Nosocomial Rotavirus Infection in European Countries

A Review of the Epidemiology, Severity and Economic Burden of Hospital-Acquired Rotavirus Disease

Olivier Gleizes, MSc, MBA, Ulrich Desselberger, MD,† Vladimir Tatochenko, MD,‡ Carlos Rodrigo, MD, PhD,§ Nuran Salman, Prof., Dr,‖ Zsofia Mezner, MD, PhD,¶ Carlo Giaquinto, MD,# and Emmanuel Grimprel, MD***

Abstract: The data currently available on the epidemiology, severity and economic burden of nosocomial rotavirus (RV) infections in children younger than 5 years of age in the major European countries are reviewed. In most studies, RV was found to be the major etiologic agent of pediatric nosocomial diarrhea (31–87%), although the number of diarrhea cases associated with other virus infections (eg, noroviruses, astroviruses, adenoviruses) is increasing quickly and almost equals that caused by RVs. Nosocomial RV (NRV) infections are mainly associated with infants 0–5 months of age, whereas community-acquired RV disease is more prevalent in children 6–23 months of age. NRV infections are seasonal in most countries, occurring in winter; this coincides with the winter seasonal peak of other childhood virus infections (eg, respiratory syncytial virus and influenza viruses), thus placing a heavy burden on health infrastructures. A significant proportion (20–40%) of infections are asymptomatic, which contributes to the spread of the virus and might reduce the efficiency of prevention measures given as they are implemented too late. The absence of effective surveillance and of reporting of NRV infections in any of the 6 countries studied (France, Germany, Italy, Poland, Spain and the United Kingdom) results in severe underreporting of NRV cases in hospital databases and therefore in limited awareness of the importance of NRV disease at country level. The burden reported in the medical literature is potentially significant and includes temporary reduction in the quality of children's lives, increased costs associated with the additional consumption of medical resources (increased length of hospital stay) and constraints on parents'/hospital staff's professional lives. The limited robustness and comparability of studies, together with an evolving baseline caused by national changes in health care systems, do not presently allow a complete and accurate overview of NRV disease at country level to be obtained. RV is highly contagious, and the efficiency of existing prevention measures (such as handwashing, isolation and cohorting) is variable, but low at the global level because of the existence of numerous barriers to implementation (eg, lack of staff, high staff turnover, inadequate hospital infrastructure). Prevention of RV infection by mass vaccination could have a positive impact on the incidence of NRV by reducing the number of children hospitalized for gastroenteritis, therefore reducing the number of hospital cross-infections and associated costs.

Key Words: nosocomial rotavirus, children, epidemiology, economic burden, vaccination

(*Pediatr Infect Dis J* 2006;25: S12–S21)

Rotavirus (RV) infection is a major cause of infectious diarrhea in children worldwide. In developing countries, RV infections contribute considerably to morbidity and mortality among young children; 93% of the estimated 140 million annual RV episodes occur in children younger than 5 years of age, and 98% of the estimated 440,000 annual deaths from RV disease occur in developing countries.[1]

Although mortality from RV disease is very low in developed countries, community-acquired RV infections (CARV) are responsible for a significant morbidity, with a major impact on the total medical costs. There is also the risk of nosocomial RV (NRV) infections, which are a major component of hospital-acquired infections in children. However, medical costs associated with both CARV and NRV are still insufficiently documented, and they vary in different countries and organizations of the health care system.

This review article attempts to assemble existing information on the epidemiology, severity and costs associated with NRV disease in the 6 largest European countries (France, Germany, Italy, Poland, Spain and the United Kingdom) and highlights the importance of this viral pathogen for the overall burden of diarrheal infections.

MATERIALS AND METHODS

The burden of NRV infections is studied according to 5 main parameters: (1) the frequency of RV in nosocomial infections; (2) the epidemiology and clinical characteristics of NRV infections (describing clinical manifestations and trans-

From *Smart Pharma Consulting, Paris, France; †Cambridge, United Kingdom; the ‡Institute of Pediatrics, Research Centre for Child Health, RAMS, Moscow, Russia; §Hospital Universitario Germans Trias i Pujol and Universidad Autónoma de Barcelona, Barcelona, Spain; the ‖Institute of Child Health, Istanbul, Turkey; the ¶National Institute of Child Health, Budapest, Hungary; the #Department of Pediatrics, University of Padova, Padova, Italy; and **Hôpital d'Enfants Armand Trousseau, Paris, France

Dr Desselberger's current address is the International Centre for Genetic Engineering and Biotechnology, Trieste, Italy.

Address for reprints: Olivier Gleizes, Smart Pharma Consulting, 1, rue Houdart de Lamotte, 75015 Paris, France. Fax 33 1 45 57 46 59; E-mail ogleizes@smart-pharma.com.

ISSN: 0891-3668/06/2501-0012

DOI: 10.1097/01.inf.0000197563.03895.91

mission patterns, risk factors and seasonality, as well as incidence of the infections); (3) the severity of NRV infections (estimating morbidity, mortality and duration of hospitalization, as well as assessing the potential coinfections and complications); (4) the economic burden of NRV infections; and (5) the existing policies against hospital cross-infections (looking at existing surveillance systems and prevention procedures for nosocomial infections in Europe) and their potential effects.

RESULTS

Frequency of RV in Nosocomial Infections

The major burden of nosocomial infections occurs in the adult population, with nonviral infections representing the large majority of all nosocomial infections (85–95% of the total). Urinary tract (80% associated with the presence of a catheter), respiratory tract and surgical site are the predominant sites of infections, whereas gastrointestinal infections are less common.[2–4] The most frequent agents are Gram-positive (eg, *Staphylococcus* spp., *Streptococcus* spp.) and Gram-negative (*Escherichia coli*, *Klebsiella* spp.) bacteria. Fungi (*Candida* spp. and *Aspergillus* spp.) also play a significant role in some settings.[5]

Very few studies have looked at the nosocomial infection rate in the pediatric population. Gastrointestinal and respiratory tract (upper and lower) infections are the 2 most common pediatric nosocomial infection locations, accounting for up to 65–90% of all pediatric hospital-acquired infections (with gastrointestinal infections occurring more frequently than respiratory tract infections).[2,6–8] Viral nosocomial infections are predominant in children, with a rate ranging from 23 to 34%.[6,9,10] Viruses account for 91–94% of all causes of pediatric nosocomial diarrhea, RVs being the single major etiologic agent (31–87% of cases).[6,11–25] However, the role of other viruses (eg, noroviruses, astroviruses and adenoviruses) has been underestimated until recently because of limitations with diagnostic techniques, mainly lack of sensitivity and difficulty in handling.[20,26–29] Specifically noroviruses have been shown to account for 17–46% of causes of nosocomial diarrhea among pediatric population in studies where they have been sought.[9,16]

Epidemiology and Clinical Characteristics of the Nosocomial Infections

Clinical Manifestations of NRV Infections. NRV is generally introduced to pediatric wards after hospitalization of children with CARV and disease, and/or following a stay in the emergency room before hospitalization. NRV infections usually become apparent between the 2nd and the 6th day of hospitalization.[6] Typical symptoms are fever (60–100% of cases), together with acute vomiting and diarrhea.[6,30] RV excretion can begin shortly before the start of clinical symptoms and might be prolonged well after resolution of diarrhea (up to 57 days), although the period of transmissibility is limited to 2 weeks;[31] excretion is longer in immunosuppressed patients.

Asymptomatic infection is frequent in neonates and young infants (younger than 3 months), ranging from 18 to 39% of all NRV cases.[13,17,32–36] Several explanations have been brought forward to explain the limited expression of clinical symptoms in this population, such as specific strains of RV ("nursery strains") or the presence of transitory maternally acquired immunity.

Transmission Patterns. The main transmission mode of NRV is by contact, through a direct or indirect fecal-oral route.[35,37] The infective dose is very small, and RV is excreted in very high amounts in stools of infected children, both elements contributing to the highly contagious nature of RVs.[9,38] Vomiting can be another route of transmission, although rarely documented.[39] Airborne transmission (through respiratory droplets) has been suggested but remains controversial,[40,41] although it could explain, in some instances, the failure to document fecal-oral transmission during outbreaks of RV diarrhea.[42]

The main vectors of transmission are contaminated (mostly uninfected) health care workers; RVs are found on the hands of 76–78% of health care workers taking care of the children with CARV, and also on 20% of health care workers not taking care of children.[11,35,37,43–45] The environment is a key reservoir of RV, with the virus able to survive for a few days on hands and from 1 to 10 days on dry and nonporous surfaces (eg, toys, medical tools) in a low humidity environment (<50%).[43,46,47] The large share of asymptomatic carriage contributes to the spread of RV, given that no precautions are taken in the absence of (typical) symptoms.[36,48]

Risk Factors for NRV Infections. A set of risk factors in otherwise healthy children has been associated with an increased risk of acquiring NRV infection. The first is the duration of hospitalization because the rate of NRV infection can rise to 70% if patients stay hospitalized for >6 days.[30,35,49] Others risk factors are: young age,[16,49] because of age-specific susceptibility to RV infection and the importance of nursing care and diapering;[16] insufficient organization of pediatric services because of insufficient staff; limited respect of hygiene procedures; limited availability of disposable equipment;[9,50,51] and the presence of a nonmedical population (including parents and relatives) on the wards (playing the role of either RV carrier or primary case in nosocomial transmission). Further underlying risk factors for NRV have also been identified: prematurity and low birth weight;[9,52] severe immunodeficiencies; malnutrition; and other diseases (eg, bronchiolitis) associated with a prolonged duration of hospital stay.[49,53–56]

Seasonality of the RV Infections. In Europe, RV infection has been described as highly seasonal, with most CARV and NRV outbreaks occurring during late autumn, winter and early spring (Fig. 1).[6,19,21,30,50,53,57–64] In the United States, the RV epidemic follows a unique progressive wave from South West States towards North East States from winter to spring, with no clear explanation.[65] An unexplained shift of the peak of RV epidemic activity from winter to early spring has been reported in Japan during the last 2 decades.[66] This phenomenon was not observed with respiratory viruses [ie, respiratory syncytial virus (RSV) and influenza] or norovirus infections and has not been reported in other countries.

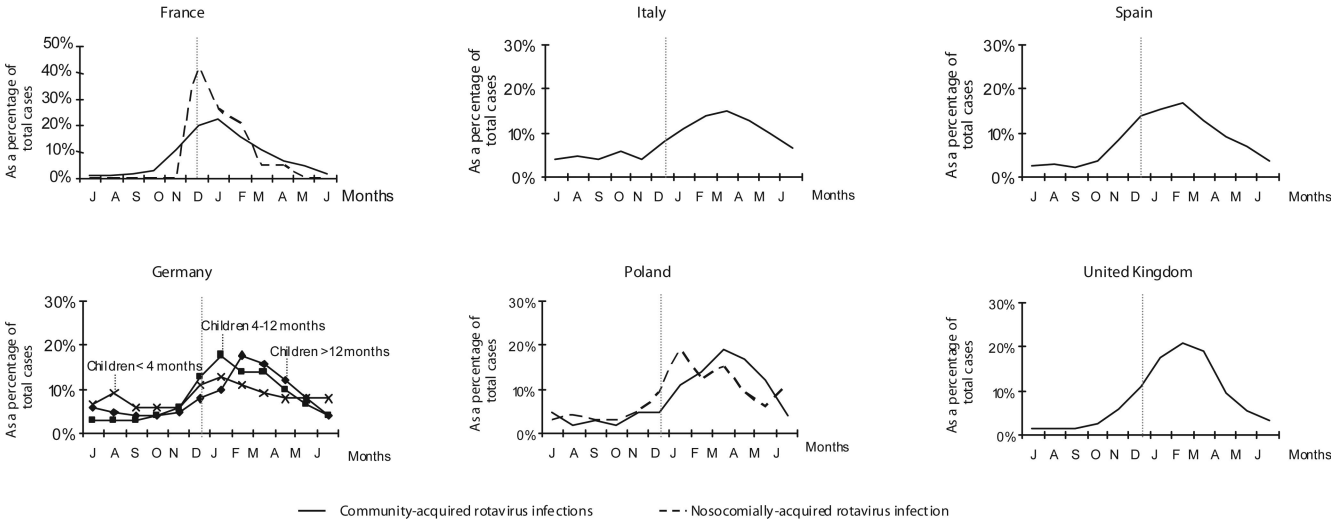

FIGURE 1. Seasonality of rotavirus infections in the 6 largest European countries (rates shown as a percentage of total rotavirus cases).[6,19,21,30,50,53,57–64]

A difference in seasonality from South West (in autumn-early winter) to North and East (late winter-early spring) has been observed in Europe.[67] Data on the seasonality of NRV from France and Poland showed an early nosocomial peak (in December and January, respectively).[19,30] This could be explained by the acquisition of RV infection after hospitalization for RSV or influenza virus infections, both having a coincidental epidemic pattern with RV infection. In a Moscow pediatric infectious disease hospital, seasonality of nosocomial RV cases closely followed that of admissions of the RV infections.[68]

In very young children (younger than 4 months of age), the winter seasonality seems to be less pronounced, with cases of NRV occurring all year round (see pattern for Germany in children younger than 4 months of age in Fig. 1).[58]

Incidence of NRV Infections. Five indicators have been analyzed to measure the incidence of NRV: (1) the number of NRV cases/number of hospitalizations for children; (2) the number of NRV cases/100,000 children; (3) the number of NRV cases/number of community-acquired RV infections followed by hospitalization; (4) the incidence of NRV per 1000 days of hospitalization; and (5) the total number of NRV cases (extrapolated from the incidence per 100,000 children or from the incidence per 1,000 days of hospitalization).

The resulting figures reveal a significant burden of NRV infections in the 6 European countries studied (Table 1), although wide variations were observed.[13,14,19,36,50,51,58,69–77] NRV infections represent 0.3–27.7% of all hospital admissions, have an incidence ranging from 160 to 630 cases/100,000 children younger than 5 years of age, represent 1.6–15.8 per 1000 hospitalization days and account for a yearly estimate of 3000–20,000 RV infection cases in children younger than 5 years of age. However, the reported studies reveal a significant heterogeneity in methodology, which makes the extrapolation of the results from a single study to the entire country difficult, as well as the comparison between countries. Main variations in study parameters are: the size of samples; the nature of selected samples (eg, inclusion of all children admitted, or only children admitted during the day and/or the night) and type of ward (eg, general pediatric, surgical, reanimation); the target age groups (eg, all children younger than 5 years of age or younger than 2 years; or between 3 months and 2 years); the type of study (prospective versus retrospective); the delay before considering a diarrhea/gastroenteritis episode as hospital-acquired (varying from 24 to 72 hours after hospitalization); the recall of families after discharge from hospital to identify additional infections acquired at hospitals but declared at home; the duration of the studies (implemented only during RV epidemics or covering the entire year or several years); the focus on symptomatic cases only or consideration of both symptomatic and asymptomatic infections (or cases with no typical symptoms); the date/age of the study; and the type of hospital contributing to the study (eg, general hospital, pediatric hospital, general hospital with pediatric unit).

In addition, many limitations related to study parameters impact on the significance and comparability of the results and question their robustness (accuracy of reporting and relevance for today's reality). Typical limitations are: small sample size; retrospective studies (instead of prospective) that rely on officially reported figures, and therefore underestimate largely the true rate of nosocomial infections in the absence of systematic detection of RV in cases of diarrhea/gastroenteritis, as well as the absence of a mandatory reporting system in any of the countries studies; the absence of recall of families after discharge from hospital, which leaves aside an additional 10–60% of NRV cases;[13,17,18,28] and the time of publication of studies, older studies being less relevant than more recent ones, given the progress achieved in detection methods and in preventing nosocomial infections. Moreover countries are undergoing major changes in their health care systems, which will probably significantly impact on the incidence of NRV infection and disease. For

TABLE 1. Incidence of Nosocomial Infection and Disease Expressed According to 5 Key Indicators[13,14,19,36,50,51,58,69–77]

Country	Incidence (% of Total Admissions)	Age Group	Incidence/ 100,000 Children	Age Group	Ratio of NRV/CARV Infections Hospitalized	Age Group	Incidence/1000 d of Hospitalization	Age Group	No. of NRV Cases/yr (Estimates)	Age Group
France	2.9–3.7	1 mo–3 yr			0.61	Younger than 16 yr	15.8	Younger than 2 yr	14,134	Younger than 2 yr
	4.3	Younger than 3 yr					9.0	1 mo—younger than 5 yr	15,267	1 mo—younger than 5 yr
	5.3	1 mo—younger than 5 yr					8.1	Younger than 5 yr	20,079	Younger than 5 yr
	6.6	1 mo—younger than 2 yr								
	19.4	3 mo—younger than 3 yr								
Germany	15.1	Children	191	Younger than 5 yr	1.04	Children	2.3	Younger than 4 yr	6933	Younger than 5 yr
							1.6	Younger than 4 yr	10,182	Younger than 4 yr
									7083	Younger than 4 yr
Italy	27.7	Younger than 18 mo								
Poland			198	Younger than 5 yr	0.64	Younger than 5 yr			3613	Younger than 5 yr
			499	Younger than 2 yr					3647	Younger than 2 yr
			630	Younger than 5 yr					11,497	Younger than 5 yr
			1,891	Younger than 2 yr					13,823	Younger than 2 yr
Spain	7.0	Younger than 2 yr	160	Younger than 5 yr	0.96	Younger than 2 yr	13.0	Younger than 2 yr	3030	Younger than 5 yr
United Kingdom	0.3	Younger than 15 yr	333	Younger than 5 yr	0.76	Children			10,796	Younger than 5 yr

instance, France and Germany are reviewing their hospital reimbursing mode, adopting the Diagnostic Related Groups classification system in Germany and the Tarification à l'Activité in France. Under these systems, hospitals will get paid a fixed amount of money to treat a particular disease based on an estimated duration of stay (including the development of potential complications), instead of a payment by day of hospitalization. If hospitalization lasts longer than the estimated duration, the hospital will carry most of the additional costs. It is unclear currently whether NRV infection will be considered as a normal complication/comorbidity (and potentially justifying additional funding for hospitals in cases of NRV disease), but hospitals will have financial incentives to reduce the duration of stay (including the extra length of stay because of hospital-acquired infections).

The management of children with diarrhea has also changed over time and in different countries. Less severe cases are seen more often as outpatients, and hospital admissions have shifted toward more severe cases. As a result, there are less RV disease cases introduced in the wards, thus in theory, reducing the risk of nosocomial spread, although NRV cases might be more severe because patients being infected are more severely ill.

Studies on the incidence of RV infection by age showed that younger age groups are more affected by NRV than CARV infections, with a peak incidence in the 0- to 11-month age group for NRV versus 6–23 months for CARV (Fig. 2).[18,19,36,50,58,60,70,74,77,78] A Spanish study showed that asymptomatic infections were more frequent in infants younger than 6 months and even younger than 3 months of age.[36] In addition to hospital-acquired infections, a significant number of RV infections are transmitted between siblings at home, or within child-care centers.[79] These events should not be underestimated and require more detailed evaluation.

Severity of NRV Infections

RV Morbidity and Mortality. Mortality associated with RV is very low in developed countries,[1,21,81] and no figures are available estimating deaths caused by NRV infections.[1,20,80] As a consequence, considerations relating to the NRV morbidity burden in Europe are focused much more on aspects such as the temporary reduction of the quality of children's lives and the increased direct and indirect costs (eg, increased consumption of medical resources, time loss from work for parents) rather than mortality.

Hospitalization and Rehospitalization. Several studies report increased duration of hospitalization caused by NRV infections from 1.7 to 5.9 days.[13,18,19,36,49,50,69,70,77,81] Despite this general trend, conclusions are hard to draw because most studies gathered samples from different hospitals, in different settings (age group, recall of the families after discharge), and often not matching the characteristics of cases with controls (Table 2).

Only 2 studies were found on rehospitalization in France, which estimate the proportion of nosocomial diarrhea requiring rehospitalization to be between 2 and 13%.[50,75]

NRV Coinfections. There are no specific coinfections reported in association with RV in developed countries. However, additional enteric pathogens coexist in 20–30% of commu-

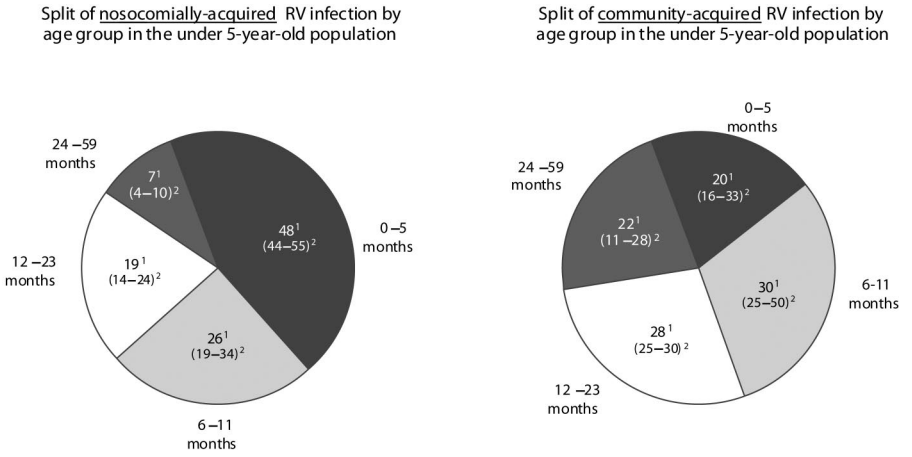

FIGURE 2. Comparison of nosocomially acquired[18,19,36,50,70,77] and community-acquired[19,58,60,74,78] rotavirus incidence by age class. Figures shown as median percentages (1) and range of percentages (2).

nity-acquired gastroenteritis cases where RV is found (norovirus, astrovirus, adenovirus, *Campylobacter jejuni*).[77] Furthermore a strong association between hospitalization for RSV bronchiolitis and NRV infections has been reported in France and Spain.[30,49] However, in these cases, we should speak about concomitant or overlapping infections.

Complications of NRV Infections. Dehydration is the "standard" complication of RV illness,[20] and there are no known complications specifically caused by NRV. Other complications can be split between acute (such as consequences of dehydration, poor tolerance to fever or febrile convulsions, bacterial superinfection) and chronic complications (secondary intolerance to lactose, failure to thrive). There is evidence suggesting that RV infection can lead to convulsions, possibly through the induction of nitric oxide, although this remains to be proved.[82] On the other hand, the increased severity of RV disease that was observed in vitamin A-deficient mice might help to explain the high mortality of RV infections in developing countries.[83]

Economic Burden of NRV Infections

The evaluation of the economic burden of NRV infections must consider the different types of costs as well as the cost drivers involved in nosocomial infection and the valuation of those factors. Costs are defined as quantitative/qualitative, and/or direct/indirect and/or fixed/variable, and different combinations are used by authors depending on the information available.[84–87] The definition of the different types of costs depends also on the perspective, ie, hospital, community or payers' perspective (eg, a community perspective would define missing working days for parents as direct costs, whereas a hospital perspective would consider these costs as indirect).[88,89] The cost drivers considered can be the duration of hospital stay, the additional drug treatments, the ward closures/opening measures and contamination of staff members and the loss of working days for parents and staff (Table 3). The valuation of the cost drivers is achieved using concurrent or comparative methodology. Most studies used comparative methodology, comparing the length of stay and costs of infected patients with those of uninfected patients.[84,85,90,91]

Only a few publications estimated the cost of NRV infections in selected countries. Among them, the cost per NRV case is reported to be as high as 2500 euros per infection (Table 4).[19,50,69,77,92] These figures cover only di-

TABLE 2. Impact of Nosocomial Rotavirus Infections on Duration of Hospitalization by Country

Country	Duration of Hospital Stay (d)		Extra Length of Stay	Selected Study Parameters		Reference
	Hospitalizations With RV	Hospitalizations Without RV		Sample Size*	Age Group	
France	N/A	N/A	+3.3	70	Children	81
	8.9	4.0	+4.9	410	1–24 mo	69
	6.3 (4.3–8.3)[†]	3.6 (2.3–5.9)	+2.7	N/A	Children	49
	8.1 (5.5–10.7)[‡]	3.1 (2.2–4.0)[‡]	+5.0[‡]	108	3 mo–3 yr	50
	8.3 (4.6–12.0)[§]	3.9 (2.3–5.2)[§]	+4.4[§]	5470	Younger than 5 yr	70
	7.7[‖]	4.1[‖]	+3.6[‖]	68	Younger than 3 yr	36
Italy	6.4	4.7	+1.7	220	Younger than 18 mo	13
Poland	N/A	N/A	+5.9	757	Younger than 5 yr	19
Spain	8.5 (2.7–14.3)[‖]	6.7 (2.1–11.3)[‖]	+1.8[‖]	666	Younger than 2 yr	18
United Kingdom	15.0	11.0	+4.0	295	Younger than 15 yr	77

*Total number of children tested.
[†]Numbers in parentheses, range.
[‡]This study compares the duration of hospital stay for nosocomial RV with the duration of hospital stay for community-acquired gastroenteritis.
[§]This study compares the duration of hospital stay for nosocomial diarrhea with the duration of hospital stay without nosocomial diarrhea.
[‖]This study compares the duration of hospital stay for nosocomial gastroenteritis with the duration of hospital stay for community-acquired gastroenteritis.
N/A, not available.

TABLE 3. Cost Drivers Potentially Considered for Nosocomial Rotavirus Infections

	Quantitative	Qualitative
Direct	The major direct cost categories are:	Decline in staff morale
	Additional length of hospital stay	Lower hospital image
	Additional drug consumption	
	Medical interventions	
	Ward closures and contamination of staff members	
	Rehospitalization costs	
	These costs include:	
	Fixed costs: mortgage, hospital overheads, utility bills, salaries, hostelry, etc.	
	Variable costs: treatment, laboratory tests, nurses' salaries in some countries, overtime work, etc.	
Indirect	Relatives' missing working days	Pain and suffering
	Medication and physicians' costs outside hospital	Possible death
	Other indirect (home nursing, private car or other transportation, etc.)	

rect quantitative costs (taking the hospital perspective) and usually using the additional length of stay as the unique cost driver. Even though those costs represent a large share of the total costs,[84,93–96] the studies significantly underestimate the true cost associated with NRV.[97] Moreover only 2 studies matched cases and controls to ensure relevance of results.[69,77]

Comparison of the figures between countries is difficult for several reasons, including differences in health systems[3,19,50,69,84,86,92] and the age and characteristics (such as the severity of the disease requiring hospitalization) of the studied population (eg, nosocomial infections are more frequent in neonatal intensive care units than in general pediatric wards). Thus studies allowing for the calculation of the total cost of NRV at country level are of limited reliability in any of the countries studied.

Existing Policies Against Hospital Cross-infections

Nosocomial Infections Surveillance Systems. Thus far, most studies have been conducted in countries more or less advanced for the reporting of severe nosocomial infections (blood-borne pathogens, antibiotic-resistant bacteria such as methicillin-resistant *Staphylococcus aureus*). However, none of them has structures and procedures in place to monitor and report NRV cases (no mandatory reporting of cases, absence of dedicated International Classification of Disease code). As a result, incidence figures based on national/hospital databases severely underestimate the burden of NRV infections, and little is known in countries where prospective studies are scarce (eg, Italy, Poland, Spain).

Prevention and Treatment of NRV Infections and Their Efficiency. Theoretically prevention of nosocomial infections should be achieved through the implementation of physical

TABLE 4. Cost of Nosocomial Rotavirus Infections by Country

Country	Additional Cost/Nosocomial Episode	Study Parameters						References
		Year	Age Group	Perspective	Cost Drivers	Cost Valuation Method	Costs Included	
France	€+2485	2004	3 mo–3 yr	Hospital	Extra length of stay	Unreported	Average direct costs	50
	€+1974*	2003	Younger than 2 yr	Hospital	Extra length of stay	Comparative matched control	Average direct costs (fixed and variable)	69
Poland†	€+135*	1996 (1993 data)	Younger than 5 yr	Hospital	Extra length of stay	Unreported	Average direct costs	19
United Kingdom (Ireland)	€+1070*	2000	Younger than 15 yr	Hospital	Extra length of stay + additional treatment	Matched control	Average direct costs	77
Austria	€+1539*	2001	Younger than 4 yr	Hospital	Extra length of stay	Comparative	Quantitative direct and indirect costs	
	€+2602*	2001	Younger than 4 yr	Hospital, community and payers	Extra length of stay, indirect costs	Comparative	Quantitative direct and indirect costs	92

*Costs adjusted with inflation. Inflation rate sources: www.europe.eu.int/comm/eurostat.
†This study estimated the cost of a nosocomial rotavirus episode to be much lower than other published results. This could be explained by an estimate of the hospitalization cost of €46/d.

and/or biologic measures. Broad guidelines for physical prevention exist in most countries, but in the absence of formal detailed procedures, it is up to each hospital to decide which measure to implement. These guidelines apply to infection acquired by contact (mostly stools, sometimes vomit), thereby usually excluding airborne transmission, a potential infection route of RV infection. Illustrative guidelines from the Comité Technique National des Infections Nosocomiales in France are: hand washing and/or disinfection after discharge of disposable gloves between patients and activities, with detailed instruction leaflets for each case; glove discharge (changed between patients), eye protection, mask, over clothing; isolation of children with diarrhea (isolation or cohorting, single use medical instruments, etc.); child care given in the patient room, with no interruptions; limitation of "traffic" around patients (short visits, patient transport); handling and disposal of spoiled material and biologic samples.

Appropriate hand washing is the most important and effective measure.[98–104] Specifically the use of alcohol-based hand sanitizers (60–70% ethanol or isopropanol), instead of soap and water, is very effective in reducing the number of viable pathogens on the hands.[98,101–105] A recent study conducted in a U.S. pediatric hospital showed that a vigorous hand washing hygiene program lowered the rate of nosocomial RV infection from 5.9 to 2.2 episodes per 1000 hospitalizations.[106] However, compliance with hand washing protocols continues to be low (20–50%).[99,107–109] Prevention measures are perceived as partially efficient (given the very highly contagious nature of RV) but face numerous barriers to implementation such as lack of staff, high staff turnover, limited respect of hygiene procedures, inadequate hospital infrastructures which prevent patient isolation (lack of single rooms, absence of cohorting) and overcrowding of pediatric wards (patients and parents circulating on the wards). In addition, because fever can be the only symptom of RV infection for 1 or 2 days (before the start of gastrointestinal symptoms), patients can be erroneously categorized as having a serious bacterial infection and placed in general wards without precautions that otherwise would be taken.

Biologic prevention of RV infection can be achieved through breast-feeding, although there are conflicting data concerning its protective role.[110–118] Probiotics (eg, *Lactobacillus GG*) can also have a positive impact on acquisition of infection, although several studies have been published with conflicting results.[119]

No specific drug treatment is available for RV infection. However, several strategies are used for the management of children with RV disease, including oral rehydration solutions which have been shown to be highly effective and at low cost.[78,120,121] Other potential treatments might include drugs like smectite, which seems to reduce the duration of diarrhea (although unpublished data has shown a limited reduction in the duration of diarrhea of 16 hours), but not of vomiting and fever,[122] or racecadotril, proposed as a treatment against all secretory diarrheas;[123] however, the actual usefulness of both drugs is very doubtful. The use of oral immunoglobulin has been proposed for premature infants; however, randomized controlled trial data do not support their routine use.[124] Probiotics are also useful for the treatment of RV-associated diarrhea.[125–127]

DISCUSSION

NRV infections represent a significant epidemiologic and economic problem in most European countries. However, studies are limited and focus on specific populations and cannot be simply extrapolated to reflect the total European situation. Additional large scale, multicentric prospective studies are required to provide a fair and reliable view of the situation at a national level.

Numerous prevention measures exist that have shown variable efficiency in different settings. However, these measures have to be combined and rigorously applied by everyone in hospital wards (health care workers, patients, visitors) to be efficacious. Many barriers to implementation of such prevention policies exist and might explain their global relative usefulness.

The availability of an effective vaccine against RV infection may have a major impact in reducing both community-acquired infections and, as a consequence, NRV infections. At present, no study has been performed to demonstrate the potential efficacy of individual vaccination in preventing acquisition and transmission of NRV infection in hospitalized infants.

Finally, because multiple pathogens are involved in acute and severe diarrhea in infants and children, vaccination should be considered as a major constituent, but not the only one, of the entire prevention measures battery needed against NRV infections.

REFERENCES

1. Parashar UD, Hummelman EG, Bresee JS, Miller MA, Glass RI. Global illness and deaths caused by rotavirus disease in children. *Emerg Infect Dis*. 2003;9:565–572.
2. Lizioli A, Privitera G, Alliata E, et al. Prevalence of nosocomial infections in Italy: result from the Lombardy survey in 2000. *J Hosp Infect*. 2003;54:141–148.
3. Plowman R, Graves N, Griffin MA, et al. The rate and cost of hospital-acquired infections occurring in patients admitted to selected specialties of a district general hospital in England and the national burden imposed. *J Hosp Infect*. 2001;47:198–209.
4. Pittet D, Tarara D, Wenzel RP. Nosocomial bloodstream infection in critically ill patients: excess length of stay, extra costs, and attributable mortality. *JAMA*. 1994;271:1598–1601.
5. Trick W, Fridkin S, Edwards J, Hospitals NNIS. Secular trend of hospital-acquired candidemia among intensive care unit patients in the United States during 1989–1999. *Clin Infect Dis*. 2002;35:627–630.
6. Languepin J, Doit C, Cezard JP, Bingen E, Navarro J. Pediatric nosocomial diarrhea. *Pathol Biol (Paris)*. 2000;48:764–769.
7. Urrea M, Iriondo M, Thio M, et al. A prospective incidence study of nosocomial infections in a neonatal care unit. *Am J Infect Control*. 2003;31:505–507.
8. McLaws ML, Gold J, King K, Irwig LM, Berry G. The prevalence of nosocomial and community-acquired infections in Australian hospitals. *Med J Aust*. 1988;149:582–590.
9. Aho LS, Simon I, Bour JB, et al. Epidemiology of viral nosocomial infections in pediatrics. *Pathol Biol (Paris)*. 2000;48:885–892.
10. Graman PS, Hall CB. Nosocomial viral respiratory infections. *Semin Respir Infect*. 1989;4:253–260.
11. Piednoir E, Cyvoct C, El Riffai R, et al. Epidémiologie nosocomiale à rotavirus en pédiatie au cours de l'été 1997 au CHU de Dijon. *J Pharm Clin*. 1999;18:90–91.
12. Jusot JF, Vanhems P, Benzait F, et al. Reported measures of hygiene and incidence rates for hospital-acquired diarrhea in 31 French pedi-

atric wards: is there any relationship? *Infect Control Hosp Epidemiol*. 2003;24:520–525.
13. Gianino P, Mastretta E, Longo P, et al. Incidence of nosocomial rotavirus infections, symptomatic and asymptomatic, in breast-fed and non-breast-fed infants. *J Hosp Infect*. 2002;50:13–17.
14. Fruhwirth M, Heininger U, Ehlken B, et al. International variation in disease burden of rotavirus gastroenteritis in children with community- and nosocomially acquired infection. *Pediatr Infect Dis J*. 2001;20: 784–791.
15. Hjelt K, Krasilnikoff PA, Grauballe PC, Rasmussen SW. Nosocomial acute gastroenteritis in a paediatric department, with special reference to rotavirus infections. *Acta Paediatr Scand*. 1985;74:89–95.
16. Ford-Jones EL, Mindorff CM, Gold R, Petric M. The incidence of viral-associated diarrhea after admission to a pediatric hospital. *Am J Epidemiol*. 1990;131:711–718.
17. Ringenbergs ML, Davidson GP, Spence J, Morris S. Prospective study of nosocomial rotavirus infection in a paediatric hospital. *Aust Paediatr J*. 1989;25:156–60.
18. Le Roux P, Marshall B, Toutain F, et al. Nosocomial viral infections in a pediatric service: example of rotaviral gastroenteritis and respiratory syncytial viral bronchiolitis. *Arch Pediatr*. 2004;11:908–915.
19. Mrukowicz JZ, Krobicka B, Duplaga M, et al. Epidemiology and impact of rotavirus diarrhoea in Poland. *Acta Paediatr Suppl*. 1999;88: 53–60.
20. Fourquet F, Desenclos JC, Maurage C, Baron S. Acute gastro-enteritis in children in France: estimates of disease burden through national hospital discharge data. *Arch Pediatr*. 2003;10:861–868.
21. Moulin F, Marc E, Lorrot M, et al. Hospitalization for acute community-acquired rotavirus gastroenteritis: a 4-year survey. *Arch Pediatr*. 2002;9:255–261.
22. Oh DY, Gaedicke G, Schreier E. Viral agents of acute gastroenteritis in German children: prevalence and molecular diversity. *J Med Virol*. 2003;71:82–93.
23. McIver CJ, Hansman G, White P, et al. Diagnosis of enteric pathogens in children with gastroenteritis. *Pathology*. 2001;33:353–358.
24. Noone C, Banatvala JE. Hospital acquired rotaviral gastroenteritis in a general paediatric unit. *J Hosp Infect*. 1983;4:297–299.
25. Pacini DL, Brady MT, Budde CT, et al. Nosocomial rotaviral diarrhea: pattern of spread on wards in a children's hospital. *J Med Virol*. 1987;23:359–366.
26. Bassetti M, Topal J, Di Biagio A, et al. The organization of infection control in Italy. *J Hosp Infect*. 2001;48:83–85.
27. Nakata S, Honma S, Numata KK, et al. Members of the family Caliciviridae (Norwalk virus and Sapporo virus) are the most prevalent cause of gastroenteritis outbreaks among infants in Japan. *J Infect Dis*. 2000;181:2029–2032.
28. Grassano Morin A, de Champs C, Lafeuille H, Meyer M. Nosocomial intestinal infections in an infant ward: the importance of phone inquiries of the families. *Arch Pediatr*. 2000;7:1059–1063.
29. Lopman B, Reacher M, Vipond I, et al. Epidemiology and cost of nosocomial gastroenteritis, Avon, England, 2002–2003. *Emerg Infect Dis*. 2004;10:1827–1834.
30. Maille L, Beby-Defaux A, Bourgoin A, et al. Nosocomial infections due to rotavirus and respiratory syncytial virus in pediatric wards: a 2-year study. *Ann Biol Clin (Paris)*. 2000;58:601–606.
31. Richardson S, Grimwood K, Gorrell R, et al. Extended excretion of rotavirus after severe diarrhea in young children. *Lancet*. 1998;351: 1844–1848.
32. Gouyon JB, Guerin MN. Infections nosocomiales virales. In: Aujard Y, ed. *Maladies infectieuses de l'enfant*. Paris: Pradel; 1998:513–520.
33. Guerin MN, Gouyon JB. Les infections nosocomiales neonatales. *Lettre Infectiol*. 1993;16:519–525.
34. Bishop RF, Barnes G, Cipriani E, Lund J. Clinical immunity after neonatal rotavirus infection: a prospective longitudinal study in young children. *N Engl J Med*. 1983;309:72–76.
35. Cone R, Mohan K, Thouless M, Corey L. Nosocomial transmission of rotavirus infection. *Pediatr Infect Dis J*. 1988;7:103–109.
36. Roman Riechmann E, Wilhelmi de Cal I, Cilleruelo Pascual ML, et al. Gastroenteritis aguda nosocomial e infeccion asintomàtica por rotavirus y astrovirus en niños hospitalizados. *An Pediatr (Barc)*. 2004;60: 337–343.
37. Wenzel RP. *Prevention and control of nosocomial infections*. Philadelphia, PA: Lippincott Williams & Wilkins; 2003:354.
38. Ward RL, Bernstein DI, Young EC, et al. Human rotavirus studies in volunteers: determination of infectious dose and serological response to infection. *J Infect Dis*. 1986;154:871–880.
39. Vipond IB. The role of viruses in gastrointestinal disease in the home. *J Infect*. 2001;43:38–41.
40. Caul EO. Small round structured viruses: airborne transmission and hospital control. *Lancet*. 1994;343:1240–1242.
41. Zheng BJ, Chang RX, Ma GZ, et al. Rotavirus infection of the oropharynx and respiratory tract in young children. *J Med Virol*. 1991;34:29–37.
42. Parashar UD, Holman RC, Clarke MJ, Bresee JS, Glass RI. Hospitalizations associated with rotavirus diarrhea in the United States, 1993 through 1995: surveillance based on the new ICD-9-CM rotavirus-specific diagnostic code. *J Infect Dis*. 1998;177:13–17.
43. Ansari SA, Sattar SA, Springthorpe VS, Wells GA, Tostowaryk W. Rotavirus survival on human hands and transfer of infectious virus to animate and nonporous inanimate surfaces. *J Clin Microbiol*. 1988;26: 1513–1518.
44. Keswick BH, Pickering LK, DuPont HL, Woodward WE. Survival and detection of rotaviruses on environmental surfaces in day care centers. *Appl Environ Microbiol*. 1983;46:813–816.
45. Samadi AR, Huq MI, Ahmed QS. Detection of rotavirus in handwashings of attendants of children with diarrhoea. *Br Med J*. 1983;286:188.
46. Hall CB, Douglas RG Jr. Modes of transmission of respiratory syncytial virus. *J Pediatr*. 1981;99:100–103.
47. Wilde J, Van R, Pickering L, Eiden J, Yolken R. Detection of rotaviruses in the day care environment by reverse transcriptase polymerase chain reaction. *J Infect Dis*. 1992;166:507–511.
48. Gendrel D, Bourrillon A. Diarrhées infectieuses. In: Aujard Y, ed. *Maladies infectieuses de l'enfant*. Paris: Pradel; 1998:337–346.
49. Branger B, Vaillant JM, Jehan P, et al. Nosocomial rotavirus infections in pediatrics. *Arch Fr Pediatr*. 1993;50:831–833.
50. Sermet-Gaudelus I, de La Rocque F, Salomon JL, et al. Rotavirus nosocomial infection in pediatric units: a multicentric observation study. *Pathol Biol (Paris)*. 2004;52:4–10.
51. Pina P, Le Huidoux P, Lefflot S, et al. Nosocomial rotavirus infections in a general pediatric ward: epidemiology, molecular typing and risk factors. *Arch Pediatr*. 2000;7:1050–1058.
52. Aujard Y, Rajguru M, Bingen E. Nosocomial infections in pediatrics. Problems and perspectives. *Pathol Biol (Paris)*. 2000;48:909–920.
53. Clark HF, Offit PA, Glass RI, Ward RL. Rotavirus vaccines. In: Plotkin SA, Orenstein WA, eds. *Vaccines.* 4th ed. Philadelphia, PA: W.B. Saunders; 2004:1327–1345.
54. Mullet MD, Cook FE, Gallagher R. Nosocomial sepsis in the neonatal intensive care unite. *J Perinatol*. 1998;18:112–115.
55. Gaynes RP, Martone WJ, Culver DH, et al. Comparison of rates of nosocomial infections in neonatal intensive care units in the United States: National Nosocomial Infections Surveillance System. *Am J Med*. 1991; 91:S192–S196.
56. Wilson CB. Immunologic basis for increased susceptibility of the neonate to infection. *J Pediatr*. 1986;108:1–12.
57. Gendrel D, Basse N, Palmer P, et al. Coincidental outbreaks of rotavirus and respiratory syncytial virus in Paris: a survey from 1993 to 1998. *Arch Pediatr*. 1999;6:735–739.
58. Berner R, Schumacher RF, Hameister S, Forster J. Occurrence and impact of community-acquired and nosocomial rotavirus infections: a hospital-based study over 10 y. *Acta Paediatr Suppl*. 1999;88:48–52.
59. Ruggeri FM, Declich S. Rotavirus infection among children with diarrhoea in Italy. *Acta Paediatr Suppl*. 1999;88:66–71.
60. Cilla G, Perez-Trallero E, Lopez-Lopategui MC, Gilsetas A, Gomariz M. Incidence, seasonality and serotypes of rotavirus in Gipuzkoa (Basque Country), Spain: a 14-year study. *Epidemiol Infect*. 2000;125: 677–683.
61. Rytlewska M, Bako W, Ratajczak B, et al. Epidemiological and clinical characteristics of rotaviral diarrhoea in children from Gdańsk, Gdynia and Sopot. *Med Sci Monit*. 2000;6:117–122.
62. Sobrino Vegas L, Cano Portero R, et al. Infecciones por rotavirus notificadas al Sistema de informacion Microbiologica. Temporada 1999–2000. *Bol Epidemiol Sem*. 1999;7:197–208.

63. Reina J, Hervas J, Ros MJ. Estudio de las caracteristicas clinicas diferenciales entre los pacientes pediatricos con gatroenteritis causadas por rotavirus y adenovirus. *Enferm Infecc Microbiol Clin*. 1994;12: 378–384.
64. Sanchez-Fauquier A, Wilhelmi I, et al. Diversity of group A human rotavirus types circulating over a 4-year period in Madrid, Spain. *J Clin Microbiol.* 2004;1609–1613.
65. Torok TJ, Kilgore PE, Clarke MJ, et al. Visualizing geographic and temporal trends in rotavirus activity in the United States, 1991 to 1996. *Pediatr Infect Dis J*. 1997;16:941–946.
66. Suzuki H, Sakai T, Tanabe N, Okabe N. Peak rotavirus activity shifted from winter to early spring in Japan. *Pediatr Infect Dis J*. 2005;24: 257–260.
67. Koopmans M, Brown D. Seasonality and diversity of group A rotaviruses in Europe. *Acta Paediatr Suppl*. 1999;88:14–19.
68. Bokovoi AG. Nosocomial rotavirus infection among children. *Detskie Infectcii*. 2002;1:28–32.
69. Piednoir E, Bessaci K, Bureau-Chalot F, et al. Economic impact of healthcare-associated rotavirus infection in a paediatric hospital. *J Hosp Infect*. 2003;55:190–195.
70. Thuret A, Patural H, Berthelot P, et al. Prospective follow-up of hospital-acquired diarrhoea in 28 paediatric wards of the south-east part of France during a winter season. *Pathol Biol (Paris)*. 2004;52:131–137.
71. Visser LE, Cano Portero R, Gay NJ, Martinez Navarro JF. Impact of rotavirus disease in Spain: an estimate of hospital admissions due to rotavirus. *Acta Paediatr.* 1999;88(suppl):S72–S76.
72. Rouget F, Chomienne F, Laurens E, Radet C, Seguin G. Evaluation of a prevention program against nosocomial rotavirus infections in a pediatric ward. *Arch Pediatr*. 2000;7:948–954.
73. Ehlken B, Laubereau B, Karmaus W, et al. Prospective population-based study on rotavirus disease in Germany. *Acta Paediatr*. 2002;91: 769–775.
74. Ryan MJ, Ramsay M, Brown D, et al. Hospital admissions attributable to rotavirus infection in England and Wales. *J Infect Dis*. 1996; 174(suppl 1):S12–S18.
75. Branger B. Incidence of nosocomial rotavirus infection in paediatric wards. *Bull Epidemiol Hebd*. 1995;7:28–29.
76. Mrukowicz JZ, Kowalska-Duplaga K, Krobicka B, et al. The epidemiology and disease burden of RV GE in Poland: prospective, sentinel surveillance at 6 pediatric hospitals. Presented at the European Society for Paediatric Gastroenterology, Hepatology and Nutrition Annual Meeting, Prague, 2003. Abstract P028.
77. Harrington M, Butler K, Cafferkey M. Rotavirus infection in hospitalised children: incidence and impact on healthcare resources. *Ir J Med Sci*. 2003;172:33–36.
78. Marie-Cardine A, Gourlain K, Mouterde O, et al. Epidemiology of acute viral gastroenteritis in children hospitalized in Rouen, France. *Clin Infect Dis*. 2002;34:1170–1178.
79. Grimwood K, Abbott GD, Fergusson DM. Spread of rotavirus within families: a community based study. *BMJ*. 1983;287:575–576.
80. Crowley DS, Ryan MJ, Wall PG. Gastroenteritis in children under 5 years of age in England and Wales. *Commun Dis Rep CDR Rev*. 1997;7:R82–R86.
81. Brouard J, Chesnel B, Freymuth F, Duhamel JF. Infections simultanées à virus respiratoires et rotavirus. *Méd Mal Infect*. 1993;106(suppl): S520–S526.
82. Koopmans M. Outbreaks of viral gastroenteritis: what's new in 2004? *Curr Opin Infect Dis*. 2005;18:295–299.
83. Reifen R, Mor A, Nyska A. Vitamin A deficiency aggravates rotavirus infection in CD-1 mice through extensive involvement of the gut. *Int J Vitam Nutr Res*. 2004;74:355–361.
84. Lauria FN, Angeletti C. The impact of nosocomial infections on hospital care costs. *Infection*. 2003;31(suppl 2):S35–S43.
85. Haley RW. Measuring the costs of nosocomial infections: methods for estimating economic burden on the hospital. *Am J Med*. 1991; 91(suppl):S32–S38.
86. O'Brien K, Donato R. Hospital acquired rotavirus infection: the economics of prevention. *Aust Health Rev*. 1993;16:245–267.
87. Hollenbeak CS, Murphy D, Dunagan WC, Fraser VJ. Nonrandom selection and the attributable cost of surgical-site infections. *Infect Control Hosp Epidemiol*. 2002;23:177–182.
88. Carabin H, Gyorkos TW, Soto JC, et al. Estimation of direct and indirect costs because of common infections in toddlers attending day care centers. *Pediatrics*. 1999;103:556–564.
89. Stone PW, Larson E, Kawar LN. A systematic audit of economic evidence linking nosocomial infections and infection control interventions: 1990–2000. *Am J Infect Control*. 2002;30:145–152.
90. Wakefield DS, Pfaller MA, Hammons GT, Massanari RM. Use of the appropriateness evaluation protocol for estimating the incremental costs associated with nosocomial infections. *Med Care*. 1987;25:481–488.
91. Wakefield DS, Pfaller M, Ludke RL, Wenzel RP. Methods for estimating days of hospitalization due to nosocomial infections. *Med Care*. 1992;30:373–376.
92. Fruhwirth M, Berger K, Ehlken B, et al. Economic impact of community- and nosocomially acquired rotavirus. *Pediatr Infect Dis J*. 2001; 20:184–188.
93. Haley RW, Quade D, Freeman HE, Bennett JV, The SENIC Project. Study on the efficacy of nosocomial infection control (SENIC Project): summary of study design. *Am J Epidemiol*. 1980;111:472–485.
94. McGowan JE Jr. Cost and benefit in control of nosocomial infection: methods for analysis. *Rev Infect Dis*. 1981;3:790–797.
95. McGowan JE Jr. Cost and benefit: a critical issue for hospital infection control. Fifth Annual National Foundation for Infectious Diseases Lecture. *Am J Infect Control*. 1982;10:100–108.
96. Freeman J, Rosner BA, McGowan JE Jr. Adverse effects of nosocomial infection. *J Infect Dis*. 1979;140:732–740.
97. Lopman BA, Reacher MH, Vipond IB, et al. Epidemiology and cost of nosocomial gastroenteritis, Avon, England, 2002–2003. *Emerg Infect Dis*. 2004;10:1827–1834.
98. Bloom BT, Craddock A, Delmore PM, et al. Reducing acquired infections in the NICU: observing and implementing meaningful differences in process between high and low acquired infection rate centers. *J Perinatol*. 2003;23:489–492.
99. Jusot JF, Vanhems P, Benzait F, et al. The procedures of hygiene to control hospital-acquired diarrhea in pediatric wards: a multicentre audit. *J Hosp Infect*. 2004;57:44–51.
100. Jarvis WR. Handwashing: the Semmelweis lesson forgotten? *Lancet*. 1994;344:1311–1312.
101. Rotter ML. Hand washing and hand disinfection. In: Mayhall CG, ed. *Hospital Epidemiology and Infection Control*. Baltimore, MD: Williams & Wilkins; 1999:1339–1355.
102. Rotter ML. Alcohols for antisepsis of hands and skin. In: Ascenzi JM, ed. *Handbook of Disinfectants and Antiseptics*. New York, NY: Marcel Dekker; 1996:177–233.
103. Ali Y, Dolan MJ, Fendler EJ, Larson EL. Alcohols. In: Block SS, ed. *Sanitization, Disinfection and Sterilization*. Philadelphia, PA: Lippincott Williams & Wilkins; 2001:229–253.
104. Guilhermetti M, Hernandes SE, Fukushigue Y, Garcia LB, Cardoso CL. Effectiveness of hand-cleansing agents for removing methicillin-resistant *Staphylococcus aureus* from contaminated hands. *Infect Control Hosp Epidemiol*. 2001;22:105–108.
105. McNeil SA, Foster CL, Hedderwick SA, Kauffman CA. Effect of hand cleansing with antimicrobial soap or alcohol-based gel on microbial colonization of artificial fingernails worn by health care workers. *Clin Infect Dis*. 2001;32:367–372.
106. Zerr DM, Allpress AL, Heath J, Bornemann R, Bennett E. Decreasing hospital-associated rotavirus infection: a multidisciplinary hand hygiene campaign in a children's hospital. *Pediatr Infect Dis J*. 2005;24: 397–403.
107. Pittet D, Mourouga P, Perneger TV. Compliance with handwashing in a teaching hospital: Infection Control Program. *Ann Intern Med*. 1999;130:126–130.
108. Meengs MR, Giles BK, Chisholm CD, Cordell WH, Nelson DR. Hand washing frequency in an emergency department. *J Emerg Nurs*. 1994; 20:183–188.
109. Bischoff WE, Reynolds TM, Sessler CN, Edmond MB, Wenzel RP. Handwashing compliance by health care workers: the impact of introducing an accessible, alcohol-based hand antiseptic. *Arch Intern Med*. 2000;160:1017–1021.
110. Weinberg RJ, Tipton G, Klish WJ, Brown MR. Effect of breast-feeding on morbidity in rotavirus gastroenteritis. *Pediatrics*. 1984;74:250–253.

111. Glass RI, Stoll BJ, Wyatt RG, et al. Observations questioning a protective role for breast-feeding in severe rotavirus diarrhea. *Acta Paediatr Scand*. 1986;75:713–718.
112. Duffy LC, Riepenhoff-Talty M, Byers TE, et al. Modulation of rotavirus enteritis during breast-feeding: implications on alterations in the intestinal bacterial flora. *Am J Dis Child*. 1986;140:1164–1168.
113. Gurwith M, Wenman W, Hinde D, Feltham S, Greenberg H. A prospective study of rotavirus infection in infants and young children. *J Infect Dis*. 1981;144:218–224.
114. Berger R, Hadziselimovic F, Just M, Reigel F. Influence of breast milk on nosocomial rotavirus infections in infants. *Infection*. 1984;12:171–174.
115. Cunningham AS. Breast-feeding and health. *J Pediatr*. 1987;110:658–659.
116. Totterdell BM, Chrystie IL, Banatvala JE. Rotavirus infections in a maternity unit. *Arch Dis Child*. 1976;51:924–928.
117. Chrystie IL, Totterdell BM, Banatvala JE. Asymptomatic endemic rotavirus infections in the newborn. *Lancet*. 1978;1:1176–1178.
118. Howie PW, Forsyth JS, Ogston SA, Clark A, Florey CD. Protective effect of breast feeding against infection. *BMJ*. 1990;300:11–16.
119. Szajewska H, Mrukowicz JZ. Use of probiotics in children with acute diarrhea. *Pediatr Drugs*. 2005;7:111–122.
120. Sentongo TA. The use of oral rehydration solutions in children and adults. *Curr Gastroenterol Rep*. 2004;6:307–313.
121. Desselberger U. Rotavirus infections: guidelines for treatment and prevention. *Drugs*. 1999;58:447–452.
122. Guarino A, Bisceglia M, Castellucci G, et al. Italian Society of Pediatric Gastroenterology and Hepatology Study Group for Smectite in Acute Diarrhea. Smectite in the treatment of acute diarrhea: a nationwide randomized controlled study of the Italian Society of Pediatric Gastroenterology and Hepatology. *Pediatr Gastroenterol Nutr*. 2001;32:71–75.
123. Salazar-Lindo E, Santisteban-Ponce J, et al. Racecadotril in the treatment of acute watery diarrhea in children. *N Engl J Med*. 2000;343:463–467.
124. Mohan P, Haque K. Oral immunoglobulin for the prevention of rotavirus infection in low birth weight infants. *Cochrane Database Syst Rev.* 2003;CD003740.
125. Isolauri E, Juntunen M, Rautanen T, Sillanaukee P, Koivula T. A human *Lactobacillus* strain (*Lactobacillus casei* strain GG) promotes recovery from acute diarrhea in children. *Pediatrics*. 1991;88:90–97.
126. Pant AR, Graham SM, Allen SJ, et al. *Lactobacillus* GG and acute *Lactobacillus* GG and acute diarrhoea in young children in the tropics. *J Trop Pediatr*. 1996;42:162–165.
127. Guarino A, Canani RB, Spagnuolo MI, Albano F, Di Benedetto L. Oral bacterial therapy reduces the duration of symptoms and of viral excretion in children with mild diarrhea. *J Pediatr Gastroenterol Nutr*. 1997;25:516–519.