Perinatal Risk Factors for Infant Hospitalization With Viral Gastroenteritis

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ABSTRACT. *Context.* A tetravalent vaccine against rotavirus, the most commonly identified etiologic agent of viral gastroenteritis (GE), has recently been licensed for use in the United States.

Objective. To evaluate whether specific groups of infants might be at sufficiently high risk to warrant a focused rotavirus vaccine policy, we investigated perinatal risk factors for hospitalization with viral GE and rotavirus in the first year of life.

Design. Population-based, case–control study.

Setting. Washington State linked birth certificate and hospital discharge abstracts from 1987 through 1995.

Patients. Infants, 1 through 11 months of age, hospitalized for viral GE (*N* = 1606) were patients in this study. Control subjects were 8084 nonhospitalized infants, frequency-matched to patients on year of birth.

Primary Outcome Measure. Maternal and infant characteristics associated with infant hospitalization for viral GE.

Results. We found a significant association between birth weight and the risk for hospitalization. Very low birth weight infants (<1500 g) were at the highest risk (odds ratio [OR] 2.6; 95% confidence interval [CI]: 1.6,4.1);, low birth weight infants (1500–2499 g), at intermediate risk (OR 1.6; 95% CI: 1.3,2.1); and large infants (>4000 g), at reduced risk (OR 0.8; 95% CI: 0.6,0.9). Other characteristics associated with GE hospitalization were male gender (OR 1.4; 95% CI: 1.3,1.6); maternal smoking (OR 1.2; 95% CI: 1.1,1.4); unmarried mother (OR 1.2; 95% CI: 1.1,1.4); Medicaid insurance (OR 1.4; 95% CI: 1.3,1.7); and maternal age <20 years (OR 1.2; 95% CI: 1.0,1.5). Infants born October through December were at decreased risk for hospitalization (OR 0.8; 95% CI: 0.7,0.9), as were infants born to Asian mothers (OR 0.5; 95% CI: 0.3,0.7), and infants born to mothers >34 years of age (OR 0.7; 95% CI: 0.6,0.9). Using these factors, the area under a receiver operating characteristic curve was 0.63. Therefore, to achieve a sensitivity of 90% in identifying high-risk infants, specificity would fall to 10%. Subanalyses of children admitted for viral GE during the peak of the Northwest rotavirus season (January to March) and children with confirmed rotavirus infection demonstrated similar risk factors and receiver operating characteristic curves.

Conclusion. We conclude that a focused rotavirus vaccination policy using readily identifiable potential high-risk groups would be unlikely to prevent most infant hospitalizations associated with rotavirus infection. However, the safety of rotavirus vaccine in low birth weight and premature infants must be established, because these children appear to be at greater risk for hospitalization with viral GE and rotavirus. *Pediatrics* 1999;103(1). URL: http://www.pediatrics.org/cgi/content/full/103/1/e3; *gastroenteritis, rotavirus, vaccines, infant, birth weight.*

ABBREVIATIONS. GE, gastroenteritis; BERD, Washington State Birth Events Record Database; CHARS, Comprehensive Hospital Abstract Reporting System; ICD–9CM, International Classification of Diseases, Ninth Revision, Clinical Modification; OR, odds ratio; CI, confidence interval; HMO, health maintenance organization; ROC, receiver operating characteristic; AUC, area under the curve.

Diarrhea remains a major cause of worldwide mortality, causing an estimated 3 to 3.5 million deaths per year and accounting for the yearly loss of ~100 million disability-adjusted life years as of 1990.[1–3] In the United States, an estimated 21 to 37 million episodes of diarrhea occur among 16.5 million children younger than 5 years of age per year.[4] There are ~2.1 to 3.7 million diarrhea-associated physician visits per year,[4] and 163 000 hospitalizations, representing 13% of all hospitalizations in this age group.[5]

Although the majority of diarrheal hospitalizations (75.9%) do not have an etiologic agent identified, viral gastroenteritis (GE) is the leading cause of identified diarrheal disease, accounting for 19.3% of diarrheal hospitalizations for all children.[6] Rotavirus, adenovirus, Norwalk virus, astrovirus, and calicivirus are the most common pathogens.[7] Of identified viral etiologies, rotavirus is the most common, accounting for 16.5% of all diarrhea-related hospitalizations.[5]

Despite the importance of GE as a cause of childhood morbidity and mortality, few studies have examined prenatal and perinatal risk factors for GE deaths,[8–10] and none have examined the risk factors for hospitalization with viral GE. Because there are only 300 to 400 diarrheal deaths per year in the United States,[4] diarrhea-associated hospitalizations probably provide a more complete estimate of the diarrheal disease burden in infants than do diarrhea-associated deaths.

With the recent licensure of a vaccine against rotavirus, it is important to determine whether there are specific subgroups of infants who are at substan-

tially increased risk for hospitalization with viral GE that might benefit particularly from rotavirus immunization if the vaccine is not initially widely available for universal use.[11] The draft of the Advisory Committee on Immunization Practices recommendations regarding the use of rotavirus vaccine advocates for universal immunization, but indicates that available data are insufficient to draw conclusions about the safety or efficacy of the tetravalent rhesus rotavirus-based vaccine in premature infants.[12] Because clinical trials have demonstrated that one of the consistent benefits of the rotavirus vaccine was prevention of severe GE,[13–15] we were interested in identifying groups of infants at risk for hospitalization with viral GE generally, or rotavirus specifically, because hospitalization is a proxy measure of disease severity.

METHODS

We conducted a retrospective population-based case–control study of prenatal and perinatal risk factors for hospitalization with GE in the first year of life using data obtained from Washington State Birth Events Record Database (BERD) linked to the Comprehensive Hospital Abstract Reporting System (CHARS) for the years 1987 through 1995. BERD links birth certificate and infant death certificate data with maternal and newborn hospital admission records and provides time and date of birth, date of discharge, sociodemographic, perinatal, maternal, and newborn characteristics. CHARS contains information abstracted from hospital discharges at all nonmilitary acute care hospitals in Washington State and provides up to five *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD–9CM) diagnostic discharge codes, length of stay, and insurance information.

Children in both BERD and CHARS are given a unique identifier consisting of the first two letters of the first name, the first two letters of the last name, and the date of birth. Children were included in the study only if records matched on this identifier, and additionally matched on gender and on four of five ZIP code digits.

Patients for the primary analysis were defined as infants who had completed the first month of life, but who were younger than 12 months of age on admission and who had an ICD–9CM code 008.6 to 008.8 (viral GE) as one of the first three discharge diagnoses.[16] This case definition likely is more specific than that used by either Matson or Parashar, which includes diarrhea coded as nonviral.[5,17] Previous studies in adults have shown that when diarrhea is listed as one of the first three discharge diagnoses, it is the primary reason for hospitalization in 95% of individuals.[18]

Control subjects were infants not hospitalized for viral GE in the first year of life and were randomly selected from the BERD file. Four control subjects per patient were frequency-matched on year of birth to account for possible secular trends in the management of GE. Because frequency-matching was performed before excluding patients whose diagnosis of viral GE was in ICD–9CM code position 4 or 5 and before excluding infants younger than 1 month of age, the final control–case ratio was closer to 5:1.

Two subanalyses were performed to assess the validity of using all viral GE hospitalizations as a proxy for rotavirus hospitalizations. In the first, we limited patients to the 625 children hospitalized from January through March, the peak of the Northwest rotavirus season.[19] In the second, we limited patients to only those children with an ICD–9CM discharge code of rotavirus. Because this code was not in use until 1992,[5] only 194 patients with confirmed rotavirus were available. In this second subanalysis, we restricted the control subjects to the 3308 children born in 1992 or later. Case and control selection for all analyses is summarized in Fig 1.

For univariate analyses, odds ratios (OR) for the association between a variety of maternal and infant characteristics and the risk of admission for viral GE from 1 through 11 months of age were calculated and their associated confidence intervals (CI) estimated using Cornfield methods.[20] Birth weight was stratified into four categories based on the clinical definitions of very low birth weight (<1500 g), low birth weight (1500–2499 g), normal birth weight (2500–4000 g), and elevated birth weight (>4000 g).

We used birth weight as a proxy measure for prematurity because estimated gestational age was missing for 2697 children (27.8%). Other infant characteristics evaluated as possible risk factors were gender, season of birth (January through March, April through June, July through September, and October through December); multiple birth (singleton, twin, or triplet); history of necrotizing enterocolitis; and history of any gastrointestinal anomaly from the birth record. Maternal characteristics evaluated as possible risk factors were age (<20 years, 20–34 years, ≥35 years); race/ethnicity (white, black, Native American, Asian, Hispanic, other); smoking (yes, no); marital status (unmarried, married); parity (0, 1, >1); and maternal insurance status (Medicaid, health maintenance organization [HMO], commercial insurance, other).

Multivariate logistic regression was used to identify perinatal factors independently associated with viral GE hospitalization. Based on the results of univariate analyses, three variables were simplified to dichotomous variables: maternal race (Asian versus all others), season of birth (October through December versus any other month), and insurance status (Medicaid versus all others). Because year of birth was not an independent predictor of patient status and did not influence our final estimates appreciably, it was not included in the final model. Independent predictors were included in the model if the associated 95% CI for them excluded 1.

To assess the sensitivity and specificity of the multivariate model in identifying infants hospitalized with viral GE, we generated a receiving operator characteristic (ROC) curve using the final logistic regression model. ROC curves plot sensitivity versus 1-specificity. The area under the curve (AUC) of an ROC plot describes the ability of a medical test to discriminate between disease and nondisease or, in this case, between hospitalized and nonhospitalized infants. An ideal test would have an AUC of 1, whereas a test that performed no better than chance would have an AUC of 0.5.[21] To account for possible data overfitting by generating a logistic regression model and testing its predictive value with the same dataset, we used bootstrap validation (100 replications).[22] This technique of sampling with replacement allows an estimation of model performance if it were applied to a different sample of children to predict viral GE hospitalization.

Before generation of the dataset, we estimated that a minimum of 1305 patients and 5220 control subjects would be required to detect a 1.5-fold increase in the risk for viral GE hospitalization associated with low birth weight with 80% power at $\alpha = .05$.
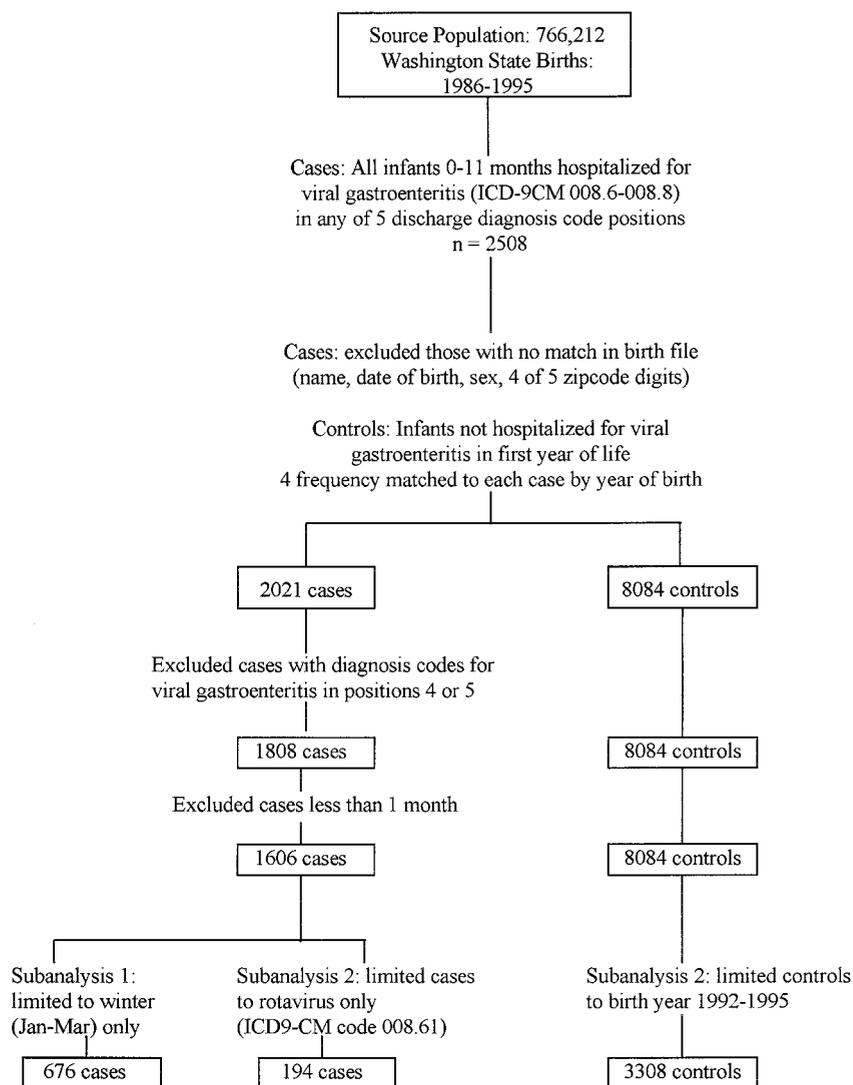
Stata Statistical Software, Release 5.0, was used for all statistical analyses (Stata Corporation, College Station, TX).

RESULTS

Infant, maternal, and pregnancy characteristics of the 1606 patients hospitalized with viral GE and 8084 control subjects are shown in Table 1. Low birth weight and very low birth weight were significantly associated with an increased risk for hospitalization. Infants born in the last quarter of the year (October through December) were at a significantly decreased risk of hospitalization with viral GE compared with infants born in the first quarter of the year (January through March). Male infants, infants born with any gastrointestinal anomaly, and infants diagnosed with necrotizing enterocolitis in the neonatal period also were at increased risk for hospitalization with viral GE. Although the great majority of mothers of both patients and control subjects were white, children of Native American mothers were at an increased risk of hospitalization, and those of Asian mothers at a significantly reduced risk. Additionally, mothers who were younger, less educated, insured through Medicaid, unmarried, and smoked during pregnancy had infants at increased risk for viral GE hospitalization.

In multivariate analyses, we also found a significant relationship between birth weight and the risk of viral GE hospitalization, with very low birth

Cases: All infants 0-11 months hospitalized for
viral gastroenteritis (ICD-9CM 008.6-008.8)
in any of 5 discharge diagnosis code positions
n = 2508

Cases: excluded those with no match in birth file
(name, date of birth, sex, 4 of 5 zipcode digits)

Controls: Infants not hospitalized for viral
gastroenteritis in first year of life
4 frequency matched to each case by year of birth

Fig 1. Flow diagram for obtaining patients
and control subjects.

| 2021 cases | | 8084 controls |

Excluded cases with diagnosis codes for
viral gastroenteritis in positions 4 or 5

| 1808 cases | | 8084 controls |

Excluded cases less than 1 month

| 1606 cases | | 8084 controls |

Subanalysis 1: limited to winter (Jan-Mar) only	Subanalysis 2: limited cases to rotavirus only (ICD9-CM code 008.61)	Subanalysis 2: limited controls to birth year 1992-1995
676 cases	194 cases	3308 controls

weight infants at the highest risk, low birth weight infants at intermediate risk, and large infants at reduced risk ($P < .001$) (Table 2). Additional characteristics associated independently with hospitalization were male gender, maternal age <20 years, maternal smoking, unmarried status, and maternal Medicaid insurance. Infants born from October through December were at decreased risk of hospitalization, as were infants born to Asian mothers and infants born to women >34 years of age.

Multivariate analyses of GE hospitalization risk for children admitted for viral GE from January through March (the peak months of the Northwest rotavirus season) and for children admitted for confirmed rotavirus-associated GE also were performed (Table 2). Using the same risk factors associated with hospitalization for all GE cases, the magnitudes of the ORs in general were similar, although the confidence limits for some of these predictors widen to include 1, particularly for the rotavirus-only analysis. Because the number of very low birth weight infants (<1500 g) is very small in the rotavirus-only analysis ($n = 3$), the ORs associated with this risk factor cannot be seen as a stable estimate.

Using the multivariate model for all viral GE ad-

missions, AUC of an ROC curve was 0.63 (Fig 2). Using bootstrap validation, we estimated that this AUC was 0.006 higher than would be expected if this model were applied to a different sample of children (data not shown). The AUCs for ROC curves generated from the two multivariate subanalyses were similar in magnitude: 0.62 for the winter-only analysis and 0.62 for the rotavirus-only analysis (data not shown). Therefore, to identify 75% of infants at high risk for viral GE hospitalization, the specificity of the model would be ~40%. To reach 90 sensitivity%, specificity would fall to near 10%.

DISCUSSION

Birth weight, gender, and maternal socioeconomic indicators all significantly predicted infants at high risk for hospitalization with viral GE in the first year of life. However, these risk factors were neither sufficiently sensitive nor specific to be used to create a focused rotavirus immunization policy for the United States.

We found a marked dose–response effect of birth weight. Compared with normal birth weight infants, infants weighing <1500 g were at the highest risk, and those weighing >4000 g at decreased risk for

TABLE 1. Univariate Analysis of Maternal, Infant, and Pregnancy Characteristics of GE Admissions and Controls*

	Cases (n = 1606)		Controls (n = 8084)		OR	95% CI
	N	%	N	%		
Infant characteristics						
Birth weight (g)						
<1500	31	1.9	70	0.9	2.25	(1.47,3.43)
1500–2499	124	7.7	370	4.6	1.70	(1.38,2.10)
2500–4000	1278	79.8	6482	80.2	1.00	(Reference)
>4000	168	10.5	1150	14.2	0.74	(0.62,0.88)
Season of birth						
January–March	414	25.8	1905	23.6	1.00	(Reference)
April–June	472	29.4	2177	26.9	0.99	(0.86,1.15)
July–September	393	24.5	2129	26.3	0.85	(0.73,0.99)
October–December	327	20.4	1873	23.2	0.80	(0.69,0.94)
Male gender	930	57.9	4091	50.6	1.34	(1.21,1.50)
Twin or triplet	34	2.1	204	2.5	0.84	(0.58,1.20)
Necrotizing enterocolitis	7	0.4	7	0.1	5.05	(1.85,13.8)
Any GI anomaly	13	0.8	9	0.1	7.32	(3.20,16.8)
Maternal characteristics						
Maternal age (y)						
<20	264	16.4	870	10.8	1.57	(1.35,1.82)
20–34	1234	76.9	6368	78.8	1.00	(Reference)
≥35	107	6.7	840	10.4	0.66	(0.53,0.81)
Maternal race						
White	1302	82.9	6466	81.9	1.00	(Reference)
Black	65	4.1	308	3.9	1.05	(0.80,1.38)
Native American	48	3.1	171	2.2	1.39	(1.01,1.93)
Asian	43	2.7	406	5.1	0.53	(0.38,0.73)
Hispanic	113	7.2	540	6.8	1.04	(0.84,1.28)
Maternal smoking	409	25.4	1495	18.5	1.53	(1.34,1.73)
Unmarried mother	546	34.0	1877	23.2	1.71	(1.52,1.91)
Insurance						
Medicaid	582	36.2	2013	24.9	1.56	(1.32,1.78)
HMO	144	9.0	824	10.2	0.95	(0.78,1.15)
Commercial	551	34.3	2982	36.9	1.00	(Reference)
Other	329	20.5	2265	28.0	0.79	(0.68,0.91)
Parity						
0	668	42.3	3299	41.8	1.01	(0.89,1.16)
1	503	31.9	2602	32.9	1.02	(0.90,1.16)
2+	408	25.8	2002	25.3	1.00	(Reference)

* Missing values excluded.

hospitalization with viral GE. Low birth weight also was a significant risk factor for infants hospitalized for viral GE in the winter months. For infants with confirmed rotavirus infection, similar associations were found, although very low birth weight and high birth weight were no longer statistically significant. These findings are consistent with those from a recent study that demonstrated that low birth weight is a significant risk factor for diarrheal mortality in the United States.[8]

In addition, proxy measures of low maternal socioeconomic status (age <20 years, smoking, unmarried status, and receiving Medicaid insurance) all were independently associated with an increased risk for viral GE hospitalization; the magnitude of these risks was generally consistent for children in the two subanalyses. Low familial socioeconomic status also has been associated with adverse outcomes ion infants with viral respiratory illnesses.[23]

We found that infants born in the months of October, November, and December were at decreased risk for viral GE hospitalization, perhaps because of the seasonal nature of rotavirus infection,[24] the duration of maternal antibody,[25] or the presence of rotavirus IgA in human human milk.[26] This association was stronger in children with confirmed rotavirus GE. Surveillance data demonstrate that the Northwest rotavirus season peak had occurred between January and March from 1991 through 1996.[19] Maternally derived IgG against rotavirus usually wanes by 5 months of age,[25] and the peak incidence of rotavirus infection occurs between 6 and 24 months of age.[27] Therefore, infants born just before the rotavirus season peak may be at the lowest risk for hospitalization because of maternal antibody protection—by means of passively acquired IgG[25] or IgA acquired by breastfeeding[26]—through their first rotavirus season.

The significant protection afforded to Asian infants is difficult to explain. This association was independent of birth weight and maternal characteristics but might be explained by breastfeeding differences in Asian mothers. It also is possible that either home care for Asian infants with diarrheal disease or admission practices of physicians caring for Asian infants with diarrhea differ, resulting in this apparent protective effect.

Interestingly, maternal age greater than 34 years was associated independently with a decreased risk for hospitalization with viral GE. Whether this finding also represents more prevalent breastfeeding among these women, experiential knowledge associated with advancing age, or a decreased overall risk

TABLE 2. Multivariate Analyses of Risk Factors for Hospitalization With GE, Winter GE, and Confirmed Rotavirus GE in the First Year of Life

Risk Factor	All Cases (N = 1606)		Winter Cases Only (Jan–Mar, N = 625)*		Rotavirus-confirmed Cases Only (N = 194)†	
	OR	95% CI	OR	95% CI	OR	95% CI
Infant characteristics						
Birth weight (g)						
<1500	2.57	(1.60,4.14)	2.43	(1.22,4.84)	1.35	(0.31,5.84)
1500–2499	1.63	(1.29,2.06)	1.43	(1.00,2.05)	2.01	(1.18,3.45)
2500–4000	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)
>4000	0.76	(0.61,0.85)	0.83	(0.63,1.08)	0.70	(0.43,1.15)
Season of birth						
January–September	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)
October–December	0.80	(0.69,0.92)	0.82	(0.66,1.01)	0.51	(0.33,0.79)
Male gender	1.42	(1.27,1.60)	1.56	(1.31,1.86)	1.38	(1.02,1.87)
Maternal characteristics						
Maternal age (y)						
<20	1.23	(1.04,1.46)	1.34	(1.04,1.73)	1.14	(0.72,1.81)
20–34	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)
≥35	0.69	(0.55,0.87)	0.61	(0.42,0.88)	0.92	(0.54,1.55)
Maternal race						
Asian	0.49	(0.34,0.70)	0.63	(0.38,1.03)	0.49	(0.20,1.21)
All other races	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)
Maternal smoking	1.21	(1.06,1.39)	1.44	(1.18,1.75)	1.16	(0.79,1.69)
Unmarried mother	1.24	(1.08,1.44)	1.07	(0.86,1.34)	0.95	(0.64,1.39)
Insurance						
Medicaid	1.44	(1.26,1.65)	1.31	(1.07,1.61)	1.46	(1.03,2.07)
All other	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)

* All 8084 control subjects used.
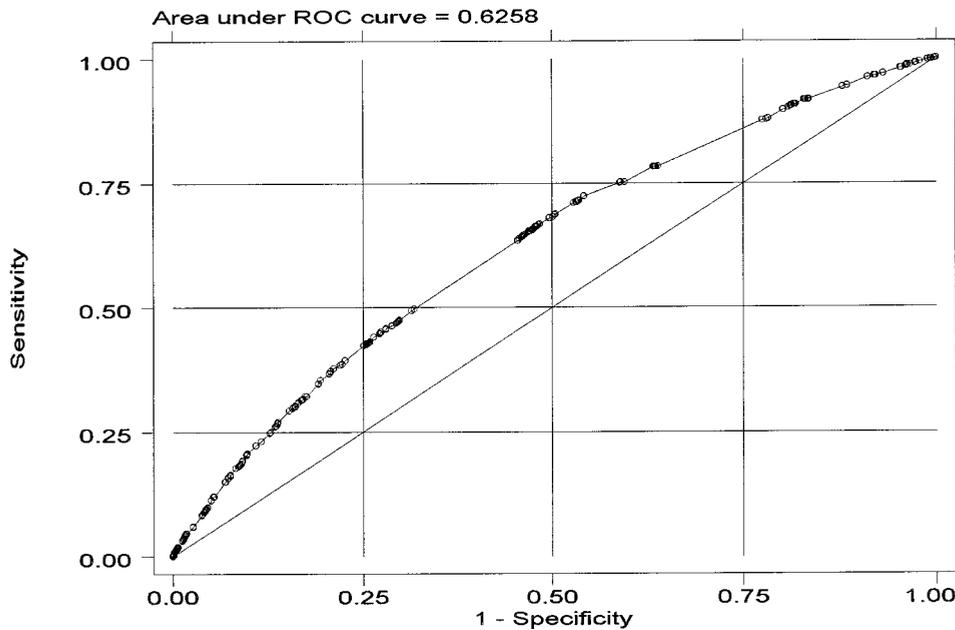† 3308 Controls, 1992 or later birth.

Fig 2. ROC curve derived from logistic regression model for all 1606 patients with viral GE and 8084 control subjects, as presented in Table 2.

for hospitalization attributable to other unmeasured characteristics is unclear.

The inability to determine breastfeeding status is a significant limitation of this article. Lack of breast-feeding has been shown to be a risk factor for diarrhea illnesses,[28] and the lower prevalence of breast-feeding among the poor[29] may be one of the mechanisms by which low socioeconomic status increases an infant's risk of hospitalization for viral GE.

Another limitation of this article is our inability to evaluate whether the decision to hospitalize a child was influenced by factors other than the child's clinical condition. Although one 6-month old infant with diarrhea and mild dehydration in a perceived stable home environment may receive outpatient treatment and close follow-up, a similar infant with different social characteristics might be admitted for inpatient therapy. These data did not allow us to evaluate clinical decision-making or the appropriateness of any given hospital admission.

Finally, as with all studies that rely on existing databases, there is likely some miscoding and, thus,

misclassification in our data. However, we have no reason to suspect a systematic bias in this misclassification.

Although we identified multiple risk factors associated with viral GE hospitalization as well as several protective factors, our multivariate model as a whole failed to demonstrate high sensitivity or specificity in identifying those infants hospitalized. The area of 0.6 under the ROC curve obtained using this model is not much different from 0.5, which would be found by random guessing of infants at high risk for hospitalization. Based on our model, even if the rotavirus vaccine were 100% effective in preventing dehydrating diarrhea, at least 90% of infants would need vaccination to protect all children from serious disease resulting in hospitalization.

In 1996, rotavirus researchers and policy-makers urged the identification of groups at increased risk for complications of rotavirus disease to "help focus the emphasis for vaccine program implementation."[30] However, the draft of the Advisory Committee on Immunization Practices rotavirus vaccine recommendations suggests that universal immunization will be recommended.[12] Recent evidence suggests that although universal rotavirus immunization would cost the medical system $107 million ($103 per case prevented), it would save society $296 million.[31] Based on these Washington State data, we conclude that despite the existence of identifiable risk factors for infant hospitalization with viral GE, a universal rotavirus vaccination program would be necessary to prevent most cases of severe rotavirus infection. However, there is an urgent need to establish definitively the safety of tetravalent rhesus rotavirus-based vaccine use in low birth weight and premature infants, because these children appear to be at greater risk for hospitalization with viral GE and rotavirus.

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