



# No Visible Dental Staining in Children Treated with Doxycycline for Suspected Rocky Mountain Spotted Fever

Suzanne R. Todd, DVM<sup>1</sup>, F. Scott Dahlgren, MSPH<sup>1</sup>, Marc S. Traeger, MD<sup>2</sup>, Eugenio D. Beltrán-Aguilar, DMD, DrPH<sup>3</sup>, Donald W. Marianos, DDS<sup>1</sup>, Charlene Hamilton, MPH<sup>4</sup>, Jennifer H. McQuiston, DVM<sup>1</sup>, and Joanna J. Regan, MD<sup>1</sup>

**Objective** To evaluate whether cosmetically relevant dental effects occurred among children who had received doxycycline for treatment of suspected Rocky Mountain spotted fever (RMSF).

**Study design** Children who lived on an American Indian reservation with high incidence of RMSF were classified as exposed or unexposed to doxycycline, based on medical and pharmacy record abstraction. Licensed, trained dentists examined each child's teeth and evaluated visible staining patterns and enamel hypoplasia. Objective tooth color was evaluated with a spectrophotometer.

**Results** Fifty-eight children who received an average of 1.8 courses of doxycycline before 8 years of age and who now had exposed permanent teeth erupted were compared with 213 children who had never received doxycycline. No tetracycline-like staining was observed in any of the exposed children's teeth (0/58, 95% CI 0%-5%), and no significant difference in tooth shade ( $P = .20$ ) or hypoplasia ( $P = 1.0$ ) was found between the 2 groups.

**Conclusions** This study failed to demonstrate dental staining, enamel hypoplasia, or tooth color differences among children who received short-term courses of doxycycline at <8 years of age. Healthcare provider confidence in use of doxycycline for suspected RMSF in children may be improved by modifying the drug's label. (*J Pediatr* 2015;166:1246-51).

Tetracycline-class antibiotics (tetracyclines) once were used widely to treat a variety of infections in children, but studies beginning in the 1950s showed a link between their use in young children and staining and enamel hypoplasia of developing teeth.<sup>1,2</sup> Tetracyclines bind to calcium, which can lead to yellow, gray, and brown staining of developing teeth if administered during tooth crown calcification, which most commonly occurs between birth and the age of 8 years for most permanent teeth except third molars.<sup>3</sup> Previous studies of children who received tetracyclines during odontogenesis showed visible staining in 23%-92% (Table I).<sup>1,2,4-7</sup> Because of these findings, the Food and Drug Administration requires that all tetracyclines, including doxycycline, carry a label warning that the medication should not be used in children under the age of 8 years because of concerns about dental staining, unless no other effective antibiotics exist.<sup>8</sup>

Doxycycline, a newer medication in the tetracycline class, has been available since 1967 and binds to calcium less readily than other tetracyclines.<sup>9</sup> There are no published studies linking doxycycline to dental staining when used at the dose and duration recommended for treating rickettsial diseases. A study in 1969 reported possible faint staining of a single deciduous tooth in 1 of 25 pre-term infants treated with doxycycline; however, dose and duration were not provided, and the authors concluded staining was negligible compared to other tetracyclines.<sup>10</sup> Several past studies have looked for evidence of visible dental staining in children treated with doxycycline prior to the age of 8 years and found no evidence, even when multiple courses were administered.<sup>7,11</sup> However, these studies examined small sample sizes of exposed patients, and employed subjective methods of tooth shade evaluation that might be subject to interpretation bias.

Rocky Mountain spotted fever (RMSF), caused by the intracellular tickborne bacterium *Rickettsia rickettsii*, is a rapidly progressive and potentially fatal illness. The lack of a rapid confirmatory diagnostic test during acute illness requires healthcare providers to make early and empiric treatment decisions in order to avert severe outcomes. Doxycycline is the treatment of choice for RMSF in patients of any age, as recommended by the American Academy of Pediatrics (AAP) and the Centers for Disease Control and Prevention.<sup>12,13</sup> Doxycycline treatment should be continued for at least 3 days after fever resolves, and the usual duration of therapy is 7-10 days.<sup>13</sup> Chloramphenicol is considered a second-line therapeutic agent, as it is significantly less effective at preventing fatal outcome; other broad-spectrum antimicrobial agents typically used to treat sepsis are not effective at preventing fatal outcome due to RMSF.<sup>14</sup>

From the <sup>1</sup>Rickettsial Zoonoses Branch, Division of Vectorborne Diseases, Centers for Disease Control and Prevention, Atlanta, GA; <sup>2</sup>Indian Health Service, Whiteriver, AZ; <sup>3</sup>Division of Oral Health, Centers for Disease Control and Prevention, Atlanta, GA; and <sup>4</sup>White Mountain Apache Tribe, Whiteriver, AZ.

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AAP	American Academy of Pediatrics
IHS	Indian Health Service
RMSF	Rocky Mountain spotted fever

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**Table 1.** Studies examining dental staining because of treatment of children with tetracyclines

Reference	Antibiotic (duration)	Study population	Proportion (%) exposed with stained teeth
Shwachman et al <sup>1</sup>	Chlortetracycline and oxytetracycline (long-term)	Patients with cystic fibrosis	40/50 (80%)
Wallman and Hilton <sup>2</sup>	Tetracycline (short-term)	Neonates	46/50 (92%)
Swallow et al <sup>4</sup>	Chlortetracycline, tetracycline, and oxytetracycline (long-term)	Patients with cystic fibrosis	24/63 (38%)
Conchie et al <sup>5</sup>	Mixed tetracyclines (unknown duration)	Children who had received tetracycline prior to age of 6 and who are now 8-11 y	55/238 (23%)
Rebich et al <sup>6</sup>	Mixed tetracyclines (unknown duration)	American Indian children 4-19 y	55/137 (40%)
Volovitz et al <sup>7</sup>	Doxycycline (short-term)	Patients with asthma	0/31 (0%)

Early administration of doxycycline has been shown to be the single most important factor influencing the survival of patients with RMSF.<sup>15</sup> Despite clear evidence that RMSF fatalities are preventable when treated early and appropriately, and despite national AAP guidelines regarding treatment of suspected RMSF in children, the case fatality rate for RMSF infection among US children under the age of 10 years currently is 5 times that of cases who are older.<sup>16</sup> Only 35% of US healthcare providers report using doxycycline to treat suspected cases of RMSF in children <8 years of age, even though 80% correctly identified doxycycline as the primary treatment for adults and older children.<sup>17</sup> Physician reluctance to prescribe doxycycline to younger children may be due to the dental staining legacy of older tetracyclines and the current doxycycline label warning against use in children <8 years of age.

RMSF recently has emerged as a significant public health issue on tribal lands in eastern Arizona.<sup>15,18,19</sup> Because of intensive education efforts at one reservation's Indian Health Service (IHS) facility, healthcare providers there have routinely prescribed doxycycline to all suspected RMSF cases, regardless of age, since 2003.<sup>19</sup> This practice has resulted in a large population of children who have received 1 or more courses of doxycycline prior to the age of 8 years. If pediatric doxycycline administration causes adverse effects on teeth, it should be detectable in this community, both visually and by means of objective measurement.

## Methods

We performed a retrospective cohort study consisting of a review of medical and pharmacy records and a cross-sectional dental examination and questionnaire. Data on tetracycline-like staining, enamel hypoplasia, and tooth shade were collected during the dental examination. Potential tooth darkening behaviors were captured through a questionnaire. Any history of receiving doxycycline was established by a review of medical and pharmacy records. The study was conducted with the approval of the Tribal Council, and the Centers for Disease Control and Prevention and the regional IHS Institutional Review Boards. Letters were mailed to reservations and additionally distributed through schools. Parents/legal guardians of study subjects gave written informed consent and children provided oral assent.

The target population was all children between the ages of 8 and 16 years residing and attending schools on 1 American Indian reservation in eastern Arizona. This target population numbered approximately 2500 children, based on US Census data.<sup>20</sup> The study was conducted August-September, 2013. Children aged 16 years at the time of the study would have had at least 1 crown still calcifying in 2003 when physicians first began using doxycycline in children for RMSF. A minimum age of 8 years was used because at this age children typically have at least 1 permanent maxillary anterior tooth erupted at time of examination.

All dental examinations were performed by licensed dentists, who were blinded to the exposure status of the children. Prior to initiation of the study, 5 dentists who would serve as dental examiners were trained by a single experienced dentist in the recognition of the typical signs of tetracycline dental staining, using a set of color photographs displaying nonstudy persons with and without tetracycline-induced defects. Training also was provided on the use and calibration of the VITA Easyshade Compact instrument (Vita Zahnfabrik H. Rauter GmbH and Co, Bad Säckingen, Germany), a handheld spectrophotometer used to evaluate the shade of teeth. The Easyshade provides 16 tooth shade measures, ranging from 1 to 16, where 1 is considered the brightest shade and 16 the darkest.<sup>21</sup> After children brushed their teeth, a trained dentist performed a visual examination of fully erupted permanent maxillary central incisors, lateral incisors, cuspids, and first premolars. Children without any of these teeth present were excluded. Teeth with orthodontic brackets, restoration, or reconstruction work which precluded examination of the labial surface of the tooth were excluded. Dentists noted the presence of decay, fluorosis, enamel hypoplasia, and presence of any tetracycline-like staining patterns on the labial aspect of these teeth. For tetracycline-like staining, dentists looked for characteristic blue-gray coloration on the enamel with a normal tooth structure, absence of enamel pitting, and regular glossiness of enamel. Typical tetracycline-associated lesions would have clear horizontal borders and may affect any area of the tooth, from bands to the entire surface. The dentist then utilized the VITA Easyshade Compact spectrophotometer to obtain a single reading of tooth shade from the upper-middle one-third of the facial aspect of each of these same teeth.<sup>22</sup> In addition to the dental examination, children were asked how many

times they brushed their teeth, how frequently they drank dark colored beverages such as coffee, tea, or cola, and how frequently they used tobacco products.

In order to obtain a complete medical history on each child, parents were questioned regarding all healthcare facilities where their child received medical care. Medical and pharmacy records were obtained from the local IHS hospital. Records from off-reservation primary care providers and tertiary care centers were reviewed if applicable. Dose, duration, and number of courses of all tetracyclines dispensed, including doxycycline, were abstracted from each child's medical and pharmacy record. No other tetracyclines were reported in any record. Following record abstraction, children who had received at least 1 course of a tetracycline-doxycycline were assigned to the exposed group. All others were assigned to the unexposed group.

### Statistical Analyses

Only those teeth presumed to still be calcifying at the time of doxycycline administration were considered in our analysis of the exposed group's dental data, as follows: age 5 years and younger, first premolar, cuspid, lateral incisor, and central incisor still calcifying; age 6, first premolar and cuspid still calcifying; and age 7, cuspid still calcifying.<sup>3</sup> All other remaining dental data were excluded from analysis of the exposed group. For the unexposed group, no dental data were excluded from the analysis.

All statistical analyses were performed at a significance level of  $\alpha = 0.05$ . All computations were performed using SAS v 9.3 (SAS Institute, Cary, North Carolina) except the CI for a zero numerator proportion, calculated using the rule of 3.<sup>23</sup> Because it is at least as powerful as other unbiased 2-sided tests and because it is robust against violations of normality, the 2-sample *t* test with equal variance was used to compare pairs of means. The association between pairs of categorical variables was tested using Pearson  $\chi^2$  test for general association; except, when any expected frequency was  $<5$ , Fisher exact test was used.

Because the mean age of children in the unexposed cohort was higher than the exposed cohort (most likely influenced by changes in clinical practice on the reservation beginning in 2009, when increasing rates of RMSF prompted wider treatment of patients and increasing the number of exposed younger patients), the Breslow-Day test for homogeneity of association was used to test for effect modification by age. Mantel-Haenszel estimates of the common prevalence ratio were used when adjusting for age.

Spearman correlation coefficient was used to test the association of exposure as the total number of days of receiving doxycycline before the age of 8 years, or simply the duration of doxycycline, with 2 outcomes: (1) average tooth shade; and (2) the proportion of teeth with enamel hypoplasia. Spearman correlation coefficient ranges from  $-1$  to  $1$ , with values approaching  $0$  showing the least correlation. To assess potential confounding by either age at the time of study or the proportion of teeth with fluorosis, Spearman correlation coefficient was used to test the

pairwise association between these potential confounders with the duration of doxycycline and both outcomes. Controlling for potential confounders associated with the duration of doxycycline or either outcome, Spearman partial correlation coefficients were used to test the association between the duration of doxycycline and both outcomes.

## Results

The records of 366 eligible children were reviewed. None had ever received a tetracycline-class antibiotic other than doxycycline. Of these, 335 children were present at school on the day of the examination and assented to participate.

Of the 335 children examined, 76 received at least 1 dose of doxycycline prior to the age of 8 years. However, only 58 children received doxycycline during the period of calcification of at least 1 tooth and had at least 1 of these exposed teeth fully erupted at the time of the dental examination. These 58 children were considered the exposed group for our analysis. Eighteen children who received doxycycline before the age of 8 without an erupted exposed tooth, and 46 children who had first received doxycycline at 8 years old or older were excluded from the analysis. The remaining 213 children who never received doxycycline were considered the unexposed group in our analysis.

The 58 children in the exposed group received a total of 107 courses of doxycycline before the age of 8 years old. The average duration of these courses of doxycycline was 7.3 days (range 1-10, SD = 2.8). The mean doxycycline dose was 2.3 mg/kg (range 0.3-2.9, SD = 0.40), which is not dissimilar from the recommended dose of 2.2 mg/kg/dose (maximum, 100 mg/dose). The average age of doxycycline administration was 4.5 years old (range 0.2-7.9, SD = 2.4). The route typically was oral (98%), and the frequency typically was 2 doses daily (97%). Doxycycline was administered according to a reservation-wide treatment algorithm recommending the antibiotic be administered to all patients presenting with fever  $\geq 2$  days, so many of these 58 children received multiple courses of doxycycline prior to 8 years of age, for an average of 1.8 courses per child.

The mean age at time of dental exam of those who received doxycycline was 9.8 years old (range 8.1-15.6, SD = 1.7), and the mean age of those who had not was 11.8 years old (range 8.0-16.9, SD = 2.2). The difference between the average age of those who received doxycycline and those who did not was 2.1 years (SD = 2.1,  $P < .001$ ). There was no significant difference between our 2 groups regarding whether they brushed their teeth twice daily ( $P = .50$ ), whether they drank any dark-colored beverages ( $P = .36$ ), or whether they used any tobacco ( $P = .18$ ); and, these results were qualitatively similar after adjusting for age at exam (Table II).

### Dental Examination

No visible tetracycline-like staining patterns were observed on any of the teeth of the 335 children examined, including those 58 children who received doxycycline before 8 years

**Table II.** The prevalence of enamel hypoplasia, the prevalence of fluorosis, and dental hygiene habits by whether exposed to doxycycline

	Doxycycline <8 y, N (%)	No doxycycline, N (%)	Crude PR (95% CI)	Crude PR, P value	Breslow-Day, P value	Age-adjusted PR (95% CI)	Age-adjusted PR, P value
Enamel hypoplasia	2 (4)	8 (4)	0.92 (0.2-4.2)	1.00	.79	1.6 (0.2-13.5)	.65
Fluorosis	5 (9)	28 (13)	0.66 (0.3-1.6)	.35	.54	0.86 (0.4-2.0)	.72
Brushes $\geq 2$ times daily	40 (75)	148 (71)	1.1 (0.9-1.3)	.50	.32	1.1 (0.9-1.4)	.34
Any dark drinks	41 (71)	163 (77)	0.9 (0.77-1.1)	.36	.32	0.93 (0.8-1.1)	.48
Tobacco use	2 (4)	21 (10)	0.4 (0.1-1.4)	.18	.64	0.75 (0.2-3.1)	.68

PR, prevalence ratio.

The crude PR and its 95% CI are presented, as well as the age-adjusted PR.

Results of the Breslow-Day test for the homogeneity of the associations are stratified by age as a whole number.

of age (95% CI 0%-5%). Enamel hypoplasia was observed in 10 children (4%), but exposure to doxycycline was not associated with the presence of enamel hypoplasia ( $P = 1.0$ ; Table II). Similarly, fluorosis-like hypomineralization was observed in 33 children (12%) but was not associated with exposure to doxycycline ( $P = .35$ ; Table II).

Children exposed to doxycycline prior to the age of 8 years had an average tooth shade of 9.5 (range 3.0-16, SD = 2.5). Those never having received doxycycline had an average tooth shade of 9.0 (range 2.1-15.0, SD = 2.3). There was no significant difference in tooth shade between the 2 groups ( $P = .20$ ). The size of the groups allowed detection of a 1.0 difference in average tooth shade with a power of 0.8, and a 1.3 tooth shade difference with a power of 0.95, assuming a SD of 2.5. No significant differences were observed in the average tooth shade of children when grouping by questionnaire responses or the presence of dental defects (Table III).

Duration of doxycycline was not correlated with the proportion of teeth with enamel hypoplasia (Spearman correlation coefficient  $r = -0.001$ ,  $P = .98$ ) nor with the average tooth shade ( $r = 0.07$ ,  $P = .28$ ). Those children who were younger at the time of the dental examination were more likely to have received a longer duration of doxycycline ( $r = -0.39$ ,  $P < .001$ ). The proportion of teeth with fluorosis was not correlated with duration of doxycycline

( $r = -0.07$ ,  $P = .27$ ), with the proportion of teeth with enamel hypoplasia ( $r = -0.07$ ,  $P = .23$ ), nor with the average tooth shade ( $r = 0.08$ ,  $P = .18$ ). Controlling for age at examination, the duration of doxycycline was not correlated with the proportion of teeth with enamel hypoplasia (Spearman partial correlation coefficient  $\theta = 0.04$ ,  $P = .53$ ) nor with the average tooth shade ( $\theta = 0.09$ ,  $P = .15$ ; Figure).

## Discussion

We found no evidence of cosmetically relevant dental staining of permanent teeth in 58 children who had received doxycycline for treatment of RMSF prior to 8 years of age. Furthermore, the study found no evidence of an increased prevalence of enamel hypoplasia, and no evidence of tooth shade difference, between exposed and unexposed children. Moreover, there was no evidence that multiple doxycycline courses resulted in dental effects, even when children received 3 or more courses of doxycycline while teeth were developing.

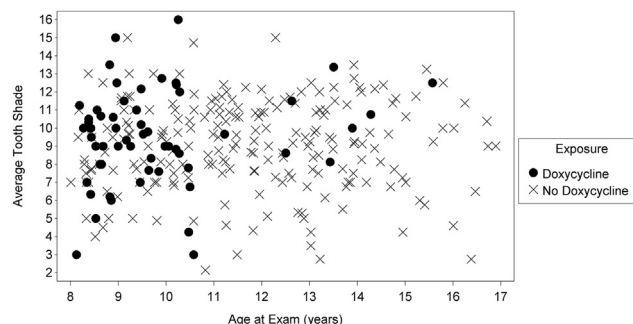
In a study of similar design and methodology, although of smaller patient sample size, Volovitz et al used licensed dentists to examine 31 children who had received a mean number of 2.1 courses of doxycycline (4 mg/kg twice on the first day, and then 2 mg/kg per day for 9 days, 10 day total course) for treatment of resistant asthma.<sup>7</sup> The dentists also examined 30 children who had not

**Table III.** Mean tooth shade of children at dental examination, grouped by exposure to doxycycline, presence of enamel hypoplasia, presence of fluorosis, and dental hygiene habits

	N	Mean tooth shade (SD)	P value
Doxycycline before 8 y	58	9.5 (2.6)	.20
No doxycycline	213	9.0 (2.5)	
Any enamel hypoplasia	10	9.8 (3.1)	.38
No enamel hypoplasia	261	9.1 (2.5)	
Any fluorosis	33	9.7 (2.7)	.16
No fluorosis	238	9.1 (2.5)	
Brushes teeth $\geq 2$ times daily	188	8.9 (2.6)	.10
Brushes teeth <2 times daily	74	9.5 (2.3)	
Any dark drinks*	204	9.1 (2.4)	.98
No dark drinks*	67	9.1 (2.8)	
Any tobacco*	23	9.1 (2.4)	.86
No tobacco*	242	9.2 (2.6)	

The SD and the P value from the 2-sample *t* test with equal variance are presented.

\*Not all participants provided answers.

**Figure.** A scatterplot of average tooth shade by age at examination, stratified by doxycycline exposure.



received doxycycline. The study consisted of a visual exam, and subjective evaluation of tooth color. Similar to our findings, Volovitz et al found no evidence of dental staining in patients treated with doxycycline. When the data regarding visible dental staining from our study are combined with the findings from Volovitz et al, the conclusions are even more compelling, with a combined dental staining prevalence rate of 0% (0/89, 95% CI 0%-3%) among children treated with doxycycline.<sup>7</sup> In contrast, in the published literature, dental staining was reported in 23%-92% of children treated with older tetracyclines (Table I).<sup>1,2,4-6</sup>

This study is subject to several limitations. Only externally visible dental effects (staining, tooth shade, and hypoplasia) were evaluated, as these factors were believed to be the most cosmetically relevant. Although most children received care and had prescriptions dispensed at the IHS facility, it is possible that parents did not recall all locations where a child received care and that some children in the unexposed group may have received doxycycline outside of our knowledge. Although the prescribed dosage, duration, date of administration, and quantity dispensed of doxycycline recorded in the medical and pharmacy records were used in our analysis, we could not confirm whether a child completed the entire course of doxycycline prescribed to them. Children's answers to the questions on dental habits could be biased based on the child's ability to recall behaviors, to understand the question, and to admit to unhealthy behavior. The wide range of tooth shades seen among both exposed and unexposed children suggests that objectively determined tooth shade can be highly variable among individuals, and may not be a wholly reliable means of assessing tooth shade differences when comparing individuals with individuals (Figure); however, our comparison looked at average tooth shade between groups, lessening the effect of individual variability. Finally, although every effort was made to train dentists providing examinations according to a single identification standard, there may have been inter-rater variability in both visual assessments and use of the spectrophotometer.

Administering short courses of doxycycline of 10 days or less to children <8 years of age for treatment of RMSF does not darken the shade of teeth, cause visible staining, or increase the risk of enamel hypoplasia. Despite strong AAP recommendations to treat suspected RMSF in children with doxycycline, pediatric mortality because of RMSF remains higher than adult mortality, and US healthcare providers report reluctance to prescribe doxycycline for suspected RMSF in children.<sup>16,17</sup> To improve healthcare provider confidence in their treatment choices and reduce pediatric mortality due to RMSF, current doxycycline label warnings about possible dental effects should be reconsidered, especially given the cumulative lack of evidence for dental staining. ■

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Reprint requests: Jennifer H. McQuiston, DVM, MS, Centers for Disease Control and Prevention, 1600 Clifton Rd, MS D-25, Atlanta, GA 30333. E-mail: xxx@xxx.xxx

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