period when Rotarix® and RotaTeq® were simultaneously available in Spain (2007-2009) with the previous three-year period (2003-2005), by calculating the incidence rate ratios (IRRs) with each method. The year 2006 was considered to be a transitional period, as only Rotarix® was then commercially available in Spain.

All analyses were carried out with SPSS 15.0 software and the Epi Info™ 7 application for Windows. A p value of 0.05 indicated statistical significance.

RESULTS

Between 2003 and 2009, a total of 9,602 children were hospitalized for any reason in the UHG, 21 % in the neonatal ward. A DIAG1 of 008.61 appeared for 381 of the children hospitalized, with another 65 admissions listing it as a DIAG2 (Fig. 1). According to method 1, seven of every 10^3 children hospitalized at the UHG in the 2003-2009 period had acquired NAGER, with a prevalence 6 ‰ higher in neonatal patients than in pediatric patients (Table I).

No registry entries coded as 780.06 appeared as a DIAG1 or DIAG2 concomitantly with PMR. Two of the 65 entries in the MBDS with a DIAG2 of 008.61, both for pediatric admissions, had no PMRs. We found 37 registry entries with a DIAG1 other than 008.61 with PMR 72 hours after hospitalization, 36 with a DIAG2 of 008.61, and 1 with a DIAG2 of 558.9, belonging to a pediatric patient (Fig. 1). Of the 36 patients with a DIAG2 of 008.61, 2 of the 23 entries coming from the pediatric ward corresponded to the same patient, but they were episodes from different years. In addition, we found 5 entries with a DIAG2 of 008.61 that corresponded to newborns with PMRs obtained ≤ 72 hours after hospitalization. Furthermore, there were 16 entries with a DIAG1 of 008.61 and 2 with a DIAG1 of 558.9, all with PMRs and a prior hospitalization for a DIAG1 other than rotavirus, who had been discharged in the previous 72 hours, all from the pediatric ward (Fig. 1). The final tally of *probable nosocomial cases* was 62, all of which were under 5 years of age and 18 of which were neonatal patients. According to method 2, seven of every 10^3 children hospitalized between 2003 and 2009 had acquired NAGER, with a prevalence a 3 ‰ higher in neonatal patients (Table I).

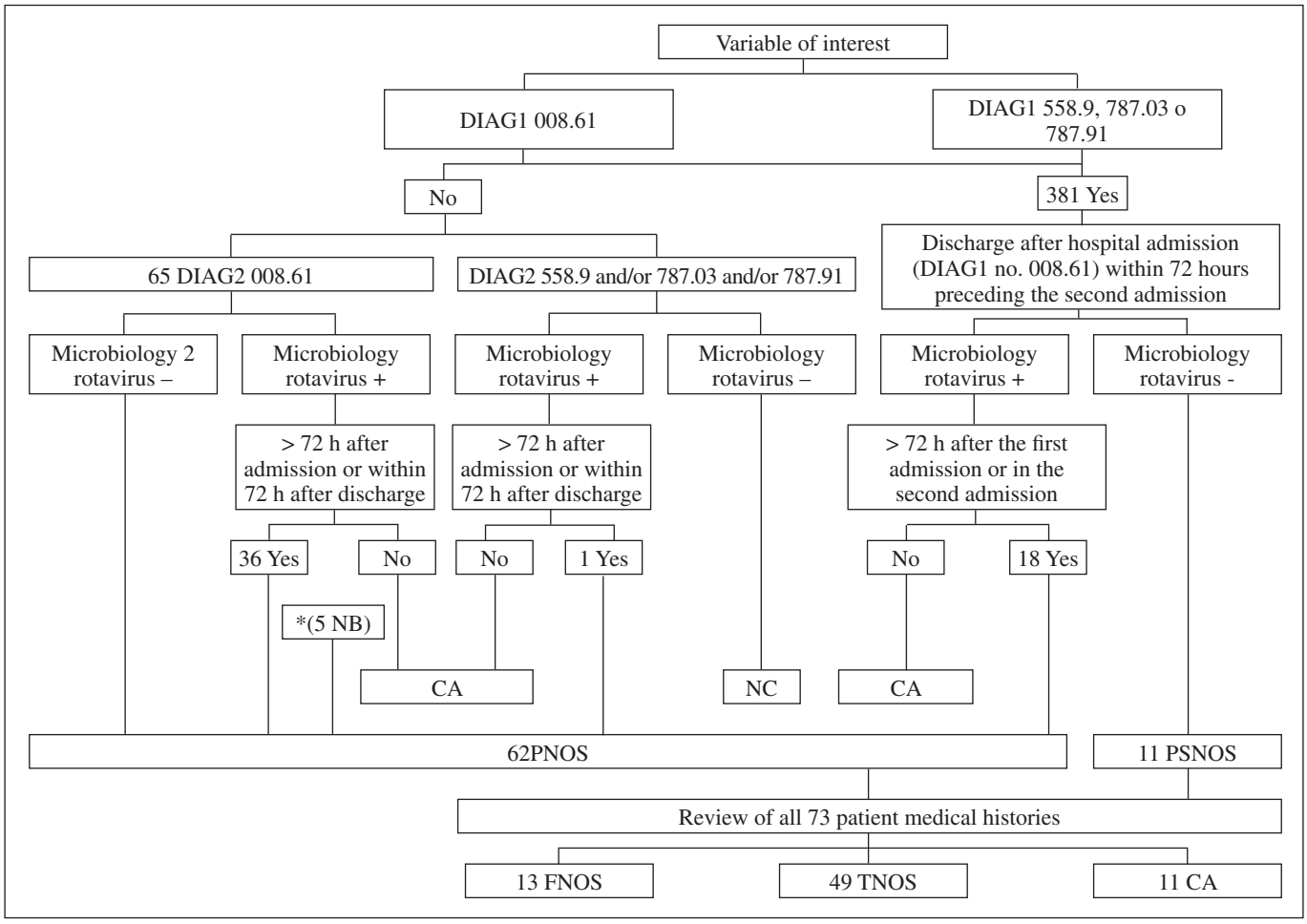


Fig. 1. Definition and number of NAGER cases in the Pediatric and Neonatal wards, applying the three estimation methods. UHG, 2003-2009 (NAGER: Nosocomial acute gastroenteritis due to rotavirus; UHG: Hospital Universitario de Guadalajara (Spain); DIAG1: Principal diagnosis field (cause of hospital admission); MBDS: Minimum basic data set; DIAG2: Secondary diagnosis fields. CIE9-MC CODES: 008.61 (rotavirus), 558.9 (unspecified AGE), 787.03 (vomiting), 787.91 (diarrhea); PNOS: Probable nosocomial cases; PSNOS: Possible nosocomial cases (less probable); CA: Community-acquired; NC: Not classificable (not applicable for rotavirus); TNOS: True nosocomial cases; FNOS: False nosocomial cases (coding errors or infectious AGE not caused by rotavirus). *Exception: Newborns (NB) with positive microbiology results occurring ≤ 72 hours after hospitalization were included).

Table I. Overall mean prevalence and incidence of NAGER, according to method used and by ward. UHG, 2003-2009*

		‰ (N.º of cases)[a]	*CI (per 10^3)[b]; IR*	*IRR (per 10^4)[c]; IR*
	Total	*6.7 (65)*	*6.90 (5.11-8.22)*	*17.08 (6.49-27.67)*
MBDS (DIAG2 008.61)	Pediatrics	5.5 (42)	5.28 (4.05-6.42)	18.95 (8.36-29.54)
	Neonatal	11.4 (23)	3.42 (0-20.00)	14.43 (3.84-25.02)
	Total	*6.5 (62)*	*4.14 (4.04-9.27)*	*11.47 (2.29-20.65)*
CMBD and micro	Pediatrics	5.8 (44)	4.36 (4.06-6.31)	19.85 (10.67-29.03)
	Neonatal	9.0 (18)	3.42 (0-18.10)	11.29 (2.11-20.47)
	Total	*5.1 (49)*	*4.14 (2.69-7.77)*	*11.07 (6.18-19.93)*
MBDS, micro, and MH (reference)	Pediatrics	4.1 (31)	3.49 (1.33-4.48)	13.98 (5.12-22.84)
	Neonatal	9.0 (18)	3.42 (0-18.10)	11.29 (2.43-20.15)

*NAGER: Nosocomial acute gastroenteritis due to rotavirus; CI: (Cumulative) incidence; IR: Interquartile range; MBDS: Minimum basic data set; DIAG2: Secondary diagnosis fields; micro: Microbiology lab data base; MH: Medical histories. [a]Number of hospitalizations 2003-2009: 9,602 (Pediatrics 7,591; Neonatal 2,011). [b]Overall mean accumulated incidence (cases per 10^3 hospitalizations/year). [c]Overall mean incidence rates (cases per 10^4 stays/year).

We identified 11 entries with a DIAG1 of 008.61, 558.9, 787.3, or 787.91 who had been discharged within 72 hours prior to being readmitted, but without PMRs; these were classified as *possible nosocomial cases* and were added to the 62 *probable nosocomial cases* (Fig. 1). In total, 73 medical records were reviewed. The 2 *probable nosocomial cases* with a DIAG2 of 008.61 and no PMR turned out to be coding errors and were reclassified as *false nosocomial cases.* Of the 37 entries in the MBDS with a DIAG1 other than 008.61 and PMRs 72 hours after hospitalization, 6 turned out to have been community-acquired and 31, including all the neonatal cases, were *true nosocomial cases.* The 5 newborns with PMRs obtained ≤ 72 hours after hospitalization were also *true nosocomial cases.*

Of the 18 hospitalizations for a DIAG1 of 008.61 or 558.9, with PMRs and a prior hospitalization for a DIAG1 other than rotavirus, and with a discharge in the previous 72 hours, 5 turned out to have been community-acquired (of those, the 2 categorized as 558.9) while 13 were *true nosocomial cases.* The 11 cases thought to be *possible nosocomial cases* all had medical histories that were incompatible with NAGER and were thus classified as *false nosocomial cases.* We were thus able to categorize 67.1 % (n = 49) of the medical histories reviewed as *true nosocomial cases* (Fig. 1). Of these, 36.7% (n = 18) occurred in neonates (Table I). Overall, 51 % of these *true nosocomial* cases occurred in male patients, 90 % (n = 44) occurred under the age of 2, a 35 % (n = 17) occurred in newborns; and 30 % (n = 15, all pediatric patients) had been discharged within the previous 72 hours. According to the reference method, 5 of every 10^3 children hospitalized in the 2003-2009 period had contracted NAGER in hospital, with a 5 ‰ higher prevalence in neonatal patients (Table I) and a post-discharge attack rate of 2 ‰. A statistically significant difference was observed between the calculation method used and the prevalence of NAGER (p = 0.001).

The sensitivity and PPV of method 1 in detecting NAGER were 67 % and 51 %, respectively, while for method 2 they were 100 % and 79 %, respectively. The LR+ and LR- of method 1 were 67 and 0.33, respectively, in contrast with 100 and 0 for method 2. The degree of positive agreement with respect to the reference method was 52 % greater for method 2 (Table II). The reliability of the MBDS was greater when contrasted with the microbiology results (kappa indices of 0.58 *vs.* 0.88) (Table II).

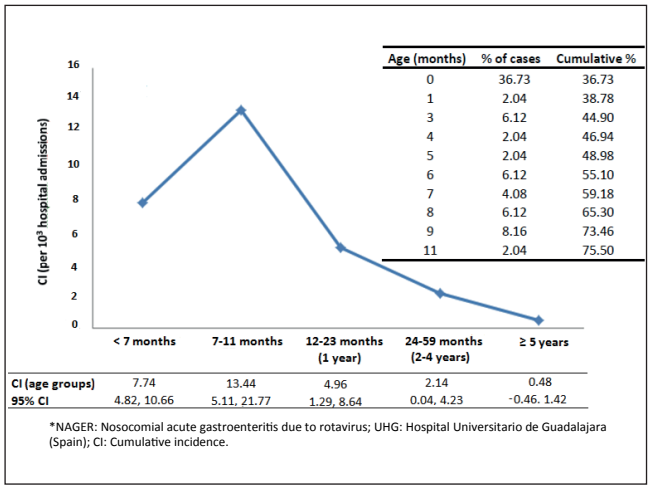
For neonatal patients, the mean age of children with NAGER was 0 days (minimum = 0, maximum = 29) while for pediatric patients it was 10 months (minimum = 1, maximum = 89). The cumulative percentage in children under 1 year of age was 75.5 %, with a greater incidence between 7 and 11 months (Fig. 2). The illness was significantly associated with age, with children under 2 years of age having a 9-fold risk of infection by rotavirus compared to children being 2 and over (p < 0.001). The main reason for hospitalization in neonatal patients was "preterm or prematurely born newborn" (73 %) while for pediatric patients it was for bronchiolitis/bronchospasms (32 %) and lower respiratory tract infections (19 %).

Cases of NAGER followed a seasonal pattern similar to that of AGE caused by community-acquired rotavirus, with higher peaks in the second half of autumn and the first half of winter (November-January), when a little over half of all the annual cases occurred, along with other minor peaks in spring (Fig. 3). The greatest amount of cases occurred in November. There were also summer outbreaks in 2005 and 2007.

Table II. Validity and reliability of methods 1 and 2 in estimating NAGER, with respect to method 3 or reference. UHG, 2003-2009*

		Method 1 (DIAG2 008.61 in the MBDS)	*Method 2 (Method 1 and PMRs)*
Diagnostic accuracy			
Internal validity (or exactitude)	S	0.67 (33/49)	1.00 (49/49)
	Sp	0.99 (9.521/9.553)	0.99 (9540/9553)
External validity	PPV	0.51 (33/65)	0.79 (49/62)
	NPV	0.99 (9.521/9.537)	0.99 (9.540/9.540)
Plausibility	LR+	67 [0.67/(1-0.99)]	100 [1/(1-0.99)]
	LR-	0.33 [(1-0.67)/0.99]	0 [(1-1)/0.99]
Diagnostic agreement			
Chamberlain's positive agreement[a]		0.41 (33/(33+16+32))	0.93 [49/(13+49)]
Reliability (or consistency)[b]		0.58[c]	0.88[c]

*NAGER: Nosocomial acute gastroenteritis due to rotavirus; UHG: University Hospital of Guadalajara; micro: Positive microbiology results for rotavirus; S: Sensitivity; Sp: Specificity; PPV: Positive predictive value; NPV: Negative predictive value; LR+ and LR-: Positive and negative likelihood, respectively. [a]Percentage of positive agreement between methods = TPx100 / (TP + FP + FN). TP: True positives; FP: False positives; FN: False negatives. [b]Cohen's kappa coefficient. [c]p < 0.001.

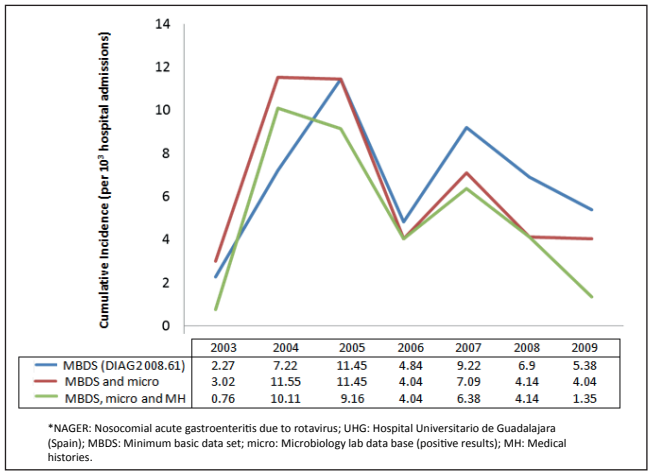


Age (months)	% of cases	Cumulative %
0	36.73	36.73
1	2.04	38.78
3	6.12	44.90
4	2.04	46.94
5	2.04	48.98
6	6.12	55.10
7	4.08	59.18
8	6.12	65.30
9	8.16	73.46
11	2.04	75.50

CI (age groups)	7.74	13.44	4.96	2.14	0.48
95% CI	4.82, 10.66	5.11, 21.77	1.29, 8.64	0.04, 4.23	-0.46, 1.42

*NAGER: Nosocomial acute gastroenteritis due to rotavirus; UHG: Hospital Universitario de Guadalajara (Spain); CI: Cumulative incidence.

Fig. 2. Incidence (per 10^3 hospitalizations) of NAGER by age groups in the Pediatric and Neonatal wards. UHG, 2003-2009*.

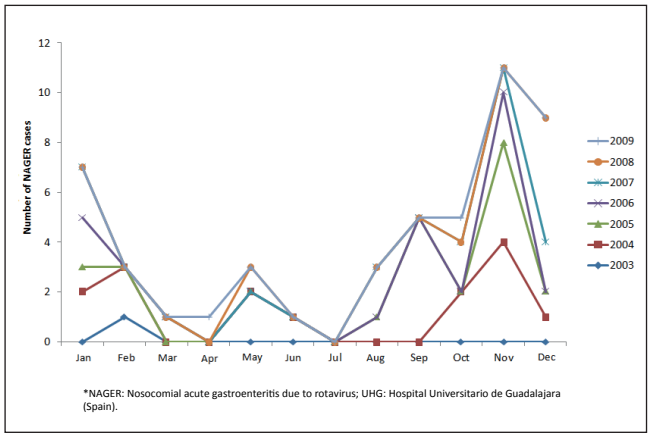


	2003	2004	2005	2006	2007	2008	2009
MBDS (DIAG2 008.61)	2.27	7.22	11.45	4.84	9.22	6.9	5.38
MBDS and micro	3.02	11.55	11.45	4.04	7.09	4.14	4.04
MBDS, micro and MH	0.76	10.11	9.16	4.04	6.38	4.14	1.35

*NAGER: Nosocomial acute gastroenteritis due to rotavirus; UHG: Hospital Universitario de Guadalajara (Spain); MBDS: Minimum basic data set; micro: Microbiology lab data base (positive results); MH: Medical histories.

Fig. 4. Yearly distribution of NAGER incidence (per 10^3 hospitalizations) in the Pediatric and Neonatal wards, by estimation method. UHG, 2003-2009*.

Between 2003 and 2009, the mean number of NAGER cases was 4.14 per 10^3 hospitalizations per year (Table I) The incidence rate was similar when calculated with method 2, and was much higher when calculated with method 1. The difference between methods 1 and 2 with respect to the reference method was found mostly in pediatric cases, where the two methods estimated 2 and 1 cases more per 10^3 hospitalizations/year, respectively, than the reference method (Table I). By the reference method, incidence reached 2 maximum peaks, one in 2004 and another lesser peak in 2007. Incidence decreased in 2008 and again, albeit not significantly, in 2009 (Fig. 4). The annual incidence distribution reflects a similarity among the different methods for assessing seasonal evolution (Fig. 4). The mean hospital stay for all hospitalizations in 2003-2009 was 4 days (interquartile range [IQR]= 3.7-4.3): Three (2.5-3.4) for pediatric cases and 7.9 (7.3-8.5) for neonates.



*NAGER: Nosocomial acute gastroenteritis due to rotavirus; UHG: Hospital Universitario de Guadalajara (Spain).

Fig. 3. Seasonal distribution of the number of NAGER cases per year of study period. UHG, 2003-2009*.

For patients with NAGER, it was 9 days (IQR = 5-20): 7 (4-9) for pediatric cases and 25 (16-37.3) for neonates. In premature infants, it was 29 days (IQR = 20-39; minimum = 15, maximum = 44).

In the period between 2007 and 2009 there was an overall decrease of 5 cases for every 10^3 hospitalizations (approx. 2.8 ‰ less frequent) with respect to the 2003-2005 period ($p < 0.001$). When measured with method 2, this decrease was even greater, at 3.6 ‰ ($p < 0.001$) (Table III). In contrast, no significant differences between the two three-year periods were observed when calculated with method 1 ($p = 0.33$). When the reference method was used, the IR went down by 9 cases for every 10^4 days of hospital stay ($IRR_{2007\text{-}2009/2003\text{-}2005} = 0.55$; 95 % CI 0.54-0.56; $p < 0.001$). The IRR between the two three-year periods with method 2 was 0.45 (95 % CI 0.44-0.46); when measured with the MBDS, it was 1.08 (95 % CI 1.06-1.10) (Table III).

DISCUSSION

The DIAG2 taken from the MBDS detected 67 % of NAGER cases during the 2003-2009 period, with a safety of 51 % and a moderate power of agreement with respect to the clinical method. In contrast, the MBDS taken together with microbiology results produced maximum detection, with a 28 % higher safety and very good agreement. Although both methods showed an excellent level of diagnostic evidence (LR+ > 10), method 1 was only moderately effective for ruling out the illness (LR- = 0.33) when it was not detected. Throughout the study period, the mean incidence of NAGER showed high variability, with a range of 2.7-7.8 cases per 10^3 hospitalizations/year. This was also true for the mean IR, which ranged from 7.0 to 77.7 cases for every 10^4 days of hospital stay. The disease was

Table III. Mean prevalence, incidence, and incidence rate of NAGER by three-year study period, according to estimation method. UHG, 2003-2005 and 2007-2009*

Method	2003-2005			2007-2009		
	‰ (n)[a]	CI (per 10^3)[b]; IR	IR (per 10^4)[c]; IR	‰ (n)[a]	CI (per 10^3)[b]; IR	TI (per 10^4)[c]; IR
MBDS (DIAG2 008.61)	7.0 (28)	7.22 (4.74-9.34)	17.08 (11.17-21.20)	7.1 (31)	6.90 (6.14-8.06)	18.45 (16.87-22.10)
MBDS and micro	8.7 (35)	11.45 (7.24-11.50)	25.31 (16.16-26.32)	5.1 (22)	4.14 (4.09-5.62)	11.47 (11.27-15.64)
MBDS, micro, and MH	6.7 (27)	9.16 (4.96-9.63)	20.25 (12.0-22.08)	3.9 (17)	4.14 (2.74-5.26)	11.07 (7.45-14.45)

*NAGER: Nosocomial acute gastroenteritis due to rotavirus; UHG: University Hospital of Guadalajara (Spain); CI: Cumulative incidence; IR: Interquartile range; MBDS: Minimum basic data set; DIAG2: Secondary diagnosis fields; micro: Microbiology lab data base; MH: Medical histories. [a]Number of hospitalizations during the period 2003-2005: 4,018. Number of hospitalizations during the period 2007-2009: 4,345. [b]Mean three-year cumulative incidence: Cases per 10^3 hospitalizations/year. [c]Mean three-year interquartile range: Cases per 10^4 hospital stays/year.

56 % more frequent in neonatal than in pediatric patients. On average, the hospital stay for children who contracted NAGER in the hospital was 4 days longer in pediatric cases and 17 days more for neonates. In the 2007-2009 period, the illness was almost 2 times less prevalent compared to 2003-2005, with the risk of contracting the illness per day of hospital stay decreasing almost by half. While in the three-year period in which privately funded vaccines were available, the number of cases/year showed a decrease of 55 %, universal vaccination programs in Europe in the same time period showed a prevention of up to 72 % of cases/year (25).

The selected study period was selected for convenience, to evaluate the efficacy of vaccines before 2010, when the Spanish Agency for Medicines and Health Products interrupted the supply of Rotarix® and Rotateq® because of the detection of porcine circovirus in March and June of that year, respectively (18). Maximum vaccine coverage, despite the fact that the vaccines were not subsidized by the Spanish healthcare system, would have thus occurred when the drugs were first made available, from 2007 to 2009, a time when pediatricians were recommending the health benefits of vaccination during well child visits, thereby promoting their commercialization. Although in November, 2010, Rotateq® was re-released into the market, Rotarix® is still unavailable in Spain (17). We then decided to compare the 2007-2009 period with an immediately preceding period of equal length, leaving out the year 2006, as explained above in the methods section.

Overall, the MBDS *per se* overestimated the incidence by 3 cases for every 10^3 hospitalizations and the mean IR by 6 cases for every 10^4 days of hospital stay. Besides, it did not detect the decrease during the 2007-2009 period. Together with microbiology results, the MBDS did indicate this decrease, although it overestimated it by 2 cases per 10^3, as well as the decrease in risk per day of hospital stay by 10 %. It is difficult to compare the incidence found in other Spanish studies due to the heterogeneity in the designs and methodologies used (3,4,6,8). In this context, the variability of the assessment methods would be an important source of error (26). Furthermore, the majority of previous studies have been retrospective, which supposes a lack of follow-up in the 72 hours after discharge and the exclusion of mild or asymptomatic cases (4,8,10). Previous studies based solely on hospital discharge data with the specific code of CIE-9-MC 008.61 have been shown to underestimate the real burden of the disease (4). To evaluate the validity and reliability of the MBDS, we took the patients' medical histories as a reference, as they contain more complete information on patient hospitalizations and, together with the PMRs, they offer more accurate data. The fact is, as mentioned above, that almost a third of identified as *true nosocomial cases* had been discharged less than 72 hours before being readmitted with NAGER as their DIAG1; that is, the disease became symptomatic after the first discharge.

The difficulty in comparing different studies in this field is an even greater challenge in the European context, with discrepancies among public health systems and different epidemiological patterns (5,10). The changes observed between the two three-year periods under study, as well as any comparisons made between national and international results must be taken with caution given the low number of cases of NAGER and the low statistical power of the sample.

The UHG was an ideal place to carry out this study because its microbiology lab is a place of reference throughout the region. Feces sample collection to check for rotavirus in children is routinely carried out if there is any suspicion of AGE whenever any symptoms of the disease are observed. Because of this, the date of the microbiology results was taken to be the start of symptomatic AGE in order to estimate *probable nosocomial cases*, *possible nosocomial cases*, and *true nosocomial cases* (Fig. 1). For those entries with PMRs within the first 72 hours after hospitalization, a community origin was assigned. Nevertheless, a PMR after this period did not necessarily indicate a nosocomial origin since there is sometimes a time lapse between the start of symptoms and a PMR. These cases were thus defined as *probable nosocomial cases.* Those in which a PMR was obtained within 72 hours of discharge were considered to be nosocomial, but even after this period, we could not entirely rule out a nosocomial origin since in cases with mild symptoms, outpatient feces

sampling may be delayed or not performed. In order not to lose these cases, we reviewed all medical histories with PMRs obtained up to one month after hospital discharge with a DIAG2 of 00.861, and/or 558.9, and/or 787.03, and/or 787.91. As mentioned above, we identified 37 cases with PMRs on the third day after discharge, 36 with a DIAG2 of 008.61 and one with a DIAG2 of 558.9 (Fig. 1). In one month follow-up of hospitalizations due to rotavirus, readmitted patients usually are within three days after the initial discharge (27). Still, this would not have identified mild or asymptomatic cases after discharge with no DIAG2 entries of 558.9, and/or 787.03, and/or 787.91, and/or without microbiology sample collection. This has prompted a call to include in future a new label of "present on admission" (POA), which would accompany each diagnostic code to differentiate diagnoses made at the time of hospital admission (POA = Y, yes) from those appearing during the actual hospital stay (POA = N, no).

The mean incidence of NAGER calculated through the DIAG2, namely 6.90 per 10^3, is higher than the national average (obtained by the same means) of 4.50 per 10^3 (8). Although the reliability of the MBDS is only moderate, this comparison reveals a high incidence of NAGER in the UHG. Moreover, the mean IR of 11.07 per 10^4 (IR: 7-77.72) obtained with the clinical method is double that described for Western Europe, which is 4.6 per 10^4 (range: 0-6.8 per 10^4) (13). Indeed, the mean IR reported for Europe as a whole is similar to those reported in prospective studies (1,11). In this context, the incidence observed in the UHG of 4.14 per 10^3 is quite low if we compare it with prospective studies carried out in Spain (3,6,28). This difference may be due to the aforementioned loss of mild or asymptomatic cases, especially in the absence of follow-up period, as well as to the loss of symptomatic cases that remain unclassified as such in the MBDS because they were not properly entered in the medical histories or for lack of microbiology results. This could be a possible source of selection bias in our study. Even in prospective studies which only record results of symptomatic infection, the observed prevalence is higher than in our study (3). Taking these considerations into account, the main limitation of this study is the type of information in the MBDS. Indeed, it has been estimated that post-discharge appearance of NAGER occurs in up to 11 cases for every 10^3 hospitalizations (29). Even so, it would be necessary to perform feces analyses both before and after discharge to identify asymptomatic cases (30).

In addition to all the aforementioned, and with respect to the difficulty in making comparisons, it must be remembered that the incidence is influenced by the seasonal period followed (epidemic season *vs.* complete year) and the age range of the patients (14). Surveillance studies have determined a combined incidence of NAGER that can reach up to 8.1 cases during epidemic months (95 % CI 6.4-9.9) (31).

The use of medical histories as a reference also presents several limitations such as *interviewer bias*. The form in which each clinic records the beginning and the course of digestive symptoms in each patient's medical history may differ depending on his or her particular interest the pathology observed or the severity of its evolution. For this reason, we chose to also review the nursing records, in which the number and consistency of stools is recorded with greater accuracy, as is the presence of vomiting. Further, as the medical records were all reviewed by the same person, interobserver agreement could thus not be calculated, which could produce observer bias (erroneous differential classification of disease). We attempted to minimize this by elaborating a systemized data collection form. But this same error could occur in the process of codification, depending on the experience of those applying the disease codes.

To date, no studies have specifically evaluated the efficacy of the MBDS as a surveillance system for NAGER, although it has been used to monitor other nosocomial infections such as surgical site infections, catheter-associated urinary tract infection, central line-associated bloodstream infection, ventilator-associated pneumonia/events, postprocedure pneumonia, as well as infections caused by bacteria associated with hospital health care (methicillin-resistant *Staphylococcus aureus* and *Clostridium difficile*) (32). It has also been used to determine the prevalence of nosocomial infections (33) and its agreement with other data sources in detecting cancer (34), emergency pathologies (35), postoperative risk factors and secondary effects (36), cerebrovascular trauma (37), and surgical mortality (38) have been assessed. As in our study, other researchers have found a moderate sensitivity and high specificity of the MBDS in detecting *Clostridium difficile* and surgical site infection (32). Due to the low incidence of hospital infection, the PPV of registries like the MBDS are probably low.

This is also the first published analysis of the effects of the commercialization of both vaccines against rotavirus on NAGER incidence in Spain. In countries with a nationwide immunization schedule, the indirect benefits on the non-vaccinated public have previously been demonstrated (39,40), albeit not at the intrahospital level. Nevertheless, the decrease observed in the three-year study period after the vaccines had been made available may be due to herd immunity as well as to the "*hand washing program"* promoted by the UHG since 2008, a strategy that has proven effective in lowering the communicability of the virus within the hospital, which is found on the hands of 77 % of hospital health workers (5,41). Still, only 37 % of NAGER cases that we identified had actually been isolated, all of them in neonatal patients. Other researchers have estimated that the disease is isolated only in 50 % of patients (14).

This study has analyzed for the first time the validity and reliability of the DIAG2 of the MBDS in estimating NAGER. The clinical method ruled out 25 % of the cases categorized by this system. The MBDS, taken together with microbiology results, equivalent to the Microbiology

Information System, is more exact, safer and more reliable than the MBDS alone in estimating NAGER; and better at ruling out it. Nevertheless, because it offers a high level of diagnostic evidence, method 1 may be used to estimate nosocomial infection in contexts with various prevalences, always with caution. In this sense, future studies with larger sample sizes should be undertaken to bolster these findings. We should raise awareness among healthcare professionals about the importance of proper recording of clinical variables to improve the coding in Healthcare Information Systems. If we cannot validly and efficiently assess the quality of care, it will be impossible to design strategies to improve monitoring and control of nosocomial infections. The implementation of a specific code to register this pathology in the MBSD would be an important step forward in this regard.

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