

## ORIGINAL ARTICLE

## Early diagnosis of typhoid fever by the detection of salivary IgA

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**Background/Aims:** Current diagnostic methods for typhoid fever have low sensitivity and specificity. This study aimed to develop an enzyme linked immunosorbent assay (ELISA) with greater sensitivity and specificity.

**Methods:** The ELISA was developed and evaluated on patients with acute typhoid infection, febrile controls, and healthy controls. A sequential study on patients with culture confirmed typhoid was also carried out to determine the time period of maximum sensitivity.

**Results:** The ELISA detected anti-*Salmonella typhi* lipopolysaccharide (LPS) salivary IgA antibodies. A six month follow up study of patients with culture confirmed typhoid fever showed that the test shows maximum efficiency during the second and third weeks of fever and enables detection of the acute infection during the early phase.

**Conclusions:** This ELISA can detect typhoid fever during the early phase of infection and is most efficient during the second and third weeks of fever, the time at which patients normally present for treatment. Because the sensitivity of the assay is subsequently greatly reduced, it will be useful for the diagnosis of acute infection.

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Typhoid fever is endemic and continues to be a health problem throughout the developing countries of South East Asia, the Indian subcontinent, parts of the central and south Americas, and in much of sub-Saharan Africa. Typhoid is diagnosed using a combination of the clinical picture, the isolation of *Salmonella typhi* from body fluids, and the Widal test.

The variation in the classic picture seen during the past three decades has necessitated laboratory confirmation to diagnose typhoid. Although definitive diagnosis of typhoid fever can be made by the isolation of *S typhi* from biological fluids, the percentage of positivity gradually decreases after the first week of fever.<sup>1,2</sup> In addition, it requires at least 48 hours for confirmed bacteriological results, and tests may show up falsely negative because of previous antibiotic treatment.<sup>3,4</sup>

The most widely used serological assay, the Widal test, poses some disadvantages in endemic areas.<sup>5</sup> Previous exposure to *S typhi* or antigenically related Gram negative bacilli and vaccination against typhoid can result in raised titres in the absence of a current infection.<sup>6,7</sup> In contrast, a poor antibody response to either the “O” or “H” antigen (or both) can occur in some patients.<sup>6,8</sup> Hence, the Widal test often leads to confusion and, on occasions, to misdiagnosis of other febrile illnesses as typhoid fever.<sup>9</sup> A successful technique should be simple, rapid, and sufficiently sensitive to detect most patients with typhoid, but should be specific enough to avoid misdiagnosis of other febrile illnesses.

The usefulness of the enzyme linked immunosorbent assay (ELISA) in the diagnosis of typhoid fever has been determined by various investigators using serum<sup>10–13</sup> and urine.<sup>14,15</sup> Although they found that ELISA using these biological fluids has superior sensitivity and specificity to the Widal test, the invasiveness and the difficulty of obtaining and maintaining samples until tested have reduced the usefulness of the test. Therefore, an ELISA to detect anti-*S typhi* lipopolysaccharide (LPS) IgA antibodies in a single salivary sample of patients with typhoid was developed.

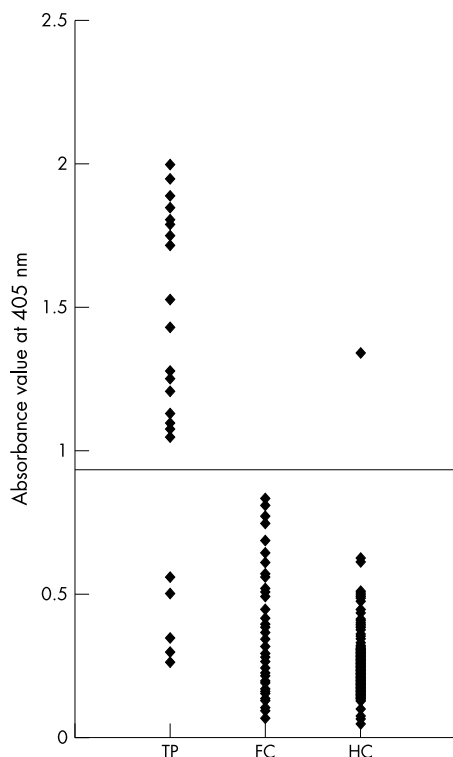
“The Widal test often leads to confusion and, on occasions, to misdiagnosis of other febrile illnesses as typhoid fever”

Saliva is easy and inexpensive to obtain and contains large amounts of IgA, so that it can play an important role in diagnosis. Several investigators have tried to ascertain the usefulness of measuring IgA during the course of typhoid infection. Salivary IgA antibodies are increased in the acute stage of illness and the detection of IgA in serum and intestinal fluids has been attempted previously.<sup>11,16</sup> Because saliva contains high concentrations of IgA antibodies (19 mg/ml) even during the resting period,<sup>17</sup> the detection of salivary IgA antibodies during the acute phase of typhoid would be useful in early diagnosis. Absence of Rh factor in salivary secretions enhances the specificity of the assay, because the Rh factor present in serum seems to affect the ELISA by non-specifically binding to the antigen used to coat the solid phase. Therefore, the objective of this study was to evaluate the usefulness of ELISA in the rapid and early diagnosis of typhoid fever in endemic areas. This was achieved by developing an ELISA to detect anti-*S typhi* LPS IgA antibodies in a single salivary sample of patients with culture confirmed typhoid and carrying out a sequential study to determine the antibody profiles during the acute and the convalescent periods.

## METHODS AND MATERIALS

Blood and salivary samples were collected from adult patients admitted to the Kandy General Hospital, Sri Lanka (1995–1997) in whom typhoid fever was included in the initial differential diagnosis. Blood cultures, the Widal test (on serum), and IgA ELISA (on saliva) were performed. This study was done in two stages.

**Abbreviations:** CSV, corrected sample value; ELISA, enzyme linked immunosorbent assay; LPS, lipopolysaccharide; PBS, phosphate buffered saline; UTI, urinary tract infection



**Figure 1** Immunoglobulin anti-*Salmonella typhi* IgA enzyme linked immunosorbent assay: absorbance values for salivary samples from patients with typhoid fever (TP), febrile non-typhoidal (FC), and healthy controls (HC). The horizontal line represents the cut off point at 0.958.

### Stage 1: evaluation of ELISA with patients having an acute typhoid infection

Group 1: 29 patients who had haemocultures positive for *S typhi*.

Group 2: 51 patients who had haemocultures negative for *S typhi* (positive or negative by the Widal test) but with a febrile illness that had a confirmed alternative diagnosis.

Group 3: 125 healthy individuals who were blood donors and volunteers.

### Stage 2: sequential study to determine anti-*S typhi* IgA antibody profiles

Twenty patients with culture confirmed typhoid fever whose salivary samples were collected serially for a period of six months during the acute and the convalescent phases were investigated. The first salivary sample was collected from all patients at presentation (week 1, number of patients presented (n) = 8; week 2, n = 9; week 3, n = 2; and week 5, n = 1). Subsequent samples were collected at weekly intervals

for the first seven weeks and monthly during the remaining four months.

Blood was processed on receipt. Salivary samples were clarified by centrifugation at 13 000  $\times g$  for 10 minutes at 4°C. All serum and salivary samples were stored at -70°C until required for ELISA.

### ELISA

Antigen (*S typhi* LPS; Sigma Chemical Company, St Louis, USA) was used at 200  $\mu g/ml$  in 0.05M carbonate buffer (pH 9.6) to coat the wells of polystyrene microtitre plates by overnight incubation. The plates were incubated for two hours with the test sample, saliva (neat). Plates, washed manually with phosphate buffered saline (PBS)/Tween 20, were filled with class specific alkaline phosphatase (Kirkegard and Perry Laboratories, Maryland, USA) diluted 1/5000 in PBS/Tween 20 containing 1% bovine serum albumin. They were incubated for two hours and washed with PBS/Tween solution and p-nitrophenyl phosphatase (Sigma Chemical Company), 1 mg/ml in 0.05M carbonate buffer (pH 9.8) containing 0.001M  $MgCl_2$ . The reaction was stopped after 30 minutes with 3N NaOH. Absorbance at 405 nm was read against a blank (antigen in buffer) on an EL 307 C spectrophotometer. The assay was performed in duplicate at 37°C. The reference positive and negative samples were included in each plate tested and the corrected sample value (CSV) was calculated using the formula:

$$(\text{CSV} = \text{measured absorbance of sample} \times \text{given absorbance of positive control}) / \text{measured absorbance of positive control}$$

The cut off value was determined by calculating the midpoint between the mean absorbance of the typhoid positive saliva and the mean absorbance of healthy controls.<sup>18</sup> The indices of sensitivity, specificity, efficiency, and the predictive value of the positive and negative tests were calculated according to Galen.<sup>19</sup>

### RESULTS AND DISCUSSION

The various indices of the test were calculated using the results of haemoculture as the gold standard. The positive cut off titre for IgA antibodies was 0.958. The ELISA results showed a clear distinction between positives (group 1) and negatives (groups 2 and 3), which is a requisite for a diagnostic test (fig 1).

Twenty four of the 29 culture confirmed cases (83%) were IgA ELISA positive and gave a very high mean (SD) absorbance value of 1.414 (0.575), which was 3.3 (mean absorbance, 0.432; SD, 0.328) and 5.2 (mean absorbance, 0.273; SD, 0.149) times greater than the mean values seen for the febrile and healthy controls, respectively. Only one (0.8%) healthy control and four (7.8%) febrile patients with an alternative diagnosis were positive in the IgA ELISA.

Febrile patients (n = 51) included in the initial differential diagnosis and finally having a confirmed alternative diagnosis other than typhoid fever had urinary tract infections (UTI; n = 17), malaria (n = 15), viral hepatitis (n = 5), viral fever

**Table 1** Comparison between anti-O and anti-H agglutinins with anti-LPS IgA antibodies in patients having a definitive diagnosis other than typhoid (group 2)

Disease	O antibody titres				H antibody titres				Mean IgA (SD)
	1/120	1/240	1/480	1/960	1/120	1/240	1/480	1/960	
UTI	6	4	-	3	2	2	-	-	0.468 (0.4)
Malaria	3	7	3	-	1	-	-	-	0.429 (0.336)
Viral hepatitis	-	2	3	-	-	-	-	-	0.428 (0.448)
Viral fever	-	4	4	-	-	-	-	-	0.412 (0.36)
Pulmonary TB	-	4	-	-	-	-	-	-	0.404 (0.182)
Pneumonia	-	1	-	-	-	-	-	-	0.161 (0.161)

LPS, lipopolysaccharide; TB, tuberculosis; UTI, urinary tract infection.

**Table 2** Diagnostic accuracy of enzyme linked immunosorbent assay

Parameter	Accuracy
Sensitivity	83%
Specificity	97%
Efficiency	95%
Predictive value of the positive test	83%
Predictive value of the negative test	97%

(n = 9), pulmonary tuberculosis (n = 4), and pneumonia (n = 1). Table 1 compares anti-*S typhi* LPS salivary IgA antibodies and anti-typhoid O and H agglutinins of these non-typhoidal febrile patients.

Salivary IgA antibodies, as measured by ELISA, and the O and H agglutinins, as measured by the Widal test, were relatively high in UTI when compared with the other diseases. Although four of the 51 patients with non-typhoidal febrile illnesses showed false positive antibody titres by ELISA, the mean (SD) absorbance of the febrile controls was below the cut off value (0.432 (0.328)). The mean (SD) salivary IgA ELISA titre of the 125 healthy volunteers (HC) was 0.273 (0.149). However, a single sample showed an unusual, highly raised reading at the first instance (1.345) and gave a mean (SD) absorbance of 1.223 (0.124) during the four months of follow up. It was 4.5 times greater than that of healthy controls and this abnormal result is discussed later.

Table 2 shows the diagnostic accuracy of the ELISA.

In the Widal test, agglutinins against the O and H antigens of *S typhi* were maximally efficient at an O titre of 1/480 (68.9%) and an H titre of 1/120 (65.5%), respectively (table 3). The sensitivity of the Widal test was lower than that of the ELISA. When the specificity of the ELISA was re-calculated using only the febrile controls who caused diagnostic problems, it decreased to 92%, but was still higher than that of the Widal test.

Figure 2 shows the results of the follow up study of 20 patients with culture confirmed typhoid fever, presenting during the first (n = 8), second (n = 9), third (n = 2), and fifth (n = 1) weeks of fever. The salivary IgA ELISA antibody titres of 17 of 20 patients with culture confirmed typhoid fever were positive, whereas the remaining three were negative throughout the study period.

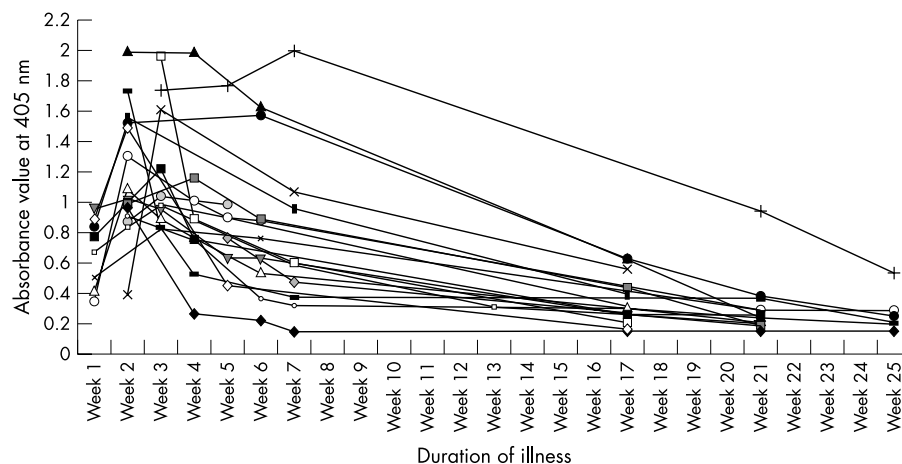
Of the 20 patients, 17 presented for treatment during the first two weeks of illness, whereas the remaining three cases presented during the third and fifth weeks. One of the eight patients who presented during the first week of illness was positive for IgA ELISA (table 4). Of the samples collected in week 2, including five samples from the patients with negative results in the first week, 11 of 15 were positive. Of the nine patients who presented for the first time during the second week, five had positive IgA titres at the time of presentation. Seventy per cent of samples were positive during the third week, including two cases presenting for the first time. However, three samples remained negative throughout the study. During the fourth, fifth, and seventh weeks, only 33% became positive, but this dropped to 8% during the 17th week. The sensitivity of samples at each week was calculated to evaluate the usefulness of the ELISA test at different times of the illness during the six months studied.

According to this study, salivary IgA antibodies reached their maximum, with mean values of 1.177 and 1.205, during the second and third weeks of the illness, respectively (fig 3). These high values subsequently decreased drastically. When all the 20 cases were considered collectively, 17 were positive during the second and third weeks of illness, but the IgA values of all the patients became negative during the course of weeks 3 to 13, except for three cases, which became negative only by week 21.

It is noteworthy that our data show a clear distinction between positives and negatives, and only one of 125 healthy subjects and four of 51 febrile controls became positive by the test, whereas 24 of 29 culture confirmed cases became positive. The sensitivity, specificity, and efficiency of the test were 83%, 97%, and 95%, respectively. A test is generally

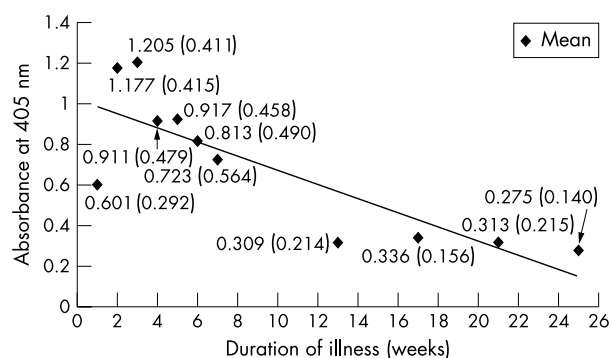
**Table 3** Comparison of sensitivity and specificity of IgA enzyme linked immunosorbent assay (ELISA) and O and H agglutinins of the Widal test for culture confirmed typhoid (n=29) and febrile (n=51) cases

Diagnostic accuracy	IgA ELISA	O agglutinin		H agglutinin	
		1/240	1/480	1/120	1/240
Sensitivity	83%	89.7%	69%	65.5%	51.7%
Specificity	92.2%	31.4%	74.5%	90.0%	96%

**Figure 2** IgA antibody responses of 20 patients with culture confirmed typhoid fever: acute and convalescent phases. A different symbol is used for each patient.

**Table 4** The sensitivity of IgA enzyme linked immunosorbent assay for specimens collected during successive weeks after the onset of fever

Duration of illness	Positive cases at first presentation as detected by salivary IgA	Sensitivity for all the tests performed
Week 1	1/8	12.5%
Week 2	5/9	73.3%
Week 3	2/2	70.0%
Week 4	0	33.3%
Week 5	0/1	33.3%
Week 7	0	33.3%
Week 17	0	7.7%
Week 21	0	0%
Week 25	0	0%

**Figure 3** Mean absorbance values (SD) of anti-*Salmonella typhi* lipopolysaccharide IgA antibodies in the saliva of patients with typhoid fever: acute and convalescent phase. The line represents the linear regression.

considered useful in clinical decision making only if it gives a predictive value of at least 80%.<sup>20</sup> In our study the predictive values of the positive and negative tests were 83% and 97%, respectively.

In patients with febrile illnesses, O agglutinins were present at titres of 1/120 and 1/240 in two and four of the 17 patients with UTI, three and seven of the 15 patients with malaria, and none and four of the nine patients with viral fever, respectively (table 1). Three of 17 patients with UTI showed very high titres of O (1/960). The raised titres seen in patients with non-typhoidal illnesses can be explained by cross reactions occurring between LPS and other Gram negative bacilli and the high prevalence of O agglutinins seen in endemic countries, where the population is frequently exposed to typhoid fever. The H agglutinins, which are long lasting, were also present in patients at different values. H agglutinin titres of 1/120 and 1/240 were seen in two of the 17 patients with UTI and a titre of 1/120 was seen in one of the 15 patients with malaria.

When the sensitivity and specificity of the salivary IgA ELISA and the Widal test were compared considering only the culture positives and febrile cases, the specificity of the ELISA decreased to 92%, but it was still higher than that of the Widal test (table 3), which had a specificity of 75% and 90% for the O and H agglutinins at titres of 1/480 and 1/120, respectively. The sensitivity of the salivary IgA ELISA (83%) was higher than that of the O and H agglutinins of the Widal test, which were only 69% and 66% at titres of 1/480 and 1/120, respectively. The comparison revealed that the salivary IgA ELISA was superior to the Widal test. Nardiello *et al* reported that the Widal test correlated to a lesser extent with serum IgA ( $r = 0.385$ ;  $p < 0.05$ ) than with IgM antibodies ( $r = 0.784$ ;  $p < 0.001$ ).<sup>11</sup> Our study found no correlation between salivary

IgA titres and serum O agglutinins in patients with acute typhoid fever ( $r = -0.016$ ;  $p > 0.05$ ).

The single falsely positive sample among the healthy controls, which showed high titres of salivary IgA against *S typhi* LPS on five consecutive occasions for a period of 120 days had a mean (SD) absorbance of 1.223 (0.124). The mean was 4.5 times greater than that of healthy controls, whereas the chance of occurrence was about 1% (1 of 125). The repeated stool cultures excluded the possibility of this patient being a carrier of *S typhi*.

"The sensitivity of the salivary IgA enzyme linked immunosorbent assay was higher than that of the O and H agglutinins of the Widal test"

Patients develop various types of immune responses to *S typhi* of differing magnitudes and durations. The ability of a test to detect the specific antigen/antibody in body fluids during the acute stage of the illness is very important in the rapid and early diagnosis of an infection. The time taken by specific antibodies to increase up to detectable values during an infection and to decline thereafter is of crucial importance.

According to Schroeder,<sup>6</sup> antibodies to the O and H antigens are often not detected by the Widal test in untreated patients until the second week of illness, with increased titres by the third week. However, Senewirathne and Senewirathne<sup>21</sup> demonstrated that in Sri Lanka the agglutinins could appear earlier in the disease and are raised to diagnostic values even during the first week of illness. These authors explained the difference as resulting from a hyper-immune state in a population frequently exposed to typhoid fever.

Investigators have used the ELISA technique to determine antibody responses in the serum of patients with typhoid during both the acute and convalescent phases. Beasley *et al* defined the first 10 days of illness as acute and the subsequent 11–14 days as convalescent stages, in which IgG antibodies are encountered more frequently in higher titres than IgM antibodies.<sup>10</sup> Ismail *et al* contradicted this by reporting a rise in IgM antibody titres during the acute stage of the illness.<sup>22</sup> Both IgM and IgG antibodies were seen during the mid stage, but IgG dominated during the convalescent stage. Verdugo-Rodriguez *et al* showed that IgG dominated (60%) in culture confirmed typhoid with a history of one week to one month of fever, whereas IgM (20%) and IgA remained low (12%).<sup>18</sup> These findings were in accordance with the study of Kollaritsch *et al*,<sup>23</sup> which was carried out using the LPS antigen to detect antibody. In addition, these findings were comparable to the study of Nardiello *et al*,<sup>11</sup> which reported the highest titres of IgM and IgA antibodies by two to three weeks. IgA and IgM antibodies declined to their normal values 45 to 90 days after the acute phase. Our study showed that the dynamics of salivary IgA antibodies during the acute and convalescent phases was comparable to that of serum immunoglobulins as determined by Nardiello *et al*.<sup>11</sup>

Our current study, which was carried out for a period of six months, determined IgA antibody responses throughout the acute and convalescent phases (fig 2). Six of the eight patients presenting within the first week of illness had O agglutinin titres of  $\geq 1/480$  and four had H titres of  $\geq 1/120$ . These findings support the hypothesis of Senewirathne and Senewirathne,<sup>21</sup> who postulated that an early antibody response occurs in a large proportion of patients in an endemic situation. Only one of the eight patients had a positive salivary IgA result (table 4). Under normal circumstances, patients with typhoid fever are investigated in the second week of illness. However, in a situation where patients with fever are investigated early as part of an outbreak investigation, salivary IgA ELISA may be less sensitive than the Widal test.

Eleven of the 15 samples collected in week 2 were positive by ELISA. Five of the nine patients who presented for the first

### Take home messages

- We have developed an enzyme linked immunosorbent assay that measures salivary anti-salmonella lipopolysaccharide IgA, which is highly sensitive, specific, and efficient
- The test is most efficient during the second and third weeks of fever, the time at which patients normally present for treatment
- There is a subsequent drastic reduction of the sensitivity in the assay, making it very useful for the diagnosis of acute infection
- This test needs to be validated in several different centres on a larger number of subjects before it can be used routinely

time during the second week had positive IgA ELISA titres at the time of presentation, whereas seven showed O and H agglutinins above 1/480 and 1/120, respectively. Seventy per cent of samples were positive during the third week, including the two cases that were presenting for the first time and which had O and H agglutinins  $\geq$  1/480 (one of two) and  $\geq$  1/120 (two of two), respectively. During the fourth, fifth, and seventh weeks, only 33% became positive, whereas this dropped to about 8% during the 17th week. Accordingly, salivary IgA antibodies reached their maximum, with mean values of 1.177 and 1.205, during the second and third weeks of illness, respectively (fig 3). These high values decreased drastically thereafter, meeting the requirement of an early and rapid diagnostic test.

When all the cases were considered collectively, 17 were above the cut off value 0.958 during the second and third weeks of illness and all became negative during the course of weeks 3 to 13 except for three cases, which became negative by week 21. Thus, the current study suggests that the second and third weeks of fever constitute the best time period to diagnose typhoid infection using this newly developed assay.

In conclusion, indirect ELISA developed for use with saliva (which can be obtained by non-invasive methods and is easy to use) is highly sensitive, specific, and efficient. The sequential study revealed that the test is most efficient during the second and third weeks of fever, the time at which patients normally present for treatment. The usefulness of the test is further enhanced by the subsequent drastic reduction of the sensitivity of the assay, enabling the diagnosis of the acute infection. This was a preliminary study, and this test needs to be validated in several different centres on a larger number of subjects before it can be used routinely in hospital laboratories worldwide.

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