

Rising Vancomycin-Resistant Enterococcus Infections in Hospitalized Children in the United States

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OBJECTIVE: Vancomycin-resistant *Enterococcus* (VRE) is an emerging drug-resistant organism responsible for increasing numbers of nosocomial infections in adults. Few data are available on the epidemiology and impact of VRE infections in children. We hypothesized a significant increase in VRE infections among hospitalized children. Additionally, we predicted that VRE infection would be associated with certain comorbid conditions and increased duration and cost of hospitalization.

METHODS: A retrospective study of inpatient pediatric patients was performed using data on hospitalizations for VRE from the Healthcare Cost and Utilization Project Kids' Inpatient Database from 1997 to 2012. We used a multivariable logistic regression model to establish factors associated with VRE infection and a high-dimensional propensity score match to evaluate death, length of stay, and cost of hospitalization.

RESULTS: Hospitalizations for VRE infection showed an increasing trend, from 53 hospitalizations per million in 1997 to 120 in 2012 ($P < .001$). Conditions associated with VRE included *Clostridium difficile* infection and other diagnoses involving immunosuppression and significant antibiotic and health care exposure. Patients with VRE infection had a significantly longer length of stay (attributable difference [AD] 2.1 days, $P < .001$) and higher hospitalization costs (AD \$8233, $P = .004$). VRE infection was not associated with an increased risk of death (odds ratio 1.03; 95% confidence interval 0.73–1.47).

CONCLUSIONS: VRE infections among hospitalized children are increasing at a substantial rate. This study demonstrates the significant impact of VRE on the health of pediatric patients and highlights the importance of strict adherence to existing infection control policies and VRE surveillance in certain high-risk pediatric populations.

ABSTRACT

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Enterococci are gram-positive organisms that are natural colonizers of human and animal gastrointestinal tracts. These bacteria are relatively nonvirulent and before 1970 were only rare causes of severe infection.¹ Vancomycin-resistant *Enterococcus* (VRE) was first reported in 1987 in Europe, where it established a reservoir in healthy humans and animals but remained an uncommon cause of nosocomial infection.^{2,3} In contrast, over the next decade in the United States, it rapidly emerged as a source of hospital-acquired infection among critically ill patients and in units with high rates of antibiotic use.⁴ The incidence of adult VRE infections in US hospitals has more than doubled in recent years, from 9820 cases per year in 2000 to 21 352 in 2006.⁵

Enterococci are tolerant to chlorine, heat, and some alcohol preparations and can survive for long periods on environmental surfaces, which aids in their nosocomial transmission.⁶ An additional challenge to treating infections with these organisms is their intrinsic resistance to several classes of antimicrobial agents, including cephalosporins and aminoglycosides, and their ability to accumulate additional resistance genes through plasmid transfer.⁷ It is the accumulation of the *van* genes, which code for enzymes that alter the vancomycin binding target on the bacterial cell wall, that allows enterococci to become resistant to vancomycin.⁸ VRE now make up ~30% of all enterococcal infections, >90% of which are *Enterococcus faecium*.⁹ We know from studies in adults that nosocomial spread of VRE is not benign. A study of 300 adult patients with enterococcal bacteremia revealed that those with VRE bacteremia had significantly higher proportions of clinical failure and all-cause mortality than those with vancomycin-susceptible *Enterococcus* bacteremia.¹⁰

Although the rise in incidence of VRE infection in adults is well described, there is a paucity of data on the epidemiology and impact of this infection in children. In one small pediatric study, 24% of those admitted to the hematology/oncology unit had asymptomatic carriage of VRE, highlighting the significant risk of VRE transmission among certain groups of

hospitalized children.¹¹ Using a large national database of hospitalizations in children, we sought to evaluate the scope and trend of VRE infections in children, the conditions associated with VRE infections, and the impact of VRE infections on hospitalized pediatric patients. Based on the recent rise of VRE infections in adult populations, we hypothesized a significant increase in VRE infections among hospitalized children. Additionally, we predicted that VRE infection would be associated with certain comorbid conditions and procedures involving prolonged hospitalization, immune suppression, and broad-spectrum antibiotic exposure. Finally, we hypothesized that children with VRE infection would have longer and more costly hospitalizations and higher mortality.

METHODS

Data Source

Data on hospitalizations in children and adolescents ≤ 18 years old with VRE infection were obtained from the triennial Healthcare Cost and Utilization Project Kids' Inpatient Database (HCUP-KID), sponsored by the Agency for Healthcare Research and Quality. The HCUP-KID database is made up of a stratified random sample of inpatient discharges during the 6 time periods used in our study: 1997, 2000, 2003, 2006, 2009, and 2012. The database includes discharge data from 22 to 44 states (depending on the year), and for 2012, it represented an estimated 95.6% of all pediatric hospitalizations in the United States.¹² Each database record represents a hospital discharge and, for years 1997 to 2006, includes ≤ 15 *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnostic codes and ≤ 15 current procedural terminology codes. For 2009 and after, it was expanded to include ≤ 25 diagnostic codes. Based on the scope of its representation, HCUP-KID assigns an individual-level population weight that allows for an estimation of national case rates and trends.¹²

Variable Definition

We selected cases by searching the HCUP-KID database for the ICD-9-CM code V09.8.

This code is devoted to infections with microorganisms resistant to specified drugs and includes vancomycin-intermediate *Staphylococcus aureus* (VISA), vancomycin-resistant *Staphylococcus aureus*, and VRE. VISA cases in adults are extremely rare, with an estimated US prevalence of 0.3% of all *S. aureus* isolates, and there are no reports of VISA or vancomycin-resistant *S. aureus* cases in children, thus leaving this code to primarily represent VRE infections.¹³⁻¹⁶ This code has been used to identify VRE infections in other studies.^{5,17} To minimize misclassification bias and to identify hospitalizations with VRE infection as opposed to hospitalizations in which VRE colonization was identified during screening programs, subjects must have had the diagnosis code V09.8 without the concurrent HCUP Clinical Classifications Software (CCS) code 1.5, which represents immunizations and screening for infectious disease. HCUP CCS is a health services research tool provided by the Agency for Healthcare Research and Quality for grouping ICD-9-CM diagnosis and procedure codes into clinically meaningful categories.¹⁸ We used the multilevel CCS diagnoses and procedure codes, which allow for expansion or compression to more or less specific categorization.

Available demographic data include gender, race, age, payer type, geographic region, and geographic location (rural versus urban) of the hospital. Race was grouped into white, black, Hispanic, and other, based on race classification provided in the HCUP-KID. Payer type was grouped into private insurance, public insurance, and uninsured. The hospital region was designated Northeast, Midwest, South, or West.

To evaluate associated conditions, HCUP CCS was used to classify the ICD-9-CM diagnostic codes and procedure codes into clinically meaningful categories. The third specificity level CCS diagnostic and procedure categories in patients with VRE infection were ranked in order of frequency. The most common 70% of both diagnostic and procedure CCS codes were selected for further analysis and corresponded to any code occurring at a frequency of ≥ 10 times.

Diagnoses and procedures occurring less frequently were not believed to be clinically significant risk factors for disease. A logistic regression model was then generated to determine the association of these comorbid conditions with VRE infection. Two modifications to the CCS were made. First, the ICD-9-CM code V09.8 for VRE was removed from the CCS code 1.1, which represents "bacterial infection." Second, the ICD-9-CM code 008.45 for *Clostridium difficile* infection (CDI) was removed from the CCS code 9.1 for "intestinal infection" and evaluated individually, because of our interest in evaluating the relationship between this pathogen and VRE infection.

The outcomes used to determine the impact of VRE infection included death, length of hospital stay (LOS), and hospitalization costs. Estimated costs using cost-to-charge ratios were available only for years 2003, 2006, 2009, and 2012. Therefore, the evaluation of hospitalization costs were calculated by using only those years. The outcome of death was defined as subject death during the recorded hospitalization. LOS was evaluated as the number of days hospitalized. Costs were adjusted to June 2015 dollars using the US Consumer Price Index for inpatient hospital services.¹⁹ The study was approved by our institutional review board. All patient data were deidentified.

Data Analysis

Continuous data were summarized as mean values with SDs, and categorical data were presented as frequencies and percentages. When data were not normally distributed, they were summarized as median values with an interquartile range. The χ^2 test and *t* test were used to conduct comparisons between groups. The rate of VRE infections was calculated with the total number of pediatric hospitalizations as the denominator. Analysis for trend during the 6 periods of our study was completed using the Cochran–Armitage test for trend. All summary descriptive results and logistic regression modeling used population weights, provided by HCUP-KID, to produce national estimates and appropriate standard errors for significance testing.

To evaluate the conditions associated with VRE infection among pediatric inpatients, a

multivariable logistic regression was fitted with the presence or absence of VRE as the dichotomous outcome variable. Backward selection was used to fit a model including significant second-level-specificity CCS categories, demographic variables (age, gender, race, hospital region, urban versus rural hospital location, and payer type) and calendar year. $P < .05$ was the threshold for retention during the backward selection process. To evaluate the outcomes of death, LOS, charges, and costs, a case-control match was performed. To account for unobservable confounders such as comorbid diseases and procedures, which are likely to be associated with both VRE infection and the hospitalization outcomes being evaluated, we generated high-dimensional propensity scores by logistic regression analysis.²⁰ This method has previously been used in evaluating disease outcomes for other hospital-acquired infections.^{21–23} VRE infection was the dependent variable, and demographic variables, hospital/geographic variables, and 389 of the most common comorbid diagnostic and procedure CCS codes, as discussed previously, were the independent variables in the model. Patients with an indication of VRE infection (cases) were matched by high-dimensional propensity score, using a greedy matching algorithm, to patients who did not have VRE (controls), with a 1-to-5 matching ratio.²⁴ This algorithm matched cases to 5 control subjects who had the closest propensity score, thus providing the most similar possible match based on all demographic, diagnostic, and procedure categories used for generation of the propensity score.

Balance after matching was assessed by visually inspecting the distribution of propensity scores as well as evaluating standardized difference for all comorbid and diagnostic variables used in the generation of the propensity score.^{25,26} Any standardized difference <0.1 is generally accepted as denoting negligible imbalance between cases and controls.²⁷ The standardized difference of the propensity scores as a collective measurement of the match balance improved from 0.4502 before the match to 0.0056 after the match.

Conditional logistic regression was used to evaluate the effect of VRE infection on the

likelihood of the categorical variable (death). Odds ratios (ORs) and 95% confidence intervals (CIs) are provided to identify the strength and significance of VRE infection. To estimate and compare the effects of the continuous variables cost and LOS between VRE and their matched controls, we used a generalized linear mixed model. A γ distribution was used to model cost, whereas LOS was modeled using a negative binomial distribution.^{22,28} The VRE indicator was used as a fixed effect along with other covariates such as age, gender, race/ethnicity, insurance, year, and propensity score (to account for variability across the matched cohorts). The matching of case and controls was taken into account by introducing a random effect for the matching identifier. Least-squares estimates and 95% CIs were obtained from the fitted models. Outcome analyses, including postmatch standardized difference calculation, did not include weights, as cases were directly compared with controls. SAS 9.3 (SAS Institute, Cary, North Carolina) was used for all statistical analysis.

RESULTS

The total weighted number of pediatric inpatients discharged during the 6 years of our study was 39 509 060. Of these, 3356 (0.008%) were identified as having VRE infection. Demographic data are summarized in Table 1. The median (SD) age of hospitalized children with VRE infection was 6.66 (6.47) years, compared with 3.13 (5.38) in those without VRE ($P < .001$). There were significant differences between these 2 groups in race/ethnicity ($P < .001$), hospital location ($P < .001$), and payer type ($P < .001$). There was a substantial and significant rise in the national trend of VRE infections in hospitalized children over the 6 time periods we analyzed (Fig 1) ($P < .001$), especially between 2003 and 2009.

The CCS code 1.1, representing bacterial infection (excluding VRE), was the CCS code most highly associated with VRE infection (Table 2). Of these infections, methicillin-sensitive *S. aureus*, group D *Streptococcus* (an older classification of *Enterococcus spp.*), *Escherichia coli*, methicillin-resistant *S. aureus*, and *Pseudomonas* were the most frequently encountered. Other highly

TABLE 1 Descriptive Profile of Patients 0 to 18 Years of Age With and Without VRE Infection

Characteristic	Indication of VRE on Hospital Discharge File	
	VRE	No VRE
Discharges, total	3356 (0.008)	39 505 704 (99.992)
Mean age in years (SD) ^a	6.66 (6.47)	3.13 (5.38)
Gender ^b		
Female	1699 (50.7)	19 597 617 (49.8)
Male	1656 (49.3)	19 717 485 (50.2)
Race/ethnicity ^{a,b}		
White	1423 (50.0)	16 709 584 (55.5)
Black	448 (15.7)	4 865 956 (16.2)
Hispanic	791 (27.8)	6 666 177 (22.1)
Other	184 (6.5)	1 879 256 (6.2)
Geographic region ^a		
Northeast	511 (15.2)	6 968 229 (17.6)
Midwest	694 (20.8)	8 638 395 (21.9)
South	1055 (31.4)	14 686 559 (37.2)
West	1095 (32.6)	9 212 521 (23.3)
Metropolitan statistical area ^{a,b}		
Rural	167 (5.2)	4 935 773 (12.7)
Urban	3039 (94.8)	33 972 884 (87.3)
Insurance ^{a,b}		
Private	1318 (39.4)	19 379 652 (49.2)
Public	1728 (51.6)	16 879 839 (42.8)
Uninsured	300 (9.0)	3 145 222 (8.0)

Data are presented as *n* (%) unless noted otherwise.

^a Across all variable categories, there is a significant difference between patients with VRE and those without VRE ($P < .0001$).

^b Missing values are the reason numbers across categories within variables do not sum to total number of discharges. Categorical percentages are based on the number of patients reported in the database.

associated comorbid diagnoses and procedures included malignancies, invasive procedures and surgeries (such as nephrotomy and nephrostomy), and diseases that involve immune suppression

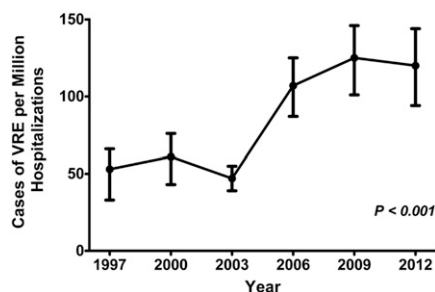


FIGURE 1 Trend in the national estimate of VRE infection in hospitalized children ages 0 to 18 years. Outer lines represent upper and lower 95% CIs. Significance was tested using the Cochrane–Armitage test of trend.

and antibiotic exposure, notably cystic fibrosis, immunity disorders, bone marrow transplant, and CDI (Table 2).

VRE infection had a significant impact on the burden of hospitalization. There were 1995 individual children with a VRE infection successfully matched to 9975 similar controls using the propensity score match system described. Using multivariable conditional logistic regression on this 1:5 case-control matched set, children with VRE had an attributable difference of 2.1 more days ($P < .001$) for LOS and \$8233 ($P = .004$) greater hospitalization costs than children without VRE (Table 3). VRE infection was not associated with an increased risk of death, however. There were 41 (2.1%) patients with VRE who died during their hospitalization compared with 189 (1.9%) matched controls (OR 1.03; 95% CI 0.73–1.47).

DISCUSSION

Our study identified a substantial rise in the hospitalization rate of VRE infection among pediatric patients over the past decade, paralleling the rise seen in hospitalized adult populations.¹⁷ Additionally, VRE infection was associated with several comorbid diagnoses and procedures that can be broadly grouped into conditions involving immune suppression and extensive health care and antibiotic exposure. VRE infection was associated with increased duration and cost of hospitalization.

Compared with children without VRE, those hospitalized with VRE infections were significantly older and more likely to be Hispanic, to be living in the West, to be hospitalized in urban hospitals, and to have public health care insurance (Table 1). This differs from the results of other studies of VRE epidemiology, which identify the Northeast as having the most VRE hospitalizations in all age groups.^{17,29} These geographic differences in VRE prevalence could be related to strain variation or hospital-unique antibiotic prescribing practices and infection control procedures. The association of VRE with public insurance payer type may be related to longer hospital stays or may be a true health care disparity.³⁰

The cause of this increase in VRE infection may be a combination of the same factors seen in adults, including an increasing number of critically ill and immunosuppressed at-risk patients, selective pressure from broad-spectrum antibiotics, and increased nosocomial transmission due to breaches in infection control practices. Both cephalosporins and vancomycin have been shown to select for intestinal carriage of VRE.^{31,32} We know from Bolon et al³³ that more than a third of initial courses of vancomycin are inappropriate, which has led to a push for institutional antimicrobial stewardship programs to help regulate the use of vancomycin and other broad-spectrum antibiotics. Evidence of rising VRE infections among hospitalized children further highlights the importance of appropriate stewardship of these drugs.

In recent years, both the use of oral vancomycin in pediatric patients with CDI

TABLE 2 Comorbid Clinical Diagnoses and Procedure Classifications (CCS codes) Most Highly Associated With VRE Infection

Condition or Procedure	Adjusted OR (95% CI)
Bacterial infection (excluding VRE)	21.39 (19.33–23.61)
CDI	6.16 (4.37–8.68)
Cystic fibrosis	5.31 (4.47–6.30)
Neoplasms	2.89 (2.59–3.23)
Diseases of the urinary system	2.21 (2.03–2.41)
Intestinal infection (excluding CDI)	1.99 (1.62–2.45)
Spinal cord injury	1.99 (1.35–2.93)
Other infections, including parasitic	1.84 (1.44–2.35)
Immunity disorders	1.82 (1.44–2.32)
Nephrotomy and nephrostomy	3.00 (1.78–5.06)
Other therapeutic ear procedures	2.86 (1.77–4.65)
Destruction of lesion of retina and choroid	2.68 (1.45–4.94)
Microscopic examination (bacterial smear, culture, toxicology)	2.33 (1.23–4.39)
Bone marrow transplant	2.10 (1.68–2.62)

Diagnostic and procedural ICD-9-CM codes were grouped into clinically relevant categories using CCS. CCS codes have multiple levels, allowing for increasing or decreasing specificity in diagnoses and procedures. For this analysis, we used second-level CCS codes.

The CCS category most highly associated with VRE in our study was the presence of bacterial infections other than VRE. Children being treated for comorbid infections were 21 times more likely to have a diagnosis of VRE, which could represent increased exposure to antibiotics in especially vulnerable hosts. Additionally, *Enterococcus* infections (including VRE) in both adults and pediatric patients are frequently described as occurring in the presence of cocolonizing pathogens or as part of polymicrobial infections, which is consistent with the findings of our study.^{42–44} Other comorbid conditions highly associated with VRE infection include malignancies, diseases of the urinary system, and intestinal infections. The procedures most strongly associated with VRE infection were nephrotomy and nephrostomy. Involvement of the gastrointestinal tract and genitourinary tract is significant, as these are sites of *Enterococcus* colonization and serve as potential portals of entry for invasive VRE infections. Many of these highly associated conditions, such as cystic fibrosis, involve broad-spectrum antibiotic exposure, which can provide selection pressure for the development of VRE colonization. Conditions involving immune suppression, including bone marrow transplantation, place children at risk for invasive VRE infection. Children with many of these comorbid conditions and procedures spend a significant amount of time in the hospital, increasing their chance of becoming colonized with VRE through nosocomial spread. These identified risk factors are consistent with those identified in studies of both adult and pediatric patients, which include previous invasive procedures and surgery, recent exposure to antibiotics, immunosuppressive status, and presence of indwelling devices.^{45,46} In addition to the rise in hospitalizations for VRE, we also showed that VRE infection

and the overall numbers of children with CDI have been rising.^{23,34} Our study showed that patients hospitalized with CDI were 6 times as likely to have VRE infection as those without CDI. There have been reports of this association in adults, including one in a small group of VRE-colonized patients with leukemia, which identified CDI as a risk factor for developing VRE bacteremia.³⁵ To our knowledge, this is the first report of an association between VRE infection and CDI in pediatric patients. This correlation could be due to increased use of oral vancomycin in children with CDI, providing selection pressure for VRE colonization, or may simply be a reflection of broad-spectrum antibiotic use as a risk factor for the development of both conditions.

VRE outbreaks have been well described as resulting from cross-contamination through lapses in infection control practices and high colonization pressure, with contaminated equipment and health care

workers' hands being the most common modes of transmission.^{36–38} In a study of VRE bloodstream infections (BSIs) in children, 36% were proven through pulse-field electrophoresis to have resulted from nosocomial spread, and both individual and aggregate vancomycin use was not associated with VRE BSI, indicating that nosocomial spread is the largest driving force for VRE infections in children.³⁹ The significant rise in hospitalizations for VRE infection in children observed in our study is worrisome and highlights the importance of strict adherence to infection control policies. Guidelines for hospital infection control, including the prevention of VRE transmission, are available from the Health Care Infection Control Practices Advisory Committee.⁴⁰ Use of such guidelines, along with provider education, was shown to interrupt VRE transmission in an outbreak setting among pediatric oncology patients.⁴¹

TABLE 3 Estimated LOS and Costs Attributable to VRE Infection

Item	VRE	No VRE	Attributable Difference	Ratio	P value
Length of stay, d	14.3 d (14.1–14.6)	12.2 d (12.0–12.4)	2.1	1.18	<.001
Costs for years 2003–2012, \$	51 020 (43 463–59 891)	42 787 (37 797–48 434)	8233	1.19	.004

Length of stay and costs values represent least-squared estimate means (CIs).

had a significant impact on the burden of hospitalizations in pediatric patients. Children with VRE had longer hospital stays and higher hospitalization costs than patients without VRE. This clarifies a financial incentive for preventing VRE nosocomial transmission. VRE infection, however, was not associated with a greater likelihood of death. This is in contrast to the increased mortality reported among adults with VRE BSI.^{10,47} This difference in VRE outcomes may be because our study evaluated all VRE infections, including less invasive infections of the urinary tract and skin and soft tissue infections. However, a study comparing 39 children with VRE BSI to 339 with vancomycin-susceptible *Enterococcus* BSI also found no statistically significant difference in mortality between groups.⁴⁵

One limitation of this study was the use of administrative data for the case definition of VRE infection, which is prone to misclassification bias. Although other studies have used this ICD-9-CM code to represent VRE disease, in some cases it could represent asymptomatic colonization identified through targeted screening. To minimize this bias, we excluded cases containing a code for the screening of infectious diseases. In addition, lacking clinical information, we could not confirm the cause of hospitalization, source (BSI, urinary tract infection), timing of VRE infection (hospital vs community acquired), species of VRE (*E. faecium* vs *E. faecalis*), additional antibiotic susceptibilities, other medical treatments given, or long-term outcomes. Finally, because the HCUP-KID database only reports hospital discharges, some of the VRE cases could represent patients readmitted with the same diagnosis.

Our study also has major strengths. This large database is representative of the entire US pediatric hospitalized population, allowing us to report what is to date the largest study of VRE in children. We acknowledge that these cases are not culture-confirmed; however, we believe our data represent the general trend of VRE infections among hospitalized children. Beyond the rising trend of VRE cases, the use of a high-dimensional propensity score

attempted to control for confounding and burden of disease associated with both VRE and our outcome measures, providing an accurate estimation of the impact of this infection.

CONCLUSIONS

This study, the first to describe the large-scale epidemiology of VRE in US children, revealed a marked rise in the trend of this challenging infection among hospitalized pediatric patients over the last decade. The comorbid conditions identified here are helpful in highlighting the patient populations most at risk for VRE infection and support targeted surveillance programs already in place in many transplant and oncology units. Finally, we demonstrated that VRE is associated with increased costs and longer duration of pediatric hospitalization, which implies that efforts to limit its spread would both benefit individual patients and provide cost savings. We can only speculate as to the reasons for the increase of VRE in children, but regardless of the cause, the results underscore the importance of efforts to curb the spread of this pathogen.

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The Bear in the Grey Pajamas

One by one, they file in. They stand around our crib in different shapes and poses. I can see all of their faces from where I'm set. I smile at everyone and watch as they look at him. Their eyes dart around his face – first noticing the long, thin bulge under the right side of his scalp then his flickering gaze. Their tired smiles grow weary and some look away. The others keep staring. Sooner or later they gaze up from their papers and they look at him again. This time their smiles are strained and forced; smiles already made somber by the look of things. Their sadness makes me sad. If my smile weren't stitched on, mine would probably be sad too. Because I know where this is headed... I've heard them talk when the boy sleeps. But still they file in. And still they try to smile. Those same sad smiles. Then it happens. There's a real smile. Maybe at how little his feet are or how he flails his arms above his head. As soon as he sees it, he smiles back. The happiest smile that could only exist without ever knowing sadness. And their smiles become real.

*Signed,
The Bear in the Gray Pajamas*

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Rising Vancomycin-Resistant Enterococcus Infections in Hospitalized Children in the United States

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