

Article details: 2012-0012	
Title	Pediatric Salmonella typhi infections in a Canadian pediatric hospital: "An Ounce of prevention is worth a pound of cure"
Authors	Caroline Quach, Jeannette Comeau, Thai-Hoa Tran, Dorothy L Moore; Chi-Minh Phi
Reviewer 1	Pierre Joseph Plourde,
Institution	Medical Officer of Health, Medical Director, Travel Health and Tropical Medicine Services, Winnipeg Regional Health Authority, Winnipeg, Man.
General comments	<p>This case series spanning 20 years is a description of the epidemiology of S typhi infections in children requiring admission to a teaching hospital in Montreal. The first observation I would make is that there have only been 39 cases in 20 years with no fatalities (ie, only 2 admissions per year in a very large urban centre with a large immigrant population) - this would suggest to most readers that severe typhoid is relatively rare and it is successfully treated in a Canadian tertiary care setting. Hence, it is a bit surprising to me that this data would be used to conclude that typhoid vaccine should be recommended (without any risk assessment of who should or shouldn't be recommended the vaccine), despite the relatively poor efficacy of this vaccine (50-55% at best in a Cochrane review in 2007 and a systematic review published in 2009 which the authors omitted from their references) (Fraser et al, Cochrane Database Syst Rev 2007;3 CD001261) (Whitaker JA et al, J Trav Med 2009;16(1):46-52). I suspect that a cost-benefit analysis of typhoid vaccine using the author's data from this epidemiologic survey would calculate a number needed to vaccinate (NNV) to prevent one pediatric hospitalization due to typhoid fever to be somewhere in the 10,000's if not 100,000's. So although I would agree that it is important for physicians to promote the need for pre-travel health advice especially to families bringing their children to their native countries of origin where typhoid fever is endemic, I don't know that this case series data makes a very compelling case for typhoid vaccine.</p> <p>Rather, I would encourage the authors to revisit their data and conclusions as the data actually reveal some very important take home messages including:</p> <ol style="list-style-type: none"> 1) Typhoid fever in children severe enough to require admission to a tertiary care hospital is rare - as a result clinicians need to have a high index of suspicion when evaluating a febrile child with recent travel to an endemic country, especially if that child was a VFR (visiting friends and relatives). 2) The differential diagnosis of any febrile child traveller from a developing country must include typhoid (in addition to malaria) - both presenting with non-specific illnesses, both potentially fatal if untreated, and both curable when treated in a timely fashion. 3) As stool cultures are insensitive for the diagnosis of typhoid fever, blood cultures must also be performed in all febrile VFR child travellers (this is not new knowledge, but could be reinforced as this case series data reiterates this fact about S typhi infection). 4) Fluoroquinolones (often prescribed by physicians as empiric therapy for suspect typhoid fever in older children and adults) must not be used as first line empiric therapy for any child suspected of having typhoid fever, as there is significant resistance to this class of antibiotics. Hence, first line oral therapy should include cefixime or azithromycin; and first line parenteral therapy should be ceftriaxone or cefotaxime. It is encouraging to note from the data that 92% of children were treated with third generation cephalosporins (but does this reflect pre-hospitalization initial empiric therapy given, or the antibiotics that were used once the child was hospitalized?). 5) This case series cannot make any firm conclusions about the use of typhoid vaccines in children (as none of the children were immunized and no control group was included) - but given that typhoid vaccines have low toxicities and moderate efficacy, one might be able to suggest that use of typhoid vaccine might lead to reduced morbidity and hence reduced hospitalization of children with typhoid fever (but would not make any stronger statement than this about vaccine). <p>Some editorial comments:</p> <ol style="list-style-type: none"> 1) Page 3 - Introduction line 13 - there is no such thing as "typhoid endemics" - would reword to state "predispose developing countries to high typhoid endemicity". 2) Page 6 - line 34 - "The resistance patterns are shown in Figure 3" - but Fig 3 only shows resistance to ampicillin. It would have been preferable to have a figure that shows resistance patterns of all antibiotics, to be able to make comparisons between different antibiotic-resistance patterns over time. 2) Page 6 - line 39 - the difference between 4 of 18 isolates resistant to ampicillin and 6 of 18 should not be statistically significant at $p=0.05$ given such a low denominator. 3) Page 9 - line 15 - "routinely researching ciprofloxacin resistance" should be restated as "routinely detecting ciprofloxacin resistance". 4) Page 9 - line 27 - spelling of "inititation" should be "initiation".

	<p>5) Page 10 - line 39 - "redoubtable" not a word; I think you meant to say "undoubtedly".</p> <p>6) Table 1 - what was the average platelet count (mild thrombocytopenia may be a clue to the diagnosis of S typhi).</p>
Reviewer 2	John Christenson
Institution	Indiana University School of Medicine, Pediatric Infectious Diseases, Indianapolis, Ind.
General comments	<p>Retrospective analysis of cases of typhoid fever [<i>Salmonella typhi</i>] diagnosed and treated at a children's hospital in Montreal.</p> <p>1- Abstract, page 2: Well-written. Did any patient visit a travel clinic? If the answer is no, it should be stated. It is "suggested", but it should be stated as such if true. How many children were under 2 years of age? These children would have not been able to receive a vaccine.</p> <p>2- Introduction, page 3, second line: Million[s] plural?</p> <p>3- Study population, page 4: Since clinical presentations are similar, did the authors evaluate any patients with paratyphoid fever [<i>Salmonella paratyphi</i>]? If so, would it be a more appropriate manuscript if it was focused on "enteric fever." A comment by the authors could address this issue? Obviously, if the focus of the preventive measures is vaccination, then it could have been left out. However, Ty21a vaccine offers some cross-protection against paratyphoid fever.</p> <p>4- Study population and design, page 4: Did 100% of patients have a blood culture and a stool culture? Any diagnoses made by serology? Were these excluded?</p> <p>5- Results, page 5, second line, first paragraph: How many patients were under 2 years of age?</p> <p>6- Results, page 5, second paragraph, 5th line: Authors need to define "recently".</p> <p>7- Results, page 5, second paragraph, last sentence: Did any patient visit a travel clinic? If the answer is no, it should be stated. It is "suggested", but it should be stated as such if true. Was this information not available in the medical records of the children? Did a physician ever recommended it and it was not received? If children were under 2 years of age, they could not receive the vaccine. The authors could clarify these questions.</p> <p>8- Results, page 6, 3rd paragraph, first sentence: Did 100% of patients have a stool culture? Three patients with only a positive stool culture? Do we have any patients where a blood culture was not drawn?</p> <p>9- Results, page 6, 3rd paragraph, last sentence: If ciprofloxacin susceptibility was not determined on all isolates, how can the authors support such a statement? Any additional data available?</p> <p>10- Discussion, page 7, first paragraph: This is a long sentence. Should it be broken into two statements. Should there be two separate references cited? One for the American trend and one for South Asia?</p> <p>11- Discussion, page 7, second paragraph, second line: The authors should define "quasi elimination". Should a different term be used?</p> <p>12- Discussion, page 8, first paragraph, last sentence: This statement is solid only if 100% of patients had a stool culture and blood culture. Is this the case? If not, perhaps the authors may need to qualify this statement.</p> <p>13- Discussion, page 8, second paragraph, 2nd-3rd sentence: Authors need to define "chronic...carrier status".</p> <p>14- Discussion, page 8, second paragraph, 4th line: Authors could be more specific regarding the "milder" clinical presentation of their patients. Compared to what group?</p> <p>15- Discussion, page 9, second paragraph, 4th sentence: Two patients relapsed. Based on what criteria? New positive blood cultures? Return of symptoms?</p> <p>16- Discussion, page 9, last paragraph: Once again, did any patient visit a travel clinic? Did a physician ever recommended it and it was not received? If children were under 2 years of age, they could not receive the vaccine. The authors could clarify these issues.</p> <p>17- Conclusion, page 10: With vaccines being only ~50% protective, any other precautions that should be discussed with parents and guardians? Safe foods and water?</p>

<p>Author response</p>	<p>This case series spanning 20 years is a description of the epidemiology of S typhi infections in children requiring admission to a teaching hospital in Montreal. The first observation I would make is that there have only been 39 cases in 20 years with no fatalities (ie, only 2 admissions per year in a very large urban centre with a large immigrant population) - this would suggest to most readers that severe typhoid is relatively rare and it is successfully treated in a Canadian tertiary care setting. Hence, it is a bit surprising to me that this data would be used to conclude that typhoid vaccine should be recommended (without any risk assessment of who should or shouldn't be recommended the vaccine), despite the relatively poor efficacy of this vaccine (50-55% at best in a Cochrane review in 2007 and a systematic review published in 2009 which the authors omitted from their references) (Fraser et al, Cochrane Database Syst Rev 2007;3 CD001261) (Whitaker JA et al, J Trav Med 2009;16(1):46-52). I suspect that a cost-benefit analysis of typhoid vaccine using the author's data from this epidemiologic survey would calculate a number needed to vaccinate (NNV) to prevent one pediatric hospitalization due to typhoid fever to be somewhere in the 10,000's if not 100,000's. So although I would agree that it is important for physicians to promote the need for pre-travel health advice especially to families bringing their children to their native countries of origin where typhoid fever is endemic, I don't know that this case series data makes a very compelling case for typhoid vaccine. Rather, I would encourage the authors to revisit their data and conclusions as the data actually reveal some very important take home messages including:</p> <ol style="list-style-type: none"> 1) Typhoid fever in children severe enough to require admission to a tertiary care hospital is rare - as a result clinicians need to have a high index of suspicion when evaluating a febrile child with recent travel to an endemic country, especially if that child was a VFR (visiting friends and relatives). 2) The differential diagnosis of any febrile child traveller from a developing country must include typhoid (in addition to malaria) - both presenting with non-specific illnesses, both potentially fatal if untreated, and both curable when treated in a timely fashion. 3) As stool cultures are insensitive for the diagnosis of typhoid fever, blood cultures must also be performed in all febrile VFR child travellers (this is not new knowledge, but could be reinforced as this case series data reiterates this fact about S typhi infection). 4) Fluoroquinolones (often prescribed by physicians as empiric therapy for suspect typhoid fever in older children and adults) must not be used as first line empiric therapy for any child suspected of having typhoid fever, as there is significant resistance to this class of antibiotics. Hence, first line oral therapy should include cefixime or azithromycin; and first line parenteral therapy should be ceftriaxone or cefotaxime. It is encouraging to note from the data that 92% of children were treated with third generation cephalosporins (but does this reflect pre-hospitalization initial empiric therapy given, or the antibiotics that were used once the child was hospitalized?). 5) This case series cannot make any firm conclusions about the use of typhoid vaccines in children (as none of the children were immunized and no control group was included) - but given that typhoid vaccines have low toxicities and moderate efficacy, one might be able to suggest that use of typhoid vaccine might lead to reduced morbidity and hence reduced hospitalization of children with typhoid fever (but would not make any stronger statement than this about vaccine). <p>A: We have noted the above comments and altered our discussion accordingly. Some editorial comments:</p> <ol style="list-style-type: none"> 1) Page 3 - Introduction line 13 - there is no such thing as "typhoid endemics" - would reword to state "predispose developing countries to high typhoid endemicity". <p>A: Done.</p>
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2) Page 6 - line 34 - "The resistance patterns are shown in Figure 3" - but Fig 3 only shows resistance to ampicillin. It would have been preferable to have a figure that shows resistance patterns of all antibiotics, to be able to make comparisons between different antibiotic-resistance patterns over time.

A: Text has been changed; given changing laboratory testing, only ampicillin was routinely tested

3) Page 6 - line 39 - the difference between 4 of 18 isolates resistant to ampicillin and 6 of 18 should not be statistically significant at $p=0.05$ given such a low denominator.

A: This has been deleted

4) Page 9 - line 15 - "routinely researching ciprofloxacin resistance" should be restated as "routinely detecting ciprofloxacin resistance".

A: Done.

5) Page 9 - line 27 - spelling of "inititation" should be "initiation".

A: Done.

6) Page 10 - line 39 - "redoubtable" not a word; I think you meant to say "undoubtedly".

A: Sentence deleted.

7) Table 1 - what was the average platelet count (mild thrombocytopenia may be a clue to the diagnosis of S typhi).

A: Added.

Reviewer: 2

Comments to the Author

Retrospective analysis of cases of typhoid fever [*Salmonella typhi*] diagnosed and treated at a children's hospital in Montreal.

1- Abstract, page 2: Well-written. Did any patient visit a travel clinic? If the answer is no, it should be stated. It is "suggested", but it should be stated as such if true. How many children were under 2 years of age? These children would have not been able to receive a vaccine.

A: Statement added.

2- Introduction, page 3, second line: Million[s] plural?

A: "s" deleted.

3- Study population, page 4: Since clinical presentations are similar, did the authors evaluate any patients with paratyphoid fever [*Salmonella paratyphi*]? If so, would it be a more appropriate manuscript if it was focused on "enteric fever." A comment by the authors could address this issue? Obviously, if the focus of the preventive measures is vaccination, then it could have been left out. However, Ty21a vaccine offers some cross-protection against paratyphoid fever.

A: S. paratyphi was not evaluated in this study.

4- Study population and design, page 4: Did 100% of patients have a blood culture and a stool culture? Any diagnoses made by serology? Were these excluded?

A: No, this has been identified in the text: Results, paragraph 5

5- Results, page 5, second line, first paragraph: How many patients were under 2 years of age?

A: 5, this has been added.

6- Results, page 5, second paragraph, 5th line: Authors need to define "recently".

A: Wording changed.

7- Results, page 5, second paragraph, last sentence: Did any patient visit a travel clinic? If the answer is no, it should be stated. It is "suggested", but it should be stated as such if true. Was this information not available in the medical records of the children? Did a physician ever recommended it and it was not received? If children were under 2 years of age, they could not receive the vaccine. The authors could clarify these questions.

A: Not explicitly recorded whether or not a travel clinic was attended. This is now stated. The travel clinic is not located at our hospital so such a visit would not be

	<p>recorded in our records.</p> <p>8- Results, page 6, 3rd paragraph, first sentence: Did 100% of patients have a stool culture? Three patients with only a positive stool culture? Do we have any patients where a blood culture was not drawn? A: This is explained in results: paragraph 5</p> <p>9- Results, page 6, 3rd paragraph, last sentence: If ciprofloxacin susceptibility was not determined on all isolates, how can the authors support such a statement? Any additional data available? A: Statement altered.</p> <p>10- Discussion, page 7, first paragraph: This is a long sentence. Should it be broken into two statements. Should there be two separate references cited? One for the American trend and one for South Asia? A: Statement deleted and changed.</p> <p>11- Discussion, page 7, second paragraph, second line: The authors should define "quasi elimination". Should a different term be used? A: Changed to near-elimination with data in the next sentence.</p> <p>12- Discussion, page 8, first paragraph, last sentence: This statement is solid only if 100% of patients had a stool culture and blood culture. Is this the case? If not, perhaps the authors may need to qualify this statement. A: This has been qualified.</p> <p>13- Discussion, page 8, second paragraph, 2nd-3rd sentence: Authors need to define "chronic...carrier status". A: Defined.</p> <p>14- Discussion, page 8, second paragraph, 4th line: Authors could be more specific regarding the "milder" clinical presentation of their patients. Compared to what group? A: This has been qualified.</p> <p>15- Discussion, page 9, second paragraph, 4th sentence: Two patients relapsed. Based on what criteria? New positive blood cultures? Return of symptoms? A: See text: both; this has been stated.</p> <p>16- Discussion, page 9, last paragraph: Once again, did any patient visit a travel clinic? Did a physician ever recommended it and it was not received? If children were under 2 years of age, they could not receive the vaccine. The authors could clarify these issues. A: This has been clarified.</p> <p>17- Conclusion, page 10: With vaccines being only ~50% protective, any other precautions that should be discussed with parents and guardians? Safe foods and water? A: We have included this in our conclusion.</p>
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