

SUSTAINED PROTECTION FROM PENTAVALENT ROTAVIRUS VACCINATION DURING THE SECOND YEAR OF LIFE AT A LARGE, URBAN UNITED STATES PEDIATRIC HOSPITAL

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Abstract: Fecal specimens from children presenting to Texas Children's Hospital with acute gastroenteritis were tested for the presence of rotavirus. Children were grouped according to vaccination status, and pentavalent rotavirus vaccine effectiveness was calculated. Pentavalent rotavirus vaccine effectiveness against severe rotavirus gastroenteritis was sustained during the first 2 years of the vaccination program. Overall 3-dose effectiveness was 83% to 86%; it was 92% to 93% among children 6 to 11 months of age and 78% to 84% among children ≥ 12 months of age.

Key Words: diarrhea, rotavirus, rotavirus vaccine, vaccine effectiveness

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Before the introduction of pentavalent rotavirus vaccine (RV5) in the US immunization schedule in 2006, rotavirus gastroenteritis occurred in almost every US child by the age of 5 years, leading to more than 400,000 outpatient visits, 200,000 emergency department visits, and 50,000 hospitalizations each year.^{1–4} A large precensure study of RV5 demonstrated 98% efficacy against severe rotavirus gastroenteritis.⁵ In 2008, a monovalent rotavirus vaccine (RV1) was introduced in the United States that had also demonstrated high (85%–100%) efficacy against severe rotavirus gastroenteritis.⁶

We previously reported results of a postlicensure case-control assessment of RV5 effectiveness at Texas Children's Hospital during the 2007–2008 rotavirus season, in which approximately half the cases were caused by G3P[8] strains. In that study, a full 3-dose series of RV5 conferred 85% to 89% protection against severe rotavirus gastroenteritis, similar to the efficacy seen in precensure trials.⁷ In addition, national laboratory surveillance data demonstrated that during the 2 years following RV5 introduction (2007–2008 and 2008–2009), the onset of rotavirus disease across the United States was delayed and the disease burden was considerably diminished in magnitude compared with prevaccine years.⁸

Although these data are encouraging, continued monitoring of the effectiveness of RV5 vaccination is important to better assess the duration of protection following vaccination in infancy

and to assess effectiveness against a range of circulating rotavirus wildtype strains. In the present study, we report the findings of a second year assessment of RV5 effectiveness conducted at Texas Children's Hospital during the 2008–2009 rotavirus season.

METHODS

Patient Enrollment. A case-control assessment was conducted between February and June 2008 and March to June 2009 at Texas Children's Hospital. As described previously, children age-eligible to have received RV5 (15 days–23 months of age in 2008 and 15 days–35 months of age in 2009) with symptoms of acute gastroenteritis (AGE; ≥ 1 episode of vomiting and/or ≥ 3 loose stools) were offered participation and consented for enrollment.⁷ Fecal specimens were collected and tested for the presence of rotavirus using a commercial enzyme immunoassay (Premier Rotaclone, Meridian Bioscience, Inc, Cincinnati, OH). Case patients were children with AGE who tested positive for rotavirus. Information regarding symptoms and disease severity was collected through parent interview. Control patients were children in the same age range as case patients with symptoms of acute respiratory infection (ARI) and children with AGE who tested negative for rotavirus. Children who were immunocompromised, who did not reside in Texas, or whose parent/guardian did not speak either English or Spanish were ineligible to participate. ARI control patients with diarrhea in the preceding 24 hours were excluded. Immunization records for enrolled patients were collected as available from the child's immunization card, the child's medical providers, and the Texas Immunization Information System, ImmTrac.

Strain characterization of rotavirus-positive specimens was conducted at the Centers for Disease Control and Prevention using previously described reverse transcription-polymerase chain reaction and nucleotide sequencing methods.^{9–14}

Statistical Analysis. To assess the effectiveness of RV5 against laboratory confirmed rotavirus gastroenteritis resulting in hospitalization or emergency department (ED) care, unconditional logistic regression controlling for age at presentation, month and year of birth, and season of presentation was used to calculate an adjusted odds ratio. A dose of vaccine was counted if it had been administered ≥ 14 days before presentation. Case and control patients for whom an immunization record could not be obtained or who had received RV1 were excluded from analysis. Vaccine effectiveness was calculated as $(1 - \text{adjusted odds ratio of 3 doses of vaccine [vs. no doses]}) \times 100$. The vaccine effectiveness analyses were restricted to children who were age-eligible to have received 3 doses of RV5 (≥ 6 months of age). To assess duration of protection, age at presentation was dichotomized into 2 categories (6–11 months vs. ≥ 12 months). Analyses were performed using SAS statistical software (version 9.2).

Bias Indicator. To examine the possibility of bias because of health seeking behavior, socioeconomic status, or other factors in the receipt of vaccine, RV5 effectiveness against hospitalizations and ED visits for nonrotavirus gastroenteritis was assessed using the ARI controls. A lack of an association between vaccination and nonrotavirus gastroenteritis would suggest absence of major bias.

Ethical Approval. The Institutional Review Boards at Baylor College of Medicine and Texas Department of State Health Services approved this surveillance assessment.

RESULTS

A total of 686 (400 during the 2007–2008 season and 286 during the 2008–2009 season) eligible children with AGE were enrolled during both surveillance periods. Fecal specimens were collected and tested for 386 (56%) of these patients (205 during the

2007–2008 season and 181 during the 2008–2009 season). Of the 386 specimens collected, 128 (33%) tested positive for rotavirus (90 [44%] of 205 during the 2007–2008 season and 38 [21%] of 181 during the 2008–2009 season). During the same period, 467 ARI control patients were enrolled: 228 during 2007–2008 and 239 during 2008–2009. Vaccination records were available for 117 (91%) rotavirus-positive case patients, 444 (95%) ARI control patients, and 248 (96%) rotavirus-negative AGE control patients. Four ARI control patients were excluded from analysis as they had received doses of RV1. Among rotavirus-positive case patients, 79% had received no doses of RV5, compared with 38% of ARI control patients and 37% of rotavirus-negative AGE control patients, whereas 12% of rotavirus-positive case patients had received 3 doses of RV5, compared with 28% of ARI control patients and 36% of rotavirus-negative AGE control patients.

During the 2008–2009 surveillance season, effectiveness of a full 3-dose series of RV5 was 80% (95% confidence interval [CI]: 45%, 93%), 80% (95% CI: 47%, 92%), and 78% (95% CI: 47%, 91%) using rotavirus-negative AGE control patients, ARI control patients, and both control groups combined, respectively (Table 1). Vaccine effectiveness during 2008–2009 was comparable with but slightly lower than effectiveness during the 2007–2008 season. Combining data from both surveillance periods, effectiveness of a full 3-dose series of RV5 was 83% (95% CI: 66%, 91%), 86% (95% CI: 72%, 93%), and 84% (95% CI: 70%, 92%) using rotavirus-negative AGE control patients, ARI control patients, and both control groups combined, respectively. When examining effectiveness by age, a full 3-dose RV5 series was 93% (95% CI: 69%, 98%) and 92% (95% CI: 62%, 98%) effective for children 6 to 11 months of age using rotavirus-negative AGE and ARI control patients, respectively. Among children ≥ 12 months of age, a full series of RV5 was 78% (95% CI: 51%, 90%) and 84% (95% CI: 64%, 93%) effective for each control group.

The bias assessment found that RV5 did not protect against nonrotavirus AGE (vaccine effectiveness: 15%, [95% CI: –35%, 47%]).

Of the 38 rotavirus-positive case patients enrolled during the 2008–2009 season, 33 (87%) had G3P[8] infections, 3 (8%) had G9P[8] infections, 1 (2.5%) had a G2P[4] infection, and 1 (2.5%) had a mixed infection (G1,G4P[8]).

DISCUSSION

Although RV5 effectiveness was extensively studied in the preclicensure trial conducted in Europe and the United States,⁵ its effectiveness during routine clinical use has not been well assessed in the immediate years following vaccine implementation. This study extends our previous analyses demonstrating high effectiveness of RV5 in the first year of life,⁷ and the results showed that the protection conferred by vaccination is sustained during the second year of life. These findings of sustained protection in older children are encouraging because nearly 60% of all childhood hospitalizations from rotavirus in US children before RV5 implementation occurred in children aged 1 to 4 years.² G3P[8] infections predominated during both surveillance seasons (50% in 2007–2008 and 87% in 2008–2009), and our data reaffirm that RV5 protects well against this rotavirus strain. This finding is reassuring given that seroconversion rates to G3 strains were low in the clinical trials and G3 has been emerging as a predominately circulating strain in the United States.^{5,15}

The sustained protection from RV5 during the first 2 years of life is consistent with the high efficacy observed in children up to 2 years of age in preclicensure trials of RV5 conducted in Europe and the United States. In contrast, in Nicaragua, the only low income country to adopt routine immunization with RV5 to date, vaccine effectiveness appeared to be lower in the second year of life compared with the first year (32% vs. 69%, respectively).¹⁶ This difference may be attributable, in part, to a more robust immune response to vaccination among children in industrialized countries who are less likely to experience impoverished conditions, malnutrition, or possible enteric coinfections than children in low income settings.¹⁷ Data from trials of RV5 in developing countries of Africa and Asia will soon be available, and will likely further provide information on this issue.

TABLE 1. Three-dose* Vaccine Effectiveness (VE) Against Rotavirus Disease by Control Group, Year of Surveillance, and Age at Presentation

2008	Rotavirus Positive n = 67 (%)	Rotavirus Negative AGE Controls		ARI Controls		Rotavirus Negative AGE and ARI Controls Combined	
		n = 70 (%)	VE [†] (95% CI)	n = 102 (%)	VE [†] (95% CI)	n = 172 (%)	VE [†] (95% CI)
Unvaccinated [‡]	62 (93)	38 (54)	Referent	58 (57)	Referent	96 (56)	Referent
3 doses [§]	5 (7)	32 (46)	90% (70%–96%)	44 (43)	89% (65%–96%)	76 (44)	90% (72%–96%)
2009	n = 31 (%)	n = 83 (%)	VE [†] (95% CI)	n = 123 (%)	VE [†] (95% CI)	n = 206 (%)	VE [†] (95% CI)
Unvaccinated [‡]	22 (71)	26 (31)	Referent	43 (35)	Referent	69 (33)	Referent
3 doses [§]	9 (29)	57 (69)	80% (45%–93%)	80 (65)	80% (47%–92%)	137 (67)	78% (47%–91%)
2008 + 2009	n = 98 (%)	n = 153 (%)	VE [‡] (95% CI)	n = 225 (%)	VE [‡] (95% CI)	n = 378 (%)	VE [‡] (95% CI)
Unvaccinated [‡]	84 (86)	64 (42)	Referent	101 (45)	Referent	165 (44)	Referent
3 doses [§]	14 (14)	89 (58)	83% (66%–91%)	124 (55)	86% (72%–93%)	213 (56)	84% (70%–92%)
6 to <12 mo	3 (3)	46 (30)	93% (69%–98%)	48 (21)	92% (62%–98%)	94 (25)	92% (70%–98%)
≥ 12 mo**	11 (11)	43 (28)	78% (51%–90%)	76 (34)	84% (64%–93%)	119 (31)	81% (61%–91%)

*Number of doses recorded on the child's immunization card, provider record, or vaccination registry record.

[†]Adjusted for age at presentation and month/year of birth for age-eligible (≥ 6 months) children.

[‡]Restricted to children age-eligible (≥ 6 months) to receive 3 doses of RV5.

[§]Protection conferred against rotavirus diarrhea by 3 doses of RV5 ≥ 14 days after vaccine receipt for age-eligible (≥ 6 months) children.

^{||}Adjusted for age at presentation, month/year of birth, and rotavirus season for age-eligible (≥ 6 months) children.

^{||}Protection conferred against rotavirus diarrhea by 3 doses of RV5 ≥ 14 days after vaccine receipt for children 6 to <12 months of age at presentation.

**Protection conferred against rotavirus diarrhea by 3 doses of RV5 ≥ 14 days after vaccine receipt for children ≥ 12 months of age at presentation.

This study has some limitations. As specimen collection only occurred while patients were in the ED or hospitalized, children for whom a specimen was collected likely had more severe disease than those for whom a specimen was not collected. Thus, it is likely that our findings describe RV5 effectiveness among children with symptoms of more severe rotavirus gastroenteritis. In addition, we were unable to obtain immunization records for 9% of case patients, 6% of ARI control patients, and 4% of rotavirus-negative AGE control patients. Although this may have affected our results, vaccine effectiveness estimates were similar across all control groups. As this was a single site study, our findings may not be generalizable to other populations in the United States. Additionally, because of limited uptake and administration of RV1 in our population during the 2 surveillance periods, our findings apply only to RV5 and not RV1 or a combination of these vaccines.

CONCLUSIONS

These data support previous findings of the effectiveness of RV5 as administered in US clinical practice and demonstrate sustained protection from vaccination during the first 2 years of life. Additional studies are needed to examine the long-term effectiveness and extent of protection conferred by RV5 and RV1 given alone or in combination in infancy.

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BURDEN OF DISEASE AND BARRIERS TO THE DIAGNOSIS AND TREATMENT OF GROUP A BETA-HEMOLYTIC STREPTOCOCCAL PHARYNGITIS FOR THE PREVENTION OF RHEUMATIC HEART DISEASE IN DAR ES SALAAM, TANZANIA

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Abstract: To understand patient and clinician attitudes toward *Streptococcus* pharyngitis and rheumatic heart disease prevention in Tanzania, data from 3 sources were obtained: a survey of 119 clinicians, outpatient rapid test screening, and interviews with 17 rheumatic heart disease patients. Patients do not seek care for sore throat. Clinicians stated that identifying and treating *Streptococcus* pharyngitis is not prioritized.

Key Words: rheumatic heart disease, rheumatic fever, Tanzania, *Streptococcus*, rapid test

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Rheumatic heart disease (RHD) and other preventable sequelae of Group A *Streptococcus* (GAS) infection continue to burden developing countries, Tanzania among them.¹ Worldwide, 1 in 5 children develops at least 1 episode of GAS per year, leading to approximately 500,000 annual deaths due to GAS sequelae.^{1,2} Primary prevention of RHD by treating GAS pharyngitis with penicillin may be possible and cost-effective in resource-poor settings.^{3,4}

Although the prevalence of RHD in Tanzania is unknown, there is a high RHD patient load at the national referral hospital, Muhimbili National Hospital (MNH). In a country with only 822 physicians for a population of 42 million,⁵ there are potentially several reasons for the high rates of untreated GAS. Children may be treated at home without antibiotics, may be misdiagnosed in clinics, or treated without adequate antibiotics. Most hospitals and clinics in the public system do not have any means to test for GAS pharyngitis. This study aimed to assess the following: (1) practice patterns and barriers to diagnosing and treating GAS among clinicians, RHD patients, and their families; and (2) the burden of untreated GAS among 3 clinics in the Dar es Salaam municipality.

METHODS

Subjects were recruited in the Dar es Salaam region. The investigational approach used 3 data sources: (1) survey of clini-

cians, (2) measurement of GAS pharyngitis presentation rates among children aged 3 to 15 at public primary care facilities, and (3) interviews with patients or parents of patients with RHD aged 3 to 29 years.

Clinician Survey. The goal of the clinician survey was to assess current practices and barriers to care for patients with GAS pharyngitis. The survey was administered to a cross-sectional sample of 119 physicians, medical students, nurses, and clinical and medical officers practicing in public hospitals and health centers in Dar es Salaam, Tanzania, April–August 2008 in English after obtaining informed consent.

The clinician survey included a Barrier and Opportunities Scale, Demographic and Practice Questionnaire, Diffusion of Innovations Survey, and an Intention to Use Scale.⁶ The Barriers and Opportunities Scale addressed perceived barriers for the patient and clinic, personal practice, and the priorities of Ministry of Health. Treatment and prescribing patterns for GAS pharyngitis were explored, although specific dosage was not evaluated. Injected penicillin was not explored specifically. The Demographic and Practice Questionnaire examined access to journals, leadership, clinician type, age and gender, and was used previously in Muhimbili-Harvard collaborations.⁷ The Diffusion of Innovations Survey and Intention to Use Scale data were not used for this article.

Assessment of GAS Among Patients Attending 3 Clinics in Dar es Salaam. All children aged 3 to 15 presenting to 3 typical public primary care clinics were screened for the Centor Criteria for GAS pharyngitis of sore throat, fever at presentation ($\geq 38^{\circ}\text{C}$), and throat changes consistent with GAS pharyngitis (redness, hyperemia, edema, exudates, or punctuate hemorrhages of the soft palate).⁸ The parent of the child meeting these criteria was informed of the study. After consent, a modified version of the Muhimbili University College of Health Sciences-Harvard University sociodemographic survey was completed in Swahili, and the rapid test was performed. The modified questionnaire includes 5 items assessing perceived barriers and 5 items assessing opportunities to remove barriers to accessing diagnostic and medical treatment. All patients tested were compensated Tsh 3000 (equivalent 2.25 USD). Outpatient children were screened at 3 public clinics in the municipality for a total of 64 clinic hours during the months of July and August 2008. The measurement of GAS pharyngitis presentation rates was completed with a lateral flow immunoassay rapid test produced and donated by ACON Labs Inc (San Diego, CA), which uses a swab sample from the patient's oropharynx to produce a dichotomous result (sensitivity, 91%; specificity, 94%).

RHD Patient/Guardian Interviews. Interviews were performed with inpatients, outpatients, and parents of patients with RHD in August 2008 at MNH. The RHD patient/parent interviews and consent were administered in Swahili. The sociodemographic survey used in the GAS monitoring was used. Participants were asked to describe what health care services they access, if any, for a child with a sore throat or a sore throat and a fever.

These procedures were approved by the MNH and Harvard School of Public Health Institutional Review Boards.

RESULTS

A total of 280 children were screened for the inclusion criteria for GAS rapid testing. About 119 clinicians completed the survey. Of them, 36% were physicians, 36% were assistant medical officers/clinical officers, 22% were medical students, 14% were registered nurses, and 3% were listed as "other." Seventeen RHD patient/parent interviews were performed. Patients included

8 females and 9 males, with an age range of 3 to 29 years with a median age of 11. Patients were from various parts of Tanzania, including 4 from the Dar es Salaam region. Triangulating data from these sources identified the following major barriers to the diagnosis and treatment of GAS pharyngitis.

Patients Do Not Present for Care for Sore Throat. During GAS screening, only 2 children of 280 met the inclusion criteria. Both children had negative rapid tests. RHD patients and their parents uniformly stated that they would not normally take a child with a sore throat with or without fever to a professional health care provider for diagnosis and treatment. Most clinicians (61%) disagreed or strongly disagreed that parents and families are able to travel to a clinic for a GAS diagnostic evaluation. One clinician cited the "failure of children with pharyngitis to attend clinic" as a major barrier to RHD prevention.

Lack of Patient Knowledge. The majority of clinicians (87%) disagreed or strongly disagreed that patients and their families are knowledgeable about the consequences of untreated GAS infection. In interviews with RHD patients and their parents, subjects had poor knowledge of the signs/symptoms of GAS pharyngitis and the connection between GAS pharyngitis and RHD. RHD respondents reported treating sore throat alone with nothing, honey, or paracetamol. Many would additionally seek an antimalarial from a duka la dawa (pharmacy) when fever was present. Three participants would treat a sore throat with antibiotics. Ten participants typically finished a prescribed antibiotic course even if the child feels better while 7 stopped once the child improves. Thirteen of the RHD subjects did not know what had caused the RHD.

Lack of Prioritization of GAS Screening and Treatment. Clinicians use clinical signs and symptoms to diagnose GAS pharyngitis. No other testing for GAS was available at the clinics visited. Only 38% of clinicians said that their clinic prioritizes the diagnosis and treatment of GAS infection. Clinicians were conflicted over whether the Ministry of Health would see screening patients for GAS infection as interfering with other priorities including HIV and malaria. Of clinicians, 75% believed that screening patients at their clinic for GAS would not interfere with their work on other health priorities.

DISCUSSION

This study demonstrates that clinicians see RHD and GAS as major public health concerns and that barriers to care include lack of patient awareness and nonprioritization of testing and treatment. Patients do not present to major clinics in Dar es Salaam for GAS pharyngitis and have limited understanding of the link between GAS pharyngitis and its serious sequelae. They are likely to treat with home remedies, antibiotics obtained at duka la dawa, or antimalarials because fever equated malaria for many participants.

Because of the high morbidity and mortality associated with untreated RHD and the high cost and morbidity of surgical interventions, prevention is critical.^{4,9} Further patient education and public health campaigns regarding the risks of untreated GAS pharyngitis may be necessary, if a national RHD prevention program is undertaken. In the words of one clinician, "There is need to involve the community so that they understand the issue and possible consequences." In addition to patient education, further diagnostic tools may be useful. Clinicians are confident in recognizing GAS pharyngitis but they acknowledge the limitations of using clinical signs and symptoms alone for diagnosis.

This study is limited by its geographic scope. Data collection was limited to 3 typical primary care clinics in Dar es Salaam, an urban setting, and therefore may not be generalizable to other parts of Tanzania or East Africa. Additionally, little is known

about the seasonal variation of GAS pharyngitis in Tanzania, an area which would benefit from further research. Data from clinicians and patients were self-reported. This study is limited to a pediatric population. There is debate as to how much any single intervention—such as treatment of GAS pharyngitis, secondary prophylaxis, or community-wide interventions—effects rheumatic fever and RHD incidence.^{10–12}

GAS pharyngitis and RHD have a critical place in developing countries' health systems, touching on patient education and primary care and requiring costly interventions if not prevented. When vertical programs for diseases such as HIV are preferred, GAS pharyngitis and other primary care-based diseases may be lost if primary care and public health systems are not strengthened. The continued burden of RHD demonstrates a clear need for primary care and surgical options in low-income countries to restore the health of children and adults with this life-threatening illness.

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WHOLE BLOOD INTERFERON- γ RELEASE ASSAY IS A USEFUL TOOL FOR THE DIAGNOSIS OF TUBERCULOSIS INFECTION PARTICULARLY AMONG BACILLE CALMETTE GUÉRIN-VACCINATED CHILDREN

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Abstract: The performance of QuantiFERON-tuberculosis (TB) Gold-In-Tube assay was compared with the tuberculin skin test for the diagnosis of TB among children. It was shown that among non-Bacille Calmette Guérin immunized children, agreement between tests was excellent both in those with TB disease and in TB contacts. Among Bacille Calmette Guérin-immunized children, agreement was fair in those with active disease and poor among TB contacts. It is concluded that QuantiFERON-TB Gold-In-Tube compares with the tuberculin skin test in the diagnosis of TB disease and latent tuberculosis infection in TB contacts among children and has enhanced specificity.

Key Words: quantiferon, interferon gamma release assay, tuberculosis, children, diagnosis

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The identification of *Mycobacterium tuberculosis*-specific antigens has led to the development of new commercial immunodiagnostic tests that are able to distinguish the production of interferon γ in response to *M. tuberculosis* infection from that induced by either the Bacille Calmette Guérin (BCG) vaccine or environmental mycobacteria.¹ Although numerous studies have evaluated these new interferon γ release assays (IGRAs) among adults, such studies are limited among children.^{2–8} The aim of this cross-sectional study was to evaluate and compare the performance of the QuantiFERON-tuberculosis (TB) Gold In-Tube (QFT-IT) assay (Cellestis Limited, Carnegie, Victoria, Australia) and the tuberculin skin test (TST) among children with active TB or possible latent TB infection (LTBI) in a low endemicity setting.

MATERIALS AND METHODS

The study population consisted of all children at risk for TB infection referred to our Tuberculosis clinic between January 1, 2007 and December 31, 2008. The study protocol was approved by the Ethics Committee of the “P. & A. Kyriakou” Children’s Hospital and informed consent was requested from all study participants’ legal guardians.

The source population consisted of 295 children and adolescents aged ≤ 15 years. All patients underwent clinical evaluation and were tested with the TST and QFT-IT. The QFT-IT assay

could not be undertaken in 4 (1.4%) eligible participants due to refusal ($n = 2$), lost specimen ($n = 1$), and sample processing delay ($n = 1$). Among the remaining eligible population, complete assessment was achieved for 286 (98.3%) children.

Study participants were categorized as follows: (1) children with confirmed, probable, or possible active TB; (2) children with a history of contact with an adult infectious case; and (3) other children at high risk for LTBI. Active TB was defined according to the CDC criteria.⁹ In all patients with confirmed disease *M. tuberculosis* was isolated in cultures. The diagnosis of possible TB was based on a positive TST and clinical criteria.⁹ Those who additionally had a positive contact history were considered to have probable TB regardless of TST results. LTBI was diagnosed according to published criteria.¹⁰ Participants with a positive contact history were further categorized as having (1) household contact; (2) nonhousehold regular contact; and (3) nonhousehold occasional only contact. Other high-risk children were those referred to our clinic due to either their origin from a high TB prevalence country, or TST positive finding in a first degree relative.

The TST was applied and interpreted according to published guidelines by the same member of the TB Clinic staff who was blinded to the patient's history.¹⁰ The purified protein derivative (PPD) RT 23 (Statens Serum Institut, Copenhagen, Denmark) was used. The TST cutoff was ≥ 10 mm for BCG immunized children. For non-BCG immunized children, TST cut-offs were (1) active disease or positive contact history: ≥ 5 mm; and (2) other high-risk children: ≥ 10 mm.¹⁰ In a number of children in the high risk group, the TST was performed at a TB screening community center and they were referred to our TB Clinic for evaluation. The QFT-IT was undertaken according to manufacturer's instruc-

tions.¹¹ Values >10 IU/mL were treated as 10 IU/mL in all analyses.

Statistical analyses were undertaken with SAS version 9.0 (SAS Institute Inc., Cary, NC). A P value of ≤ 0.05 was considered as significant. Continuous variables were compared with the student t test and categorical variables with the chi-square test. Kappa (κ) agreement analyses were used to assess agreement between TST and QFT-IT among each patient group, stratified according to prior BCG immunization. Indeterminate QFT-IT assay results were excluded from all analyses. Multivariate logistic regression was used to model TST and QFT-IT outcomes, where independent variables included prior BCG immunization, age, and origin from a TB endemic country.

RESULTS

Among the study population ($n = 286$), 37 (12.9%) participants were diagnosed with active TB, 99 (34.6%) reported recent contact with an adult TB case, and 150 (52.4%) were at high risk for TB infection (Table, Supplemental Digital Content 1, <http://links.lww.com/INF/A535>). The QFT-IT assay mean ($\pm$ SD) quantitative value among children with active disease (7.32 ± 3.37 IU/mL) was higher than those with LTBI due to recent contact (6.80 ± 3.25 IU/mL, $P < 0.0001$) or those with other risk factors (6.71 ± 7.59 IU/mL, $P < 0.0001$). Mean QFT-IT values did not differ significantly between younger (<5 years) and older (≥ 5 years) children overall or within each patient subgroup (data not shown). The median ages of children with positive (7.4 ± 4.2 years) and indeterminate QFT-IT result (5.5 ± 4.3 years) did not differ significantly ($P = 0.69$).

TABLE 1. Concordance Between TST and QFT-IT Tests (%) and Kappa Coefficients (κ) Among Children in Different Patient Groups

Patient Category	QFT-IT			Concordance* %	κ^* (SE)
	Positive N (%)	Negative N (%)	Indeterminate N (%)		
Active TB ($n = 37$)					
TST positive [†]	30 (81.1)	3 (8.1)	2 (5.4)	88.2 (30/34)	NC
TST negative	1 (2.7)	0 (0.0)	1 (2.7)		
Confirmed ($n = 13$)				90.9 (10/11)	NC
TST positive	10 (76.9)	0 (0.0)	1 (7.7)		
TST negative	1 (7.7)	0 (0.0)	1 (7.7)		
Probable ($n = 12$)				91.7 (10/11)	NC
TST positive	11 (91.7)	1 (8.3)	0 (0.0)		
TST negative	0 (0.0)	0 (0.0)	0 (0.0)		
Possible ($n = 12$)				81.8 (9/11)	NC
TST positive	9 (75.0)	2 (16.7)	1 (8.3)		
TST negative	0 (0.0)	0 (0.0)	0 (0.0)		
Contact with an adult TB case ($n = 99$)				71.6 (68/95)	0.46 (0.08)
TST positive	29 (29.3)	24 (24.2)	2 (2.0)		
TST negative	3 (3.0)	39 (39.4)	2 (2.0)		
Household contact ($n = 60$)				82.4 (47/57)	0.65 (0.10)
TST positive	20 (33.3)	8 (13.3)	2 (3.3)		
TST negative	2 (3.3)	27 (45.0)	1 (1.7)		
Non-household regular contact ($n = 28$)				59.2 (16/27)	0.27 (0.14)
TST positive	8 (28.6)	10 (35.7)	0 (0.0)		
TST negative	1 (3.6)	8 (28.6)	1 (3.6)		
Non-household occasional contact ($n = 11$)				45.4 (5/11)	0.11 (0.11)
TST positive	1 (9.1)	6 (54.5)	0 (0.0)		
TST negative	0 (0.0)	4 (36.4)	0 (0.0)		
Other children at high risk for TB infection ($n = 150$)				50.0 (74/148)	0.10 (0.05)
TST positive	58 (38.7)	70 (46.7)	2 (1.3)		
TST negative	4 (2.7)	16 (10.7)	0 (0.0)		

*Indeterminate results were excluded from the assessment of agreement.

[†]TST cut offs as defined in the Methods section.

NC indicates not computable; SE, standard error; TST, tuberculin skin test; QFT-IT, Quantiferon-TB Gold In-Tube; TB, tuberculosis.

TABLE 2. Concordance Between TST and QFT-IT Tests (%) and Kappa Coefficients (κ) Among Children According to Prior BCG Immunization

Patient Category*	BCG Immunized Children		Non-BCG Immunized Children	
	Concordance %	κ (SE)	Concordance %	κ (SE)
Active TB (n = 34)	62.5 (5/8)	NC	100.0 (26/26)	1.00 (—)
Confirmed (n = 11)	100.0 (1/1)	1.00 (—)	100.0 (10/10)	1.00 (—)
Probable (n = 12)	50.0 (1/2)	NC	100.0 (10/10)	1.00 (—)
Possible (n = 11)	60.0 (3/5)	NC	100.0 (6/6)	1.00 (—)
Contact with an adult TB case (n = 95)	46.5 (20/43)	0.13 (0.06)	96.2 (50/52)	0.91 (0.06)
Household contact (n = 57)	60.0 (12/20)	0.28 (0.14)	100.0 (37/37)	1.00 (0.00)
Nonhousehold regular contact (n = 27)	44.4 (8/18)	0.07 (0.07)	88.9 (8/9)	0.61 (0.34)
Nonhousehold irregular contact (n = 11)	0.0 (0/5)	NC	83.3 (5/6)	0.57 (0.35)
Other at high risk for TB infection (n = 148)	33.7 (29/86)	0.02 (0.04)	72.6 (45/62)	0.34 (0.11)

*Participants with QFT-IT indeterminate results were not included in the assessment of agreement (concordance and kappa statistic) between TST and QFT-IT tests. NC indicates not computable; SE, standard error; TST, tuberculin skin test; QFT-IT, QuantiFERON-TB Gold In-Tube; TB, tuberculosis; BCG, Bacille Calmette Guérin.

Among children with active disease (n = 37) the agreement between TST and QFT-IT was 88.2% (Table 1). While the concordance between tests was 100.0% among non-BCG immunized children, it was limited to 62.5% among BCG immunized children (Fig., Supplemental Digital Content 2, <http://links.lww.com/INF/A536>). Among children with confirmed TB, TST was positive in 11 (84.6%) and negative in 2 (15.4%) patients who presented with meningitis (QFT-IT positive) and miliary TB (QFT-IT indeterminate). The concordance between tests among this patient group was 90.9%. Furthermore, among children with probable or possible disease, agreement between tests was excellent among non-BCG immunized children. However, concordance was limited to 60.0% among BCG immunized children with possible TB (Table 2).

Among children with a positive contact history (n = 99) the overall concordance between TST and QFT-IT was 71.6%, and the agreement between tests was moderate (Table 1). A discrepancy between test agreements was observed according to patients' history of BCG immunization (Fig., Supplemental Digital Content 2, <http://links.lww.com/INF/A536>), since among non-BCG immunized patients agreement was excellent, while among BCG immunized children it was fair to poor (Table 2). Agreement was highest among children with regular household contact, while moderate among those with infrequent contact.

Among children at high risk for TB infection but with no known exposure to an adult case (n = 150), agreement between TST and QFT-IT was poor (Table 1). Moreover, agreement between tests was fair even among non-BCG immunized children (Table 2).

Multivariate regression analysis showed that prior BCG immunization was the single predictor of TST outcome (adjusted odds ratio [AOR]: 20.34; 95% confidence interval [CI]: 5.60–73.89). In contrast, parents' place of birth in a high risk country (AOR: 3.32; 95% CI: 1.07–10.35), children's age (AOR: 1.14; 95% CI: 1.00–1.29), and prior BCG immunization (AOR: 0.19; 95% CI: 0.06–0.60) were significantly associated with QFT-IT outcome.

DISCUSSION

A considerable number of patients with active TB as well as with TB contact were included in this study and were stratified according to the differential risk of TB infection and BCG immunization history. It was shown that the agreement between TST and QFT-IT was excellent among non-BCG immunized children with the highest risk of TB infection and discordant results were most frequent among BCG immunized participants, particularly among those with the least likelihood of infection.

A positive result was obtained with QFT-IT in 83.8% of patients with active disease and when the 2 tests were combined, a higher percentage of patients with confirmed TB disease were identified than with each test alone. These findings concur with those indicating that the sensitivity of IGRAs among children with bacteriologically confirmed disease may range between 80% and 93% and is lower among cases with probable or possible disease.^{2–4,7,8} Highly concordant results between tests were obtained among non-BCG immunized children, whereas discordant results were observed among BCG immunized patients. These findings suggest that the performance of the 2 tests in TB disease is comparable but QFT-IT is more specific.

Among participants with a positive contact history, QFT-IT positivity rates were highest in children with the most frequent and proximal contact. Agreement between tests was excellent among non-BCG immunized children with the most proximal exposure. Similar results have been reported in previous studies wherein contact investigation was performed with the IGRAs and in school outbreaks.^{5,12} Hence, the QFT-IT may be particularly useful for the evaluation of recently exposed BCG immunized children.

Among children at high risk for TB infection but with negative exposure history, agreement between QFT-IT and TST was fair even among non-BCG immunized participants. BCG may account for the observed discordant results in vaccinated children, as also shown by the multivariate regression analysis. Discordant TST(+) /QFT-IT(–) results may also be attributed to nontuberculous mycobacterial infections, or diminished QFT-IT sensitivity, particularly among children with remote infection.¹³ The correct interpretation of such discordant results is currently uncertain. Recent findings suggest that the positive predictive value of IGRAs may exceed that of the TST.^{14,15} If these preliminary findings are confirmed, the number of children receiving chemoprophylaxis may be reduced substantially.

A population bias may have been introduced since a number of high risk children with negative exposure history were referred to our clinic following a positive or questionable TST finding during routine screening. Thus, an overestimation of TST positivity rates and discordant TST(+) /QFT-IT(–) results, potentially secondary to prior BCG immunization or to infection with nontuberculous mycobacteria, may have occurred. This bias may also account for the inverse association found between BCG immunization and QFT-IT test result.

No significant difference was found regarding the quantitative QFT-IT results between younger and older participants. Older age is a risk factor for TB infection and may explain the associa-

tion between age and a positive test result shown in the multiple regression analysis.

In conclusion, the present study results suggest that the application of QFT-IT may enhance the accuracy of diagnosing both active TB and LTBI, particularly among BCG immunized children, and contribute to the diminishment of the administration of unnecessary treatment.

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INTENSIVE CARE ADMISSIONS FOR CHILDREN WITH IMPORTED MALARIA IN THE UNITED KINGDOM

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Abstract: This study describes 977 children with imported malaria in England and Wales between 2004 and 2008, focusing on 29 (3.0%) patients admitted to intensive care, of whom 10 had cerebral malaria, 4 required inotropes, and 1 had concurrent septicemia. The remaining 14 were admitted for monitoring only. None died, but 1 child developed cerebellar infarction.

Key Words: incidence, *P. falciparum*, intensive care, severe malaria, management, outcome

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The United Kingdom has one of the highest rates of imported malaria, with 1500 to 2000 cases reported annually, and children account for 10% to 15% of cases.^{1,2} In a recent, prospective, enhanced national surveillance study, *Plasmodium falciparum*, the species responsible for most of the severe and fatal malaria cases worldwide, caused 85% of imported childhood malaria cases in the United Kingdom and Ireland.³ In addition, one-third of children with *P. falciparum* malaria fulfilled the World Health Organization criteria for severe or potentially complicated malaria, although only a quarter of those with severe malaria required intensive care, mainly for neurologic complications.³ Few studies have focused on intensive care admissions for imported childhood malaria cases in nonendemic countries, where presentation and course of severe childhood malaria, the proportion developing cerebral malaria, and the mortality by syndrome vary substantially. This study aimed to describe children with imported malaria admitted to pediatric intensive care units (PICU) in England and Wales during a 5-year period.

METHODS

Imported malaria describes an infection that was acquired in a malaria endemic area by a tourist or a native but was diagnosed in a nonendemic area after development of clinical symptoms. The Health Protection Agency Malaria Reference Laboratory (MRL) identifies cases from routine reports submitted by UK hospital laboratories, positive malaria slides sent to MRL for species verification, and notifications of malarial deaths by the Office for National Statistics.^{2,3}

The Pediatric Intensive Care Audit Network (PICANet) records core demographic and clinical details of the management of all critically ill children in National Health Service PICU, using standardized data collection forms (available at: www.picanet.org).

We requested anonymized data on all children <16 years with malaria admitted to PICU in England and Wales between 1 January, 2004 and 31 December, 2008 (data from Scotland and Northern Ireland were not available for the entire period). Data were analyzed using Stata version 11.0 (available at: www.stata.com). Ages are reported as medians and interquartile ranges (IQR) and compared using the Mann-Whitney *U* test, and proportions are compared with the χ^2 test or Fisher exact test as appropriate.

RESULTS

National Data. There were 977 childhood malaria cases in England and Wales reported to the MRL between 2004 and 2008 inclusive. The median age at diagnosis was 9 years (IQR, 5–13 years), 19.8% (193 cases) were in children aged <5 years, and 60.0% were male. *P. falciparum* accounted for 79.6% (778 cases, including 12 cases of *P. falciparum* coinfection with other *Plasmodium* species), followed by *Plasmodium vivax* (126 cases, 12.9%), *Plasmodium ovale* (51 cases, 5.2%), and *Plasmodium malariae* (22 cases, 2.3%). The number of reported cases declined gradually from 326 in 1999 to 161 in 2008 (Fig. 1). Cases showed a bimodal distribution peaking in January and August/September. Two children died (case fatality ratio, 0.2%). These 2 were Black-African children aged 5 to 14 years who had traveled to Sub-Saharan Africa without appropriate antimalarial prophylaxis and became unwell within 2 weeks of return to the United Kingdom. Both children were pronounced dead soon after being brought to the Emergency Department.

Pediatric Intensive Care Units Admissions. Over the same time, 29 children with malaria were admitted to PICU (6 cases/year; range, 3–10 cases/year), accounting for 3% of all cases (range, 1.7%–4.8% per year). Of these, 16 (55%) were male and none had comorbidities. Twenty children (69%) were admitted to a London PICU, which was similar to the proportion of malaria cases diagnosed in London (606/977, 62.0%; $\chi^2 = 0.58$; $P = 0.45$). PICU admissions for malaria increased during the months with the highest diagnosis of malaria, with greater than half the children (16/29 cases, 55%) admitted to PICU in August, September, and January. The median age of children with malaria admitted to PICU was 4 years (IQR, 2–9 years), which were significantly lower than the median age of all children diagnosed in the same period ($P = 0.0019$). Similarly, the proportion of children aged <5 years (15/29 cases, 52%) who were

admitted to PICU was higher ($\chi^2 = 17.6$; $P < 0.0001$)—7.8% (15/193 cases) children.

Ten children, including 2 with respiratory distress and 1 with hypotensive shock, presented with coma requiring mechanical ventilation for a median of 2 days (range, 1–4 days). Four others presented with hypotensive shock requiring inotropic support and mechanical ventilation. One other child presented with respiratory distress and had concurrent enteropathogenic *Escherichia coli* and *Salmonella typhi* septicemia, but did not require mechanical ventilation. The remaining 14 cases were admitted for observation only. Metabolic acidosis was uncommon, with only 3 children having a base excess more negative than -5 mmol/L. Children admitted to PICU for monitoring only were more likely to have been admitted from the same hospital (10/14 [71%] vs. 5/15 [33%]; $\chi^2 = 4.2$; $P = 0.040$). None received renal replacement therapy (dialysis, filtration, or exchange) or an exchange transfusion. Most children (21/29, 72%) remained in PICU for ≤ 48 hours and none was admitted for more than 6 days. One child developed cerebellar infarction but none died.

DISCUSSION

We have recently reported the results of a prospective study on children with imported malaria diagnosed in the United Kingdom and the Republic of Ireland over a 13-month period.³ In that study, most cases occurred in Black-African children who developed *P. falciparum* malaria while visiting family and relatives in West Africa during school holidays without appropriate antimalarial prophylaxis.³ The current study focuses on children with malaria who were admitted to PICU over a longer time-period (2004–2008), and although data collected through national surveillance are limited, we would expect the clinical, epidemiologic, and laboratory features of children with malaria to be similar to those reported in our previous study.³

The findings of this study demonstrate that lessons from endemic countries are relevant in the PICU setting, although presentations are more likely to be neurologic than in African series, possibly because children with severe malaria presenting in non-endemic countries tend to be older. In particular, respiratory distress is a serious sign in children with malaria,⁴ and clinicians should have a high index of suspicion for concomitant bacterial infection. Series suggesting a link between severe malaria and Gram-negative infection in Africa tend to have predominantly younger children but, even in the older age group, bacterial coinfection was an issue.^{5,6}

In our enhanced national surveillance study, it was concerning that one-third of children with *P. falciparum* malaria fulfilled World Health Organization criteria for severe or complicated malaria, although only a small proportion were subsequently admitted to PICU.³ We identified only one other study of 15 PICU cases in a nonendemic country, conducted in France between 1990 and 1995.⁷ Therefore, although our study is limited by the amount of information collected through PICANet, it does provide the best available data on this unique cohort of children. Considering the high proportion of children with severe or complicated *P. falciparum* malaria, the finding of so few cases admitted to PICU is surprising but consistent with our enhanced surveillance. We can, therefore, estimate that although a significant proportion of children with *P. falciparum* malaria present with World Health Organization-defined severe or complicated malaria, only 1.5% are deemed to require intensive care support, with a similar proportion admitted to PICU for close monitoring. Both this and the French study, where all 15 children had neurologic complications, confirm that most children with life-threatening imported malaria have neurologic involvement (coma, convulsions, or reduced conscious-

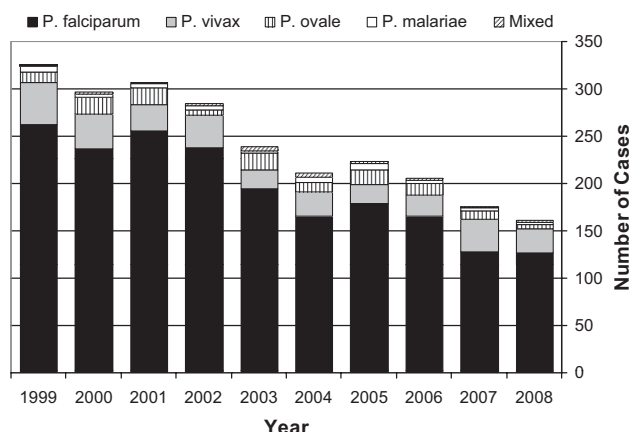


FIGURE 1. Number of childhood malaria cases in England and Wales: 1999 to 2008.

ness) rather than respiratory distress or severe anemia.⁷ In the French study, 8 children required ventilation, 4 received volume expansion, and 1 required inotropic support.⁷ The predominance of neurologic complications contrasts with pediatric malaria in African endemic areas,⁴ and is most likely to reflect the older age of children presenting with imported severe malaria. Older age is associated with a higher probability of neurologic presentation in Africa,⁸ while the higher proportion of children presenting with neurologic complications in Asian studies is also most likely because of older age at presentation.^{9,10} Presentation with circulatory collapse in malaria endemic countries is rare (0.4% and 2.9% in 2 of the studies) but associated with very high case fatality (71% and 82%, respectively).^{4,9}

Although it is reassuring that case fatality remains low, 2 children died between 2004 and 2008 and 2 other children died in the preceding 5 years.² Previous studies have identified failure to take recommended antimalarial chemoprophylaxis, refusal or delay in seeking medical care, and misdiagnosis as major risk factors for fatal malaria, particularly among nonimmune travelers.¹ Diagnostic delay is also associated with increased risk of severe malaria and intensive care admission.^{1,7}

Our study highlights several important messages. First, children traveling to malaria-endemic countries without appropriate preventive measures are not only at risk for malaria but also of other travel-related infections such as typhoid. Clinicians should, therefore, consider bacterial coinfection in children presenting with severe or complicated malaria, take appropriate cultures at presentation, and manage them accordingly, but with a low threshold for empiric antibiotics while culture results are awaited. Second, younger children (<5 years) are not only more likely to present with severe malaria,³ but are also more likely to be admitted to PICU. Third, hypotensive shock is an uncommon but potentially fatal presentation of malaria and may require aggressive fluid resuscitation and inotropic support. Finally, although case fatality remains low, a significant proportion of children with *P. falciparum* malaria presenting to PICU have coma, which may be associated with long-term neurologic sequelae. Clinicians should follow-up children with severe malaria after hospital discharge to identify and manage any long-term complications. Guidelines for the management of severe imported childhood malaria should emphasize the importance of neurologic complications and cardiovascular shock in children presenting with severe malaria.

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PNEUMOCOCCAL BACTEREMIA IN FEBRILE INFANTS PRESENTING TO THE EMERGENCY DEPARTMENT 8 YEARS AFTER THE INTRODUCTION OF PNEUMOCOCCAL CONJUGATE VACCINE IN THE BASQUE COUNTRY OF SPAIN

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Abstract: We included 3088 well-appearing infants aged between 3 and 36 months with fever without a source with a blood culture done as part of their study of fever. Rate of positive blood cultures for *Streptococcus pneumoniae* occult bacteremia (OB) was 0.58%. Rate of OB caused by PCV7-serotypes and nonvaccine serotypes were 0.16% and 0.42%, respectively. A total of 18 cases of *S. pneumoniae* OB were identified between January 1, 2006 and December 31, 2009. None of the 5 infants who had *S. pneumoniae* OB caused by vaccine serotypes had received PCV7. The decline in pneumococcal OB rates observed after PCV7 introduction in our area (Basque Country, Spain) continues 8 years later. There is no evidence of an OB rate increase caused by non-PCV7 serotypes.

Key Words: pneumococcal bacteremia, febrile infants, pneumococcal conjugate vaccine

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Since PCV7 was introduced in our area (Basque Country, Spain) in 2001, the rates of *Streptococcus pneumoniae* occult bacteremia (OB) caused by vaccine serotypes have decreased significantly with no significant emergence of nonvaccine serotypes.¹ However, these data were reported in 2005 and it is unknown if the reduction in OB rates after PCV7 introduction is still clear 8 years later. This information could be valuable to estimate the possible impact of the new PCV vaccines containing 10 and 13 serotypes² on OB rates and evaluate future changes in the management of infants with fever without a source (FWS).

This study aimed to evaluate changes in the incidence of pneumococcal OB and serotypes involved in infants aged between 3 and 36 months presenting to our pediatric emergency department 8 years after the introduction of PCV7.

PATIENTS AND METHODS

Study Design. A retrospective case series study of all the blood cultures collected from children aged between 3 months and 3 years with FWS at our pediatric emergency department from

January 1, 2006 to December 31, 2009 was performed. From our computerized database, we identified infants diagnosed with FWS and recorded their personal data, ancillary tests performed, and organisms identified in blood culture. During the study period, it was recommended in this institution to obtain a blood culture on well-appearing, 3- to 36-month-old children presenting to the emergency department with a temperature $\geq 39.4^{\circ}\text{C}$ and no recognized source on physical examination.

Cases. Cases were defined as infants with FWS who had blood cultures obtained in our pediatric emergency department. Only well-appearing infants aged between 3 and 36 months diagnosed with FWS and positive blood culture with *S. pneumoniae* were considered as having an *S. pneumoniae* OB. We obtained serotype information on all cases of *S. pneumoniae* causing OB. Immunization status with PCV7 was also recorded.

Statistical Analysis. Continuous data were compared with the Student *t* test. Categorical data were examined using the χ^2 (χ^2) test or the Fisher exact test probability test. The SPSS 10.0 for Windows (SPSS Inc., Chicago, IL) was used for all statistical calculations.

RESULTS

During the study period, 17,630 episodes of FWS in infants aged between 3 and 36 months were registered in the pediatric emergency department. Mean age was 16.86 ± 8.59 months, and 9185 (52.1%) were male. A total of 12,182 (69.1%) had received more than one dose of PCV7. Total blood cultures drawn were 3088 (17.5%). About 340 infants studied (11%) had received more than 1 dose of PCV7.

Between January 1, 2006 and December 31, 2009, 18 cases of *S. pneumoniae* OB were identified. Isolated pneumococcal serotypes are mentioned in Table 1. During the study period, 4 blood cultures were positive with other bacteria in infants aged between 3 and 36 months with FWS (overall rate, 0.71%), *Streptococcus pyogenes* (2) and *Neisseria meningitidis* (2). Of the 18 cases of *S. pneumoniae* bacteremia in study population, 5 (25%) were caused by PCV7 serotypes: 14 (3), 19F (1), and 23F (1); and 12 caused by nonvaccine serotypes: 19A (4), 6A (2), 15A (1), 22 (1), 8 (1), 17 (1), 10A (1), and 23B (1). No serotype was identified in 1 case. Seven (53.8%) were caused by serotypes now included in PCV13 and 1 in PCV10.

The rate of positive blood cultures for *S. pneumoniae* OB was 0.58%. The rates of OB caused by PCV7-serotypes and nonvaccine serotypes were 0.16% and 0.42%, respectively (Fig. 1). None of the 5 infants with vaccine serotype-induced *S. pneumoniae* OB had received PCV7. Three infants, all having a nonvaccine serotype, had received PCV7.

Ten patients (55.5%) with *S. pneumoniae* OB treated as outpatients with oral amoxicillin had a favorable clinical course. One of them was finally diagnosed with pneumonia and 2 with otitis. Eight patients were admitted and treated with intravenous ceftriaxone due to the persistence of fever. In this group, 1 patient was finally diagnosed with meningitis and 1 with pneumonia. All patients did well.

During the study years, 22 patients aged between 3 and 36 months diagnosed with diseases other than OB had positive blood cultures with *S. pneumoniae*. Five cases of meningitis (serotypes 19A [3] and 7F [2]), 9 cases of pneumonia (serotypes 19A [4], 7F [3], 1 and 10A), 2 cases of endocarditis (serotypes 18C and 7F), 2 cases of sepsis (serotype 19A and 22F), 2 cases of mastoiditis (serotypes 19A and 6A), 1 case of peritonitis (serotype 5), periorbital cellulitis (serotype 14), and arthritis (serotype 7F). Including these patients, we would have had a more pronounced rate (1.29%) of nonvaccine serotypes isolated in blood cultures.

TABLE 1. Serotypes Isolated in Patients Diagnosed With *S. pneumoniae* Occult Bacteremia

Serotypes (n)	2006	2007	2008	2009
Vaccine				
6 B	0	0	0	0
23 F	1	0	0	0
4	0	0	0	0
18 C	0	0	0	0
14	1	1	1	0
19 F	0	0	0	1
9 V	0	0	0	0
Total vaccine	2	1	1	1
Nonvaccine				
19 A	1	0	3	0
15 A	0	1	0	0
22	1	0	0	0
8	1	0	0	0
6 A	1	1	0	0
17	0	1	0	0
23 B	0	0	0	1
10 A	0	1	0	0
Unknown	0	0	0	1
Total nonvaccine	4	4	3	1

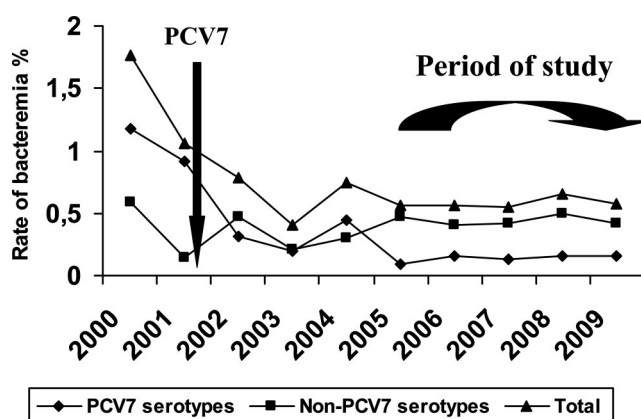


FIGURE 1. *S. pneumoniae* occult bacteremia rate (total and those caused by vaccine and nonvaccine serotypes) in the 2000 to 2005¹ period and in the 2006 to 2009 period of study.

DISCUSSION

This study has shown that the reduction in *S. pneumoniae* OB rate observed after implementation of vaccination with PCV7 in our area (1.6%–0.6%)¹ remains evident 8 years later (0.59%). This finding is attributable to a sustained decrease in the rate of disease caused by PCV7-serotypes. Several studies have been published about the incidence of invasive pneumococcal diseases (IPDs) in Europe in the last 5 years,^{3,4} but as far as we know, this is the first study on OB rates in infants in this time period.

An increase was reported recently in the incidence of IPD caused by nonvaccine serotypes in the United States and Spain following the introduction of PCV7, especially in children over 5 years old.^{5,6} These studies were conducted in hospitalized children and focused on overall IPD with lack of data about pneumococcal OB, this being the most frequent IPD in children below 3 years old. Our study, which shows a sustained effect of PCV7, gives additional information about the limited importance of replacement disease in this population.

Although PCV-7 was licensed for usage in Spain in 2001 and recommended by the Spanish Society of Pediatrics, it has not been

included in the official vaccination schedule of the Public Health System. That is why PCV7 coverage varies greatly within the different regions of Spain. In the present study, we have found that nearly 70% of infants 3 to 36 months old with FWS in our emergency department had been vaccinated with PCV7. These data support an increase in vaccine coverage compared with the rate of 50% reported in our area in 2005.¹ Both the initial decline in pneumococcal OB rate following PCV7 and its sustained effect are higher than expected with these coverage rates. Indirect protection of unvaccinated children may have played a role in this unexpected result.

Rates of IPD caused by serotype 19A have increased for all ages,⁷ making this serotype now the most common among all age groups. In our study, among the non-PCV7 serotypes isolated, the most notable was 19A (33.3% in OB cases and 40.9% in other IPD). It is significant that the absolute increases in rates of non-PCV7-type bacteremia are modest in comparison with the reductions in PCV-type observed since 2001.

Several published studies that use post-PCV7 data have suggested that the prevalence of pneumococcal OB in febrile children aged between 3 and 36 months is currently in the range of 0.17 to 0.91 and the overall prevalence in the same age group is in the range of 0.25% to 0.91%.⁸ Our results suggest that the current prevalence due to any bacteria in the 3- to 36-month age group is 0.74% in our area.

New multivalent PCV are now available and a recent review has estimated their direct impact on IPD.² The current pneumococcal serotypes found in our study suggest that the impact of PCV10 and especially PCV13 is similar to PCV7 and that more than 65% of current pneumococcal bacteremia could be prevented. The introduction of PCV13 could drive the pneumococcal OB rates below 0.25% and overall rates below 0.5%. If these rates fall below 0.5%, management strategies that involve routine testing and/or empirical administration of antibiotics should be modified.^{9,10}

The present results should be interpreted after taking some limitations of the study into account, including its retrospective basis that limited the data collection. A blood culture was not obtained from all of the febrile children aged between 3 and 36 months whose temperature was over 39.5°C. One might argue that it would be more likely that a blood culture would be obtained from the sicker appearing children. This would likely lead to an overestimation of the prevalence of OB, yielding a rate that is really higher than the true rate. Our results cannot be applied to other Spanish regions owing to their different PCV7 coverage rates.

Since PCV7 was introduced into in our area (Basque Country, Spain), rates of *Streptococcus pneumoniae* bacteremia caused by vaccine serotypes have decreased significantly and its effect is sustained 8 years later. New PCV vaccines are now available and a more pronounced decrease in pneumococcal OB is expected. Current strategies to the approach of the previously healthy febrile infant that involve routine testing and/or empirical administration of antibiotics should be modified.

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OUTBREAK OF VIM-1-CARBAPENEMASE-PRODUCING *ENTEROBACTER CLOACAE* IN A PEDIATRIC INTENSIVE CARE UNIT

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Abstract: Pediatric patients are rarely infected with metallo- β -lactamase-producing Enterobacteriaceae. We describe 3 cases of children infected with VIM-1-producing clonal *Enterobacter cloacae*. Patients were treated with amikacin and cotrimoxazole. The *bla*_{VIM-1} gene was carried into a class 1 integron and an IncHI2 incompatibility group plasmid. Emergence of pediatric infections caused by carbapenemases-producing Enterobacteriaceae is a critical issue as they are resistant to most β -lactam antibiotics.

Key Words: metallo- β -lactamases, enterobacteria, VIM-1, outbreak

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The emergence of acquired metallo- β -lactamases (MBLs) is significant because MBLs are resistant to all available β -lactams, including carbapenem, the exception being aztreonam. VIM

and IMP are the most commonly detected MBLs.¹ *Pseudomonas aeruginosa* are the most important known reservoirs of the VIM-type enzymes, but recently the dissemination of these enzyme genes in several Enterobacteriaceae has been reported.²

Enterobacter cloacae is a common nosocomial pathogen frequently resistant to extended-spectrum cephalosporins and aztreonam due to the mutational derepression of the chromosomal AmpC β -lactamase. Although the frequency of Enterobacteriaceae carrying MBLs has increased in the last years,^{3–6} MBL-producing *E. cloacae* clinical isolates are still rare, and pediatric outbreaks have not been described thus far.

In this study, we report an outbreak of VIM-1-producing *E. cloacae* in 3 children admitted to a pediatric intensive care unit (ICU) in a 3-month period.

MATERIALS AND METHODS

Patients and Isolates.

Patient 1. The index case was an 11-year-old boy who traveled from Pakistan to Spain to have a surgical correction of a congenital cardiopathy. Following surgery, which was performed 3 months after his arrival from Pakistan, the patient developed septicemia due to infection with carbapenem-nonsusceptible *E. cloacae* (isolate Entb33) (Table, Supplemental Digital Content 1, <http://links.lww.com/INF/A562>). The patient was initially empirically treated with vancomycin plus ceftazidime, treatment was subsequently changed to amikacin, after which the patient clinically recovered. A carbapenem-nonsusceptible *E. cloacae* was also isolated from the fecal flora of the patient.

Patient 2. Four weeks after patient 1 was discharged, carbapenem-nonsusceptible *E. cloacae* (Entb36) (Table, Supplemental Digital Content 1, <http://links.lww.com/INF/A562>) were isolated from a 6-month-old female patient admitted to the same pediatric ICU. This patient was diagnosed with VACTERL syndrome (congenital syndrome characterized by abnormalities of vertebrae, anus, cardiovascular tree, trachea, esophagus, renal system, and limb buds) and had been repeatedly admitted to the pediatric ICU, beginning when she was 2 months old. The patient underwent surgery for aortopexy and, during the postsurgery period, the Entb36 isolate was cultured from a gastrostomy exudate. The patient was also a fecal carrier of a carbapenem-nonsusceptible *E. cloacae* and a carbapenem-nonsusceptible *Klebsiella pneumoniae* (K481 isolate). She was successfully treated with cotrimoxazole, although the skin colonization surrounding the gastrostomy orifice persisted for 2 months.

Patient 3. Six weeks after discharge of patient 2, a 3-month-old male baby had bacteremia associated with a skin infection caused by carbapenem-nonsusceptible *E. cloacae* (Entb44 isolate) (Table, Supplemental Digital Content 1, <http://links.lww.com/INF/A562>). The patient recovered after treatment with amikacin plus cotrimoxazole. No fecal colonization with *E. cloacae* could be detected in this patient.

Susceptibility Testing. The isolates were identified by the API20E method (bioMérieux, Marcy l'Étoile, France). *E. cloacae* identification was confirmed by 16S ribosomal deoxyribonucleic acid (DNA) sequencing. Antibiotic susceptibility testing was performed by the broth microdilution MicroScan (Siemens Healthcare Diagnostics, Deerfield, IL) disk-diffusion reference method, and the *E* test method (AB-Biodisk, Solna, Sweden). Results were interpreted according to the Clinical Laboratory Standard Institute guidelines.⁷

Metallo- β -lactamase production was tested by the modified Hodge test using an imipenem disk; imipenem susceptibility alone and in combination with ethylenediaminetetraacetic acid (EDTA) was also determined (*E* test, AB Biodisk, Sweden).

Pulsed-field Gel Electrophoresis Profiles. The genetic relatedness among *E. cloacae* isolates was determined by pulsed-field gel electrophoresis (PFGE) after total chromosomal DNA digestion with *Xba*I.⁸

β -Lactamases and Class 1 Integron Characterization. Standard PCR conditions were used to amplify several β -lactamase genes coding for carbapenemases (*bla*_{KPC}, *bla*_{VIM}, *bla*_{IMP}), ESBL (*bla*_{TEM}, *bla*_{SHV}, and *bla*_{CTX-M}), plasmid-mediated AmpC (*bla*_{CMY}, *bla*_{FOX}, *bla*_{MOX}, *bla*_{DHA}, *bla*_{LAT}, *bla*_{ACT}, *bla*_{MIR}), and the aminoglycoside resistance genes (*aac*[3]-*Ia* and *aac*[6']-*Ib*).⁸ **Conjugation Assay and Plasmid Characterization.** Conjugation experiments were performed with the donor *E. cloacae* clinical isolates Entb33, Entb36, and Entb44, using the kanamycin-azide resistant *E. coli* Hb101 as a recipient. Putative transconjugants were selected on Mueller-Hinton agar plates containing kanamycin (100 μ g/mL), azide (160 μ g/mL), and cefotaxime (4 μ g/mL).

Plasmids were classified according to their incompatibility group by a PCR-based replicon-typing scheme.⁹ Class 1 integron structures, the integrase gene *intI1* and the variable regions, were screened by PCR amplification and DNA sequencing.

RESULTS

Susceptibility Testing. All 3 *E. cloacae* clinical isolates were resistant to ampicillin, amoxicillin/clavulanic acid, cefoxitin, cefotaxime, ceftazidime, and tobramycin. The *E. cloacae* isolates were, however, susceptible to ciprofloxacin, gentamicin, amikacin, and cotrimoxazole. Minimum inhibitory concentrations (MICs) to carbapenems were 4 to 16 μ g/mL to ertapenem, 2 to 16 μ g/mL to meropenem, and 2 to 16 μ g/mL to imipenem. A majority of the carbapenem MICs of the Entb33 and Entb44 isolates were categorized as susceptible by Clinical Laboratory Standard Institute criteria,⁷ with breakpoints for susceptibility being ≤ 4 μ g/mL for imipenem, ≤ 4 μ g/mL for meropenem, and ≤ 2 μ g/mL for ertapenem (Table, Supplemental Digital Content 1, <http://links.lww.com/INF/A562>). All of these isolates were within the range of MICs suggesting carbapenemase production (MIC ≥ 1 μ g/mL),⁷ and therefore the modified Hodge test was performed in all isolates as a confirmatory test, which was positive in all *E. cloacae* clinical isolates and in the one isolate from *K. pneumoniae* (K481). The imipenem/imipenem-EDTA *E* test strips were also positive, with a “keyhole” visible in the middle of the strip.

Carbapenem-resistant *E. cloacae* that caused fecal colonization in patients 1 and 2 had the same antibiotic-resistance patterns as those of clinical isolates, but additional samples were not available for further molecular studies.

Pulsed-field Gel Electrophoresis Profiles. PFGE results following *Xba*I digestion revealed that all 3 *E. cloacae* clinical isolates had the same PFGE profile, which was referred to as P1.

Conjugation Assay and Plasmid Characterization. Carbapenem-resistant *E. coli* transconjugants were obtained from the Entb33 isolate (TCEntb33) (Table, Supplemental Digital Content 1, <http://links.lww.com/INF/A562>). TCEntb33 was resistant to ampicillin, amoxicillin/clavulanic acid, cefoxitin, cefotaxime, ceftazidime, and tobramycin; and had carbapenem MICs of 2 μ g/mL to ertapenem, 1 μ g/mL to meropenem, and 2 μ g/mL to imipenem. According to a PCR-based replicon-typing scheme, a unique plasmid of the incompatibility group IncHI2 was detected in both Entb33 and TCEntb33.

β -Lactamases and Class 1 Integron Characterization. The MBL gene *bla*_{VIM-1} was identified in the Entb33, Entb36, Entb44, and TCEntb33 clinical isolates. Furthermore, the *K. pneumoniae* isolate K481 isolated from patient 2 also contained the VIM-1 enzyme gene. The *aac*(6')-*Ib* aminoglycoside-quinolone resistance gene was identified in all *E. cloacae* clinical isolates

and in TCEntb33. PCR gene amplification demonstrated remained negative for the remaining enzymes genes tested in all isolates.

Amplification and sequencing of the integrase gene and the variable region of the class 1 integrons showed that the *bla*_{VIM-1} gene was carried into a class 1 integron in the following cassette combination: *intI-1*(integrase gene)-*bla*_{VIM-1}-*aac*(6')-Ib (tobramycin-resistance gene, also called *aacA4*)-*aadA1* (streptomycin-resistance gene)-*qacE δ 1/sul-1* (quaternary ammonium compounds-resistance gene/sulfonamides-resistance gene).

DISCUSSION

E. cloacae are often resistant to all penicillins, cephalosporins, and aztreonam because of mutational derepression of the constitutive chromosomal AmpC β -lactamases. Therefore, carbapenems are considered the drug of choice for the treatment of *E. cloacae* infection.

The appearance of MBL-producing microorganisms in pediatric patients is a matter of serious clinical concern because, in addition to being resistant to all β -lactams, coresistance to other antibiotic families is also common, a fact that severely limits the available therapeutic options. The patients reported in this study were successfully treated with amikacin and cotrimoxazole, both of which demonstrated in vitro susceptibility. Colistin, a toxic and difficult-to-use drug is often the only antibiotic with in vitro activity against VIM-producing bacterial isolates.⁶

Although incidence is increasing, outbreaks caused by VIM-1 Enterobacteriaceae are still uncommon. The most affected bacterial species usually are *Klebsiella* spp. and *E. cloacae*.²⁻⁴ Even though VIM-producing *Pseudomonas* spp. clinical isolates have been previously described in children,¹⁰ infections with Enterobacteriaceae producing VIM enzymes are very rare. In a recent study,¹¹ VIM-1-producing *Klebsiella* spp. and *Escherichia coli* were detected in a Spanish hospital, with the majority of cases in pediatric patients with severe underlying illnesses.¹¹ However, to the best of our knowledge, outbreaks due to VIM-1-producing *E. cloacae* in children have not yet been described in the English literature.

There were no VIM-type-carbapenemase-producing isolates detected in the hospital before the 3 cases described here, and no other cases have since been diagnosed. Spread of the infection by staff could have been an effective manner of dissemination between patients. However, no carrier studies were conducted on the staff members of the pediatric ICU. Although not demonstrated, the index case may have already been a fecal carrier of the VIM-1-producing *E. cloacae* at the time of the admission; hospitals should be alert to the possibility of a fecal carrier and should be aware of the risk of infection with multiresistant bacteria made possible by transfer of patients between different hospitals and countries.

Carbapenem susceptibility can vary among VIM-producing isolates, even in isolates of the same species and same clone.¹¹ Commonly, MICs of carbapenem are in the low range of the susceptible category, as was the case in the Entb33 and Entb44 clinical isolates of this study. A reproducible and reliable standard method is needed for routine diagnostic and surveillance purposes, which enables accurate detection of carbapenem resistance in clinical laboratories.

Recognition of the presence of MBL-producing Gram-negative organisms is of paramount importance because strict infection control measures are required to prevent hospital infection epidemics. In this study, we observed the clonal dissemination of VIM-1 positive *E. cloacae*. *bla*_{VIM} was carried on the typically mobile genetic element class 1 integron and a plasmid of incom-

patibility group HI2, which enabled the horizontal transmission of *bla*_{VIM} both intra- and interspecies.^{2,4}

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GASTRIC LAVAGE FOR THE DIAGNOSIS OF PULMONARY BLASTOMYCOSIS IN PEDIATRIC PATIENTS

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Abstract: A case of pulmonary blastomycosis in a pediatric patient diagnosed by gastric lavage is described. Use of gastric lavage averted the need for more invasive diagnostic techniques including bronchoscopy. Further study is required to define the sensitivity of gastric lavage for recovery of *Blastomyces dermatitidis* from pediatric patients with pulmonary blastomycosis.

Key Words: blastomycosis, pediatrics, diagnosis, gastric lavage

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Blastomyces dermatitidis (teleomorph: *Ajellomyces dermatitidis*), the etiologic agent of blastomycosis, is a thermally dimorphic fungus that grows as a mold at room temperature and a yeast at 37°C.^{1,2} In nature, *Blastomyces dermatitidis* survives in warm, moist soil.¹ Humans typically become infected via inhalation of conidia, although primary cutaneous inoculation has also been reported.^{1,3} The most common clinical manifestation of blastomycosis is pulmonary disease, which may present as an acute pneumonia or a chronic pulmonary infection that resembles tuberculosis.^{1–4} Systemic dissemination may occur, with the skin, bones, and genitourinary tract being the most common sites of extrapulmonary spread.^{1,4} It is estimated that between 2% and 10% of patients with blastomycosis are younger than 15 years of age.^{1,3} Northwestern Ontario and neighboring areas of Manitoba are considered endemic for blastomycosis in Canada.

Diagnosis of blastomycosis is typically made by visualization of the characteristic yeast form (thick walled, with broad-based budding) in clinical material and/or recovery of the organism on culture.^{1,2} Sputum represents an appropriate specimen for the diagnosis of pulmonary blastomycosis. However, children under the age of 12 are often unable to produce sputum or voluntarily expectorate.⁵ For the diagnosis of pulmonary tuberculosis in pediatric patients, gastric lavage has been employed with some success.^{5,6} Young children cough up and swallow their bronchial secretions, allowing for organism recovery from the stomach.⁵ In theory, gastric lavage could also prove useful for diagnosis of pulmonary blastomycosis in children, sparing the need for more invasive diagnostic procedures (eg, bronchoscopy). A case of pulmonary blastomycosis with systemic dissemination, diagnosed by gastric lavage, is presented here. A literature review on the use of gastric lavage for recovery of *Blastomyces dermatitidis* follows the case presentation.

CASE REPORT

A 21-month-old male from Kenora (Ontario, Canada) was admitted to Winnipeg Children's Hospital (WCH), (Manitoba, Canada) in January 2010 with new onset of a left chest wall mass. Thirteen days before presentation, the child began complaining of pain on the left side of his chest. The pain appeared to be worse with inspiration. The parents also noticed an area of swelling over the left chest. There was no history of chest wall trauma, nor was there any appreciated discoloration to the skin. There was also no history of cough, respiratory distress, fever, sweats, gastrointestinal symptoms, or weight loss in the weeks leading up to the child's admission. There was no documented tuberculosis exposure. Of note, the parents did report that a dog owned by a neighbor died of blastomycosis over the preceding summer. The child had often played with the dog in the past year.

On admission, the child was afebrile. A 2 × 3-cm superficial area of swelling was appreciated on the left side of the chest, at the level of the eighth rib. There was no erythema overlying the mass. The remainder of the physical examination was unremarkable. A computed tomography scan of the chest to further define the mass demonstrated consolidation in the left upper and left lower lobes, as well as a lytic lesion of the left eighth rib with associated soft-tissue swelling. A bone scan was significant for increased uptake at the left eighth rib and the distal tibia. The child was unable to produce sputum. To investigate for possible blasto-

mycosis, gastric aspirates for fungal staining and culture were obtained daily for 3 consecutive days.

At WCH, gastric lavage is performed in the morning just after the child awakens using 10 mL of sterile saline. Aspirated fluid for mycology is submitted to the microbiology laboratory in a sterile container. Upon receipt of the specimen, the fluid is spun down in a centrifuge at 1500 RPM for 15 minutes. The supernatant is decanted and the remaining sediment is then used for preparation of slides and media inoculation. Slides are stained with Calcofluor white, methenamine silver, and periodic acid Schiff. Inhibitory mold agar, Sabouraud's dextrose agar with brain heart infusion (SABHI), and brain heart infusion with blood are inoculated for fungal culture. Plates are incubated in an aerobic atmosphere at 30°C for 4 to 6 weeks. If an organism consistent with *Blastomyces dermatitidis* is recovered, identification is performed using a *Blastomyces*-specific DNA probe (Accuprobe, Gen-Probe Incorporated, San Diego, CA).

Fungal stains of the first 2 gastric lavage samples were negative. The third gastric lavage specimen demonstrated broad-based, budding yeast cells on both wet prep (Calcofluor white) and methenamine silver staining, consistent with blastomycosis (Figure 1). Both the first and the third gastric lavage samples subsequently grew *Blastomyces dermatitidis* on culture. A bronchoscopy had been planned, but this procedure was cancelled when the results of the third gastric aspirate became available. Based on the gastric lavage results and the overall clinical picture, the child was diagnosed with pulmonary blastomycosis with systemic dissemination. Three days post admission, therapy with amphotericin B at a dose of 1 mg/kg/d was initiated. This was changed to itraconazole (10 mg/kg/d) 18 days postadmission. The plan was to continue antifungal therapy for a total of 12 months, with follow-up by the Pediatric Infectious Diseases service as an outpatient.

DISCUSSION

Between 1982 and 2008, 3 additional cases of pulmonary blastomycosis in pediatric patients were diagnosed with the use of gastric lavage at our institution (Table 1). In a review of 21 cases of pediatric blastomycosis diagnosed at WCH from 2000 onwards,

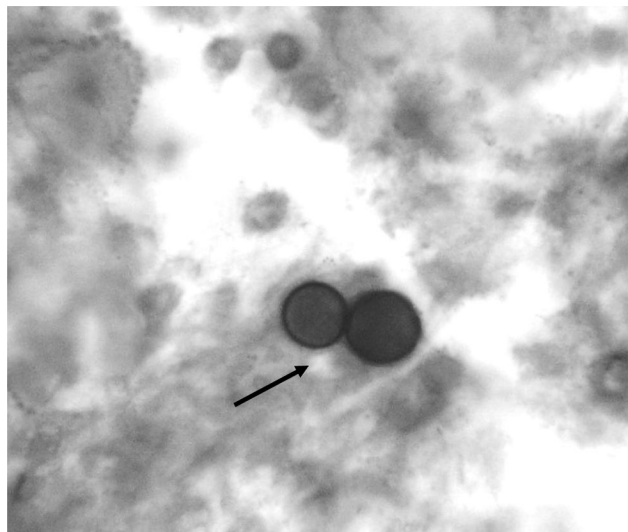


FIGURE 1. Methenamine silver stain of a gastric lavage specimen—broad-based, budding yeast (arrow) with a thick cell wall, consistent with *Blastomyces dermatitidis*.

TABLE 1. Cases of Pediatric Blastomycosis Diagnosed With Gastric Lavage at the Winnipeg Children's Hospital in Winnipeg, Manitoba, Canada Between 1982 and 2010

Patient Number	Patient Age	Year of Diagnosis	Clinical Manifestations	Diagnostic Testing	Outcome
1 (current case)	21 mo	2010	Pulmonary disease with bone and soft tissue involvement	1 of 3 gastric washings positive on direct examination, 2 of 3 positive on culture, sputum not obtained	Successful
2	6 yr	2008	Pulmonary disease	1 of 1 gastric washings positive on direct examination and culture, endotracheal secretions also positive on direct examination and culture	Died
3	10 yr	1992	Pulmonary disease	1 of 1 gastric washings positive on direct examination and culture, sputum also positive on direct examination and culture	Successful
4	8 yr	1982	Pulmonary disease	1 of 1 gastric washings positive on direct examination and culture, sputum not obtained	Successful

only 2 had gastric aspirates sent for fungal stains and culture (both positive—Table 1). Due to the small number of gastric lavage specimens submitted, and incomplete data prior to 2000, the sensitivity of gastric lavage for diagnosis of pulmonary blastomycosis in comparison with other specimen types could not be calculated.

Recovery of *Blastomyces dermatitidis* with gastric lavage has been previously described in the English language literature.^{7–9} In a case report published by Musial et al in 1987, the authors make reference to 56 patients diagnosed with blastomycosis at the Mayo Clinic between 1976 and 1986.⁷ Twenty gastric washings obtained from these 56 patients demonstrated *Blastomyces dermatitidis* on culture.⁷ The patient age distribution is not stated, nor is it reported if multiple specimens were collected on an individual patient. The number of negative gastric washings is also not provided. Martynowicz and Prakash evaluated the yield of gastric washings in a retrospective chart review at a single institution (Mayo Clinic, Rochester).⁸ In this report, noninvasive diagnostic testing for 35 patients with pulmonary blastomycosis is described. In total, 15 gastric washing specimens were obtained from 10 patients. Ten of the gastric washings were positive by culture (from 7 of the 10 patients), giving an overall diagnostic yield of 67% (10 positive samples out of 15 tested).⁸ This was comparable to sputum, which had a diagnostic yield of 75% (54 positive samples out of 72 tested).⁸ The age of the patients from whom gastric washings were obtained is not stated. Additionally, it is unclear if some of the cases reported here were included in the data published by Musial et al (given the same institution in both reports).

Case reports exist describing the recovery of *Blastomyces dermatitidis* from gastric washings in children. In a review of 10 cases of blastomycosis published by Smith et al, gastric washings were positive in 2 children with pulmonary disease, ages 9 and 16, respectively.⁹ However, cases of negative gastric washings have also been reported in children with documented extensive pulmonary blastomycosis.^{9–11} To the best of our knowledge, the sensitivity and specificity of gastric lavage for the recovery of *Blastomyces dermatitidis* in a pediatric population with pulmonary blastomycosis in comparison to other methods of collection of respiratory secretions (bronchoscopy, induced sputum) has not been evaluated systematically in a large series of patients.

In summary, we have presented a case of pulmonary blastomycosis with systemic dissemination diagnosed by recovery of *Blastomyces dermatitidis* with gastric lavage. Use of gastric lavage

may avert the need for more invasive diagnostic techniques such as bronchoscopy, as was illustrated here.

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HERPES SIMPLEX VIRUS REACTIVATION AFTER SUBTOTAL HEMISPHERECTOMY IN A PEDIATRIC PATIENT

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Abstract: We report herpes simplex encephalitis (HSE) in a toddler after a subtotal hemispherectomy for seizures related to HSE 16 months earlier. Herpes simplex virus reactivation in the cerebrospinal fluid shortly after treatment of HSE has been described, but is extremely rare in other situations. HSE reactivation is a potential complication of epilepsy surgery after HSE in children.

Key Words: herpes, encephalitis, reactivation, neurosurgery, pediatrics

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Herpes simplex encephalitis (HSE) is the most common cause of sporadic fatal encephalitis worldwide.^{1–3} Beyond the newborn period, the development of HSE is believed to be the result of reactivation of the virus from neural ganglia, but is on occasion coincident with primary infection. Recurrences have been described after short courses or with lower doses of acyclovir therapy, usually soon after stopping treatment.³ We report the case of a 23-month-old boy with a remote history of HSE and postoperative herpes simplex virus (HSV) reactivation in the cerebrospinal fluid (CSF) after a subtotal hemispherectomy for seizure control. Review of the literature revealed 1 previously reported case of HSE reactivation after neurosurgery in a child with a history of HSE in infancy, and 10 cases of HSE after neurosurgery without a prior history of HSE.

CASE REPORT

A 23-month-old immunocompetent boy, with a history of HSE associated with a right middle cerebral artery infarction and medically intractable seizures, developed fevers after a right subtotal hemispherectomy for seizure management. At 7 months of age, he had presented with fever, irritability, staring spells, and muscle rigidity. Maternal history of herpes infection was denied as was a history of neonatal herpes infection. HSV polymerase chain reaction (PCR) from CSF was positive and he completed 21 days of intravenous acyclovir therapy. Dosing of acyclovir and typing of HSV were not available for review. A right middle cerebral artery infarction was noted by magnetic resonance imaging at the time of diagnosis and subsequent left-sided hemiparesis and visual field defects. Seizures continued during and after acyclovir therapy. His refractory epilepsy was nonresponsive to multiple antiseizure medications, including phenytoin, phenobarbital, levetiracetam, and clonazepam. Topiramate led to some reduction in daily seizure frequency. Inpatient video electroencephalography revealed right hemispheric epilepsy with left arm tonic seizures and asymmetric spasms, left greater than right. Presurgical evaluation included an 18 fluorodeoxyglucose positron emission tomography, which demonstrated marked reduction of tracer in the right centrotemporal areas corresponding to an extensive area of encephalomalacia in the middle cerebral artery territory, consistent with a prior middle cerebral artery infarction. Epilepsy surgery was recommended and a right functional hemispherectomy was performed approximately 14 months after treatment of HSE. Surgery was uncomplicated and included extraventricular device (EVD) placement. Dexamethasone was started at 0.1 mg/kg/dose every 12 hours, as is routine for this surgery as well as acyclovir 20 mg/kg/dose every 8 hours. On postoperative day 1, he was febrile to 38.2°C. Daily EVD CSF Gram stain, bacterial culture, cell count, glucose, and protein were sent until removal of EVD on postoperative day 3 (Table 1). CSF bacterial cultures were nega-

TABLE 1. Cerebrospinal Fluid Results

CSF POD*	1 (EVD†)	2 (EVD)	3 (EVD)	5 (LP‡)	11 (LP)
White blood cells (cells/ μ L)	0	360	1050	4400	53
% neutrophils		88	86	61	13
% lymphocytes		7	13	4	68
% monocytes		5	1	35	11
Red blood cells (cells/ μ L)	0	30,000	37,800	38,850	196
Glucose (mg/dL)	<2	20	26	12	30
Protein (mg/dL)	<6	1023	638	377	252
HSV PCR			Positive for type 1		Negative
HSV culture					Negative

*Postoperative day.

†Extraventricular device.

‡Lumbar puncture.

HSV-PCR indicates herpes simplex virus-polymerase chain reaction; CSF, cerebrospinal fluid.

tive. Due to persistent fever and irritability, a lumbar puncture was performed on postoperative day 5. Routine CSF studies and CSF HSV PCR were sent. Empiric vancomycin and ceftazidime were initiated but discontinued when bacterial CSF, urine, and blood cultures were negative after 48 hours. Acyclovir was continued at 20 mg/kg/dose every 8 hours. Fever persisted daily, and he was extremely irritable. On postoperative day 8, CSF HSV PCR was positive for type 1. Dexamethasone was discontinued. Repeat lumbar puncture performed on postoperative day 11 had a negative CSF HSV PCR (Table 1). Magnetic resonance imaging on postoperative day 13 showed no evidence of new disease compared with prior scans. He completed a 3 week course of IV acyclovir therapy. At 3 weeks posthemispherectomy he was doing well, with daily improvement, no seizures, and resolution of irritability and fevers. Surgical pathology of the resected tissue demonstrated multiple remote infarctions consistent with remote ischemic injury and microglial nodules, suggestive of a history of HSE. Immunohistochemical stain for HSV did not reveal viral inclusions.

DISCUSSION

Reactivation of HSV after HSE is an unusual occurrence, almost always reported immediately after completion of initial treatment of a primary encephalitis.³ Ito et al reported data for 27 children, 3 months to 16 years of age, who experienced HSE relapse.⁴ Two of these children had confirmatory positive CSF HSV PCR on days 6 and 13 of the relapse, with prior negative CSF HSV PCR results and after completion of acyclovir therapy. Other cases were diagnosed clinically. Duration of acyclovir therapy was approximately 3 days shorter in the relapse group than the control group. Additionally, the daily dose was slightly lower in the relapse group (26.2 mg/kg/d vs. 30.8 mg/kg/d). In this study, a second relapse was described in a 12-year-old girl who had received a second course of acyclovir from 30 to 45 mg/kg/d for 10 to 21 days. She received a third course of acyclovir at 45 mg/kg/d for an additional 14 days and recovered. Valencia et al reported 2 cases of HSE relapse with resulting neurovegetative states in previously healthy children 2 years and 6 months of age at presentation, respectively. The 2-year-old child received acyclovir 45 mg/kg/d for 14 days with dexamethasone for 3 days, and relapsed 14 days after treatment. The 6-month-old child was treated for 21 days with acyclovir 45 mg/kg/d and dexamethasone for 4 days, with relapse 3 days after stopping acyclovir. All the cases reviewed above relapsed within 2 weeks of stopping primary therapy.³

A single case of HSV reactivation in the CSF after epilepsy surgery in a pediatric patient with a prior history of HSE and mesial temporal sclerosis has been reported in the literature.⁵ In this case, a diagnosis of HSE had been made at 16 months of age, and reactivation occurred 6 years later after a left amygdalohypopocampectomy for intractable partial epilepsy performed through a medial temporal gyrus corticotomy, the previous site of herpes infection. After 3 weeks of acyclovir, a new persistent receptive dysphasia remained.

Postoperative HSE has also been reported without a prior history of HSE, including a 35-year-old woman who underwent posterior fossa decompression for a Chiari malformation.⁶ Two weeks postoperatively, she developed progressive bifrontal and occipital headaches and was readmitted. Three weeks postoperatively, she had meningism and photophobia. CSF PCR was obtained and positive for HSV type 2. Acyclovir therapy was initiated, with an improvement in her meningitic symptoms. Perioperative dexamethasone had been given previously. Her headaches resolved after 3 months, but leg and lower back pain continued at 15 months. Of interest is that HSV type 2 was isolated from CSF as HSE is typically due to HSV type 1 beyond the neonatal period.² Such a finding supports proposed mechanisms of transient immunosuppression related to perioperative steroid therapy, surgical stress, and trauma leading to HSV reactivation after neurosurgery.^{5,7,8,9}

Our case, presenting with fever and irritability after surgery, illustrates the importance of considering HSV reactivation as a contributor to postoperative symptoms in neurosurgical patients, particularly in those with a prolonged hospital stay and ongoing complications. The diagnostic procedure of choice in identifying HSE is CSF PCR. Sensitivity and specificity have been reported at over 90%.^{2,10} However, nonstandardized methods of performing HSV PCR have been employed, with various primers in use and thereby gene expression.¹⁰ Negative CSF HSV PCR results must be interpreted with caution, as these results can be seen within 72 hours of onset of symptoms. Positive CSF HSV PCR results have been reported 4 to 7 days later. Repeat CSF HSV PCR should be obtained after therapy to ensure eradication of replicating HSV. After 14 days of therapy, CSF HSV PCR has been noted to be negative in 80% of cases.

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RETINITIS AND OPTIC NEURITIS IN A CHILD WITH CHICKENPOX

CASE REPORT AND REVIEW OF LITERATURE

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Abstract: In immunocompetent individuals, necrotizing retinopathy is a rare complication of chickenpox. Herein, we report on a 3-year-old immunocompetent boy who developed retinitis and optic neuritis 3 days after the onset of chickenpox and compare the findings to published cases. Since macula and optic nerve were affected, visual acuity remained poor. An early diagnosis and treatment of ocular manifestations in chickenpox is imperative for the preservation of a residual visual function and prevention of blinding secondary complications.

Key Words: chickenpox, varicella zoster virus, retinitis, chorioretinitis, children, acyclovir

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Primary infection with varicella zoster virus leads to generalized varicella dermatitis (chickenpox), typically in children between 1 and 9 years of age. The latent virus can also be reactivated later in life.¹ Ocular involvement in cases of primary infection with varicella zoster virus (eg, conjunctival and corneal lesions, iridocyclitis, (chorio) retinitis and optic-nerve lesions) is a rare occurrence.^{2,3} In immunocompromised children who are suffering from leukemia and who have contracted chickenpox, chorioretinitis⁴ and fulminant acute retinal necrosis⁵ have been reported. In healthy children, only few instances of chickenpox-associated retinitis have been documented. In a review by Underwood, 2 cases of bilateral and 1 unilateral optic neuritis following chickenpox were reported.⁶ Copenhagen et al describe a case of chickenpox-associated encephalitis with ocular involvement (bilateral papillitis and unilateral macular lesioning) in which the 3-year-old child underwent complete functional recovery.⁷ On the other hand, Capone et al⁸ and MacKinnon et al⁹ describe poor outcomes in children with chickenpox-associated neuroretinitis. Furthermore, fulminant acute retinal necrosis has also been observed in an immunocompetent child.³ In the present article, we describe a case of acute necrotizing retinopathy and papillitis, which developed shortly after the onset of chickenpox in a 3-year-old boy, and compare the findings to published cases.

CASE REPORT

A 3-year-old boy complaining of blurred vision in his left eye was referred to us. At the time of presentation, he had been suffering for 3 days from a typical chickenpox infection with vesicular dermal eruptions on the trunk and face. The patient was previously healthy, had no history of repetitive or opportunistic infections and was fully immunized according to the Swiss immunization recommendations; however, he was not immunized against varicella as this immunization is not part of this schedule. Visual acuity of the right eye was 20/20, whereas that of the left was reduced to the counting of fingers. Slit-lamp examination revealed conjunctival hyperemia on the left side, but otherwise, the anterior segment in both eyes had a healthy appearance. The posterior segment of the right eye likewise had a healthy appearance. However, in the left eye, the optic nerve was swollen and a puffy yellowish lesion covered the posterior pole, extending over the macula. These clinically resembled active retinitis with exudative retinal edema. The retinal veins were prominent and moderately wrinkled, perivasculitis was evident (Fig. 1A), and a relative afferent papillary defect was observed. The boy was hospitalized. Clinical examination revealed the presence of generalized nuchal, cervical, and angular lymphadenopathy but the absence of encephalitis, which was confirmed by a negative lumbar puncture for cytomegalovirus, herpes simplex virus, and varicella zoster virus. Serology disclosed the presence of *Varicella zoster* (IgM), but the absence of *Toxoplasma*, *Cytomegalovirus*, and HIV. Therapy included a 10-day-course of intravenous acyclovir (3×10 mg/kg of body weight/d) and oral prednisone (10 mg/d), after which the child was released from hospital. Thereafter, acyclovir was administered orally (400 mg t.i.d. for 7 days, followed by 200 mg t.i.d. for 3 months) and the dose of oral prednisone was gradually reduced over the ensuing weeks. Under this regimen, the active lesion healed without undergoing any increase in size. However, a macular scar and atrophy of the optic nerve developed secondarily (Fig. 1B). Visual function in the left eye did not recover beyond 20/400. At the end of the follow-up period (9 years later) no relapse had occurred and no complications had developed; the right eye had remained healthy.

DISCUSSION AND REVIEW OF LITERATURE

In rare cases, chickenpox may be complicated by an involvement of the retina and optic nerve, irrespective of the immunologic status or age of the individual. In this article, we present our findings relating to the case of a 3-year-old immunocompetent boy with chickenpox-associated retinopathy. The prompt diagnosis and onset of treatment averted the development of blinding consequences, such as retinal detachment,³ although the functional outcome remained poor. Because chickenpox-associated acute retinal necrosis usually follows a fairly mild course in elderly individuals,^{10,11} and because the complication is rare in children, a generally accepted course of treatment has not been established. Although systemic antiviral treatment with acyclovir is strongly recommended by most investigators,¹¹ the systemic administration of corticosteroids is not generally advocated. Since the disease must be expected to be fulminant in children, an early and brief pharmacological intervention is recommendable in cases of chickenpox-associated necrotizing retinopathy.^{10,12} However, no controlled and randomized studies are available due to the rarity of the disease. Early antiviral treatment may inhibit a rapid progression to blindness (as it has been reported in historical cases before acyclovir treatment was available). However, clinicians must be aware that despite early and sufficient antiviral therapy in our case only a stabilization of visual acuity over the long-term follow-up of 9 years was achieved.

To date, only 5 cases of chickenpox-associated retinitis and 10 of optic neuritis have been reported in literature (Table 1). Although Underwood highlighted the rare complication of optic neuritis in children with chickenpox, awareness of clinicians about this rare manifestation of chickenpox seems to have decreased in the last decades. In only one instance—and this in the context of encephalitis—has an involvement of both the retina and the optic disc been reported.⁷ Since a complete spontaneous functional recovery was described in this case, a viral etiology of the retinal necrosis can be excluded. In all likelihood, the condition arose secondarily as a consequence of exudative changes in the retina (stellate maculopathy).

Our findings reinforce the prevailing current opinion that children who are suffering from chickenpox and who either

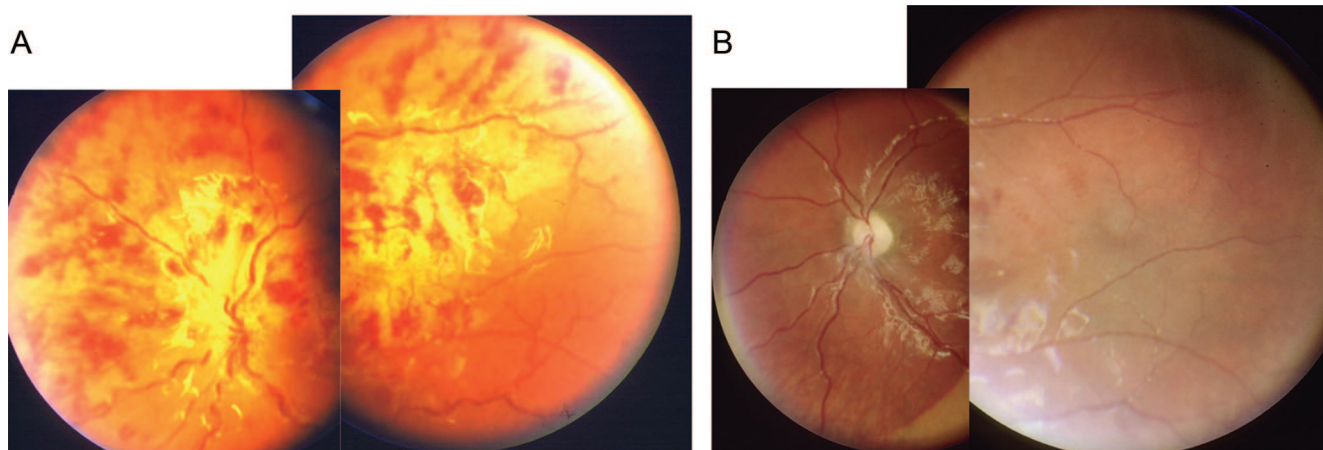


FIGURE 1. A, Composed fundus view of the retina in the left eye of the 3-year-old boy with chickenpox, revealing swelling of the optic nerve, petechial retinal hemorrhaging, and retinitis involving the left peripapillary region and posterior pole. B, Composed retinal image of the left eye of the 3-year-old boy with chickenpox, 6 weeks after the onset of antiviral and steroid therapy. The retinal edema has regressed, and the optic-nerve head manifests signs of atrophy.

TABLE 1. Published and Own Cases of Chickenpox-associated Eye Disease

Reference	Authors	Year of Publication	Age of Patient (yr)	Gender	Interval Between the Onset of Chickenpox and That of Ocular Symptoms (d)	Primary Manifestation	Further Complications
3	Lee and Charles	2000	4	Male	42	Retinitis	Retinal detachment
8	Capone and Meredith	1992	2	NA	NA	Retinitis	
9	McKinnon et al	2002	9	NA	NA	Retinitis	
	Own case	2010	3	Male	3	Retinitis	Optic neuritis/papillitis
6	Chavernac	1908	11	Male	Gradual	Optic neuritis	Bilateral
6	Paton	1917	14	Male	3	Optic neuritis	
6	Ratner	1925	4	Male	9	Optic neuritis	Bilateral
13	Hatch	1949	6	NA	14	Optic neuritis	
7	Copenhaver	1966	3	NA	2	Optic neuritis	Bilateral involvement with unilateral macular lesion
14	Walsh and Hoyt	1969	7	NA	14	Optic neuritis	Bilateral
15	Bruguier et al	1981	8	Female	NA	Optic neuritis	
16	Selbst et al	1983	10	Female	38	Optic neuritis	Bilateral
17	Purvin et al	1988	14	Female	7	Optic neuritis	Bilateral
18	Roelandt et al	2005	3	Male	7	Optic neuritis	
19	Stergiou et al	2007	6	Female	7	Optic neuritis	

NA indicates information not available.

manifest unilateral eye reddening or complain of blurred vision should be immediately subjected to an ophthalmological examination, irrespective of their immunologic status, to exclude ocular involvement, viz, papillitis or necrotizing retinopathy. Prompt handling of these conditions would help to preserve some residual visual function and to avert the development of further complications.

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