SPATIAL ANALYSIS OF THE DISTRIBUTION OF TYPHOID FEVER IN TURKEY

D. Toprak [a, *], S. Erdoğan [b]

[a] AKU, Medical Faculty, Department of Family Medicine, 03200 Afyonkarahisar, Turkey - dilekt66@yahoo.com
[b] AKU, Engineering Faculty, Department of Surveying - serdogan@aku.edu.tr

KEY WORDS: Spatial Analysis, Cluster Analysis, Typhoid Fever, Geographical Information Systems, Spatial Statistics, Spatial Autocorrelation

ABSTRACT:

Disease maps have been playing a key descriptive role in epidemiology. Hence, they are useful tools for identification of areas of the true underlying geographical distribution of the disease incidences. The development of information system technology over the last 30 years has provided a powerful ability to examine spatial patterns, so geographical information systems (GIS) are begun to use in public health and epidemiologic researches. Today many health agencies and researchers have been using GIS technology to manage and analyze their health data. Because of the geographical, economical, environmental and cultural differences among the provinces of Turkey, it is thought that typhoid fever disease can show different distributions and clusters. Therefore, a GIS based spatial analysis was carried out to explore regional clustering of typhoid fever in Turkey. Distribution of typhoid fever and infection cluster areas among provinces of Turkey were determined to implement precautionary measures and provisions effectively by health agencies in Turkey. Study showed that spatial analyses and statistic significantly contribute to the understanding the epidemiology of diseases. With the aid of these analyses it will be effective to monitor and identify high rate disease locations or regions and to implement precautionary measures and provisions.

1. INTRODUCTION

Typhoid fever is a severe multisystemic illness caused by *Salmonella typhi* (*S. typhi*) and characterized by the classic prolonged fever, sustained bacteremia without endothelial or endocardial involvement, and bacterial invasion of and multiplication within the mononuclear phagocytic cells of the liver, spleen, lymph nodes, and Peyer patches. The reservoir of the *s.typhi* is human. It is transmitted through the ingestion of uncooked food or drink contaminated by the faeces or urine of infected people. Also fly has an important role in transmission especially in summer. *S. typhi* can live in dry and cool environment so that the agent can spread with contaminated ice, dust, food and sewer system. Epidemics are more common in spring and summer; sporadic in other seasons (Tekeli, 2008).

In studies of healthy, previously unvaccinated men, ingestion of 10^7 *S typhi* bacilli caused disease in 50% of volunteers. Investigations of outbreaks seem to indicate that an inoculum of as few as 200 organisms may lead to the disease. Perhaps such a discrepancy exists because many who ingest *S typhi* are not healthy men and have any one of a number of risk factors. As the number of organisms increases, the incubation period decreases. The number of bacilli ingested does not change the subsequent clinical syndrome (Brusch, et al., 2008).

After ingestion by the host, *S typhi* invades through the gut and multiplies within the mononuclear phagocytic cells in the liver, spleen, lymph nodes, and Peyer patches of the ileum. Symptoms usually develop 1–3 weeks after exposure, and may be mild or severe. They include high fever, malaise, headache, constipation or diarrhoea, rose-coloured spots on the chest, and enlarged spleen and liver. Healthy carrier state may follow acute illness. Fecal cultures are 10-15% positive in first week and 75% positive in third and fourth weeks. Basil is 10-40% positive in urine cultures. Group agglutination (Gruber-Widal) which is a screening test for the disease is positive at the end of first week. The Widal tube agglutination test has been widely used in the serologic diagnosis of typhoid fever in Turkey. Clinicians in Turkey generally consider a titer of $\geq$1/200 as diagnostic of typhoid fever (Willke A, et al, 2002). In a study by Erdem et al. in Turkey, the most frequently isolated serotype was found as *S. Enteritidis*, also being the most common serotype in stool and blood cultures (Erdem, B. et al, 2004).

Typhoid fever's danger doesn't end when symptoms disappear. Even if the symptoms seem to go away, the patient may still be carrying *S. typhi* . If so, the illness could return, or he could pass the disease to other people. Chronic carriers, defined as individuals who excrete *Salmonella* for more than 1 year. Some individuals may continue to excrete the bacterium for decades. Stool carriage is more frequent in people with preexisting biliary abnormalities, perhaps because *S enterica* survives in gallstones, and these people have a greater incidence of cholecystitis. Chronic carriers have a greater risk for carcinoma of the gallbladder and other gastrointestinal malignancies; chronic carriers had a 6-fold increase in the risk of death due to hepatobiliary cancer. This may be due to chronic inflammation caused by the bacterium.

Typhoid fever is an important cause of morbidity in many regions of the world, with an estimated 12 to 33 million cases occurring annually (Pang et al., 1995). It is common in most parts of the world except in industrialized regions such as the United States, Canada, Western Europe, Australia, and Japan. Therefore, while travelling to the developing world, the people should consider taking precautions and should be vaccinated. (cdc, 2008) Cases are more likely to be seen in areas like India, South and Central America, and Africa with rapid population growth, increased urbanization, and limited safe water,

* Corresponding author

infrastructure, and health systems. In recent years, cases have been reported also from Eastern Europe (Hornick, 1991).

Most of the patients (75%) are in 30 and younger age group; prevalence of the disease decreases in 30 and over age. Also it is rare in children younger than 5 years old. No ethnic group, gender and heredity defined related with the disease. The overall incidence of blood culture–confirmed disease is generally highest in children aged 3-9 years and declines significantly in late adolescence (Brusch, et al., 2008).

Salmonella has mechanisms against acidic environments, but a pH level of 1.5 or less kills most of the bacilli. People who use antacids, histamine-2 receptor antagonists (H2 blockers), or proton pump inhibitors; who have undergone gastrectomy; or who have achlorhydria due to aging or other factors require fewer bacilli to produce clinical disease. Acquired immune deficiencies or hereditary deficiencies in immune modulars, such as IL-12 and IL-23 increase risk for infection, complications and death.

Typhoid fever can be prevented by avoiding risky foods and drinks; and getting vaccinated against typhoid fever. The vaccines are not completely effective so that avoiding risky foods will also help protect from other illnesses, including travellers' diarrhea, cholera, dysentery, and hepatitis A. The vaccination should be completed at least 1 week before the travel so that the vaccine has time to take effect. Typhoid vaccines 51-67% prevent the disease and lose effectiveness after several years. Antibiotics do not prevent typhoid fever but they are only used to treat the disease (Tekeli, 2008).

Health care workers caring for patients with typhoid fever should pay strict attention to adequate hand washing and safe disposal of feces and urine. Antibiotic therapy is essential and should begin empirically if the clinical evidence is strong. Patients must receive adequate fluids, electrolytes, and nutrition. Antimicrobials shorten the course, reduce the rate of complications if begun early, and drastically reduce the case-fatality rate. Surgery is only indicated in some cases like intestinal perforation. Sometimes small bowel resection is necessary for patients with multiple perforations. Also, if antibiotic treatment fails to eradicate the hepatobiliary carriage, the gallbladder should be resected. Cholecystectomy is not always successful in eradicating the carrier state because of persisting hepatic infection. The 2 most common complications of enteric fever are intestinal hemorrhage and perforation. Typhoid fever is potentially fatal if untreated. The prognosis depends on the geographical area and its demographics. Generally, the mortality rate in untreated disease is 10-20%. In properly treated disease, it is less than 1%. Between 10% and 20% of patients treated with antibiotics have a relapse after initial recovery. A relapse typically occurs approximately 1 week after. One to four percent of untreated patients become chronic carriers (Tekeli, 2008; Brusch, et al., 2008; cdc, 2007, Gotuzzo, 1998).

Disease maps have been playing a key descriptive role in epidemiology. So they are useful tools for many purposes such as: identification of areas of the true underlying geographical distribution of the disease incidence, assisting in the formulation of hypotheses about disease etiology, and assessing potential needs for geographical variation in follow-up studies (Bailey, 2001). The development of information system technology over the last 30 years has provided a powerful ability to examine spatial patterns, so geographical information systems (GIS) are begun to use in public health and epidemiologic researches. Meanwhile with the rapid development and adoption of GIS technology as a tool to visualize, manage, explore and analyze spatial data, spatial statistics and spatial analysis methods that are included in GIS software's modules, received increasing attention (Booth, 2004). Human health is an important indicator of individual quality of life and effective national economic development. Public health management and disease control are important duties for health agencies and governments. Since 1990's, computerization of spatial data, through the use of GIS has been emerging as a tool for public health care research and epidemiology. So, GIS technologies have been used more frequently for such studies due to the availability of low cost GIS with user-friendly interfaces (Erdoğan et al., 2008). Today many health agencies and researchers have been using GIS technology to manage and analyze their health data. Because of the geographical, economical, environmental and cultural differences among the provinces of Turkey, it is thought that typhoid fever disease can show different distributions and clusters. So, a GIS based spatial analysis is carried out to explore regional clustering of typhoid fever in Turkey in this study. This study aimed to explore GIS aided spatial analysis of distribution of typhoid fever among provinces of Turkey and identify infection cluster areas to implement precautionary measures and provisions by health agencies for public health.

2. METHODOLOGY

Ministry of Health requires mandatory notification of certain communicable diseases in the health facilities in Turkey. Disease data have been recorded by the province health facilities and send to Ministry of Health. These diseases are grouped in four categories as A, B, C and D according to the policy of government with the communicable disease notice No. 25635 in 2004. Spatial analyses performed to newly reported typhoid fever cases that recorded by the province health departments in A Category and sent to the Ministry of Health belong to 1996-2006 period. Population by census year, annual intercensal rate of increase and mid-year population forecasts data were obtained from Turkish Statistical Institute. Using the midyear population and the number of cases, average incidence rates were calculated for the 1996-2006 period for the 81 provinces. Empirical Bayes smoothing was used to remove background noise from the raw disease rates because of the sparsely populated cities and small number cases of cities. To detect global variations and trends in the values of smoothed rates over the neighbouring provinces, spatial rate smoothing based on spatial moving areas technique was performed. Cluster analyses were performed whether the cases of typhoid fever show clustering or located closer by chance. Different softwares were used for visualization and spatial analyses of the health data in the study. These are Arc GIS 9.0, developed by ESRI, GeoDa 0.9.5-I developed by Luc Anselin through the Center for Spatially Integrated Social Science at the University of Illinois, Clusterseer 2.2.8.1 developed by Terraseer Inc.

3. RESULTS

We analyzed a total of 361.817 recorded cases from the Ministry of Health database for the period of 1975-2006 and a total of 244.487 cases recorded for the period of 1996-2006. The morbidity values (100,000) for the periods of 1975-2006 are shown in Figure 1. Clearly, a decrease in the morbidity of

Typhoid fewer can be seen; in recent years. Because of the data availability, using the midyear population and the number of cases, incidence rates were calculated only for the 1996-2006 period by provinces (Fig.2). While we work with aggregated data if the population or the number of cases is relatively small, rate estimates may not be precise. In order to overcome this problem, smoothing methods are usually employed. The idea in smoothing is to borrow the information from other small areas for the estimation of the relative risk. The information can be borrowed either from nearest areas (local smoothing) or from all areas in the study area (global smoothing). Smoothing techniques use the values in neighbouring areas to adjust the uncertain values. The need for smoothing is determined not by the number of cases but rather by an often closely related factor, the reliability. There are a number of techniques for smoothing data such as mean or median based techniques either weighted or unweighted and Bayes techniques (Anselin et al., 2006).

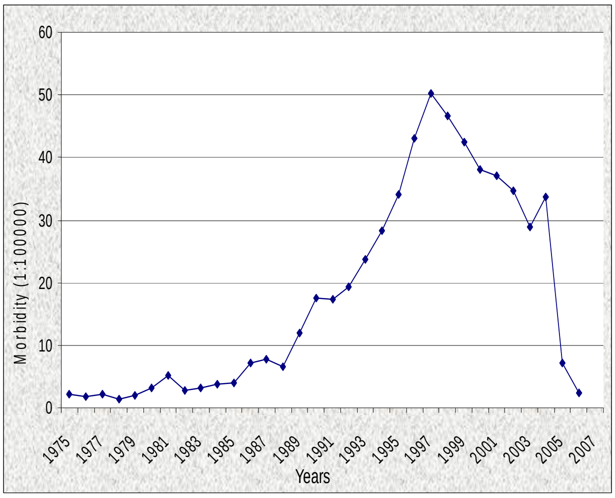

Figure 1. The morbidity values (100000) of Typhoid fever in Turkey

In this study Empirical Bayes (EB) smoothing was used and raw incidence rates were replaced with their globally smoothed values which calculated by EB tool in ArcGIS 9.2 created by National Cancer Institute (NCI) of USA (Fig. 2). Methodological details and further illustrations of EB method were discussed in Bailey and Gatrell, 1995 and Anselin et al., 2006.

Since the incidence rates were aggregated into the aerial units of provinces, an important aspect is deriving spatial weight matrix (W) for ESDA. The spatial weight matrix is the fundamental tool used to model the spatial interdependence between areal units. Determination of the proper W matrix is a difficult and controversial topic in spatial analyses. There are several techniques for deriving W such as simple contiguity that sharing a border, distance bands that locations within a given distance or general social distance, according to the aim of the studies in literature (Anselin et al., 2006, Shi et al., 2006).

Figure 2. Choropleth maps of morbidity rates of Typhoid fever (1:100000)

In this study we formed the weight matrix based on the criterion of contiguity with 6 nearest neighbour. After data smoothing were constructed, a spatial rate smoother based on the notion of a spatial moving average was constructed for explorative spatial data analysis. The purpose of integrating spatial rate smoother method is to emphasize global variations and trends in the health data. These rates of incidence showed that there seems to be a trend towards the South and Eastern Anatolian regions for the cases of typhoid fever (Figure 3).

Figure 3. Choropleth Map of spatial rate smoother values

In order to explore spatial dependence, showing how the incidence rates were correlated in the country, Moran's I and Geary c values calculated. Moran's I (I: 0.105808, z score value: 8.19) and Geary c (c: 0.493742, z score 1.97) indicated significantly clustering of Typhoid incidences in Turkey. Moran's I and Geary's c methods indicate clustering of high or low values. But these methods can not distinguish between these situations. So, General G statistic is used to understand clustering of high or low values. General G statistic indicated (G: 0.58, z score: 7.1) a significantly clustering of high values.

These global spatial data analysis shows clustering but they don't show where the clusters are. To investigate the spatial variation as well as the spatial associations, it is possible to calculate local versions of Moran's I, Geary's c, and the General G statistic for each areal unit in the data (Anselin, 1995).
Then, local approaches were used for analyzing spatial association to identify where the similar spatial patterns in the country are. One local approach was Getis Ord Gi* that identifies those clusters of points with values higher in magnitude than you might expect to find by random chance. According to Getis-Ord Gi* Gaziantep, Diyarbakır, Bingöl,

Mardin, Batman, Siirt, Şırnak and Bitlis provinces were determined as clusters with the significance level of 0.05. Another local approach was local Moran (LISA) statistic that assessed using a normal distribution approximation. Four situations are identified trough LISA. First, a cluster of provinces with high-high rates, second a cluster of provinces with high-low rates, third a cluster of provinces with low-high rates and fourth a cluster of provinces with low-low rates.

According to LISA results Batman, Şanlıurfa, Diyarbakır, Bitlis, Siirt, Mardin and Şırnak provinces were determined as clusters. Figure 3 shows the results obtained from G_i^* statistical values; (selected province with turquoise color: $p<0.05$) and results (red colored provinces indicate significantly high-high provinces) obtained with the second method LISA.

Figure 4. Choropleth Map of typhoid fever clusters with LISA and G statistics

4. DISCUSSION

According to our study, Karabük, Kahramanmaraş, Adıyaman, Elazığ, Gaziantep, Şanlıurfa, Mardin, Şırnak, Hakkari, Siirt, Bitlis, Muş, Batman and Diyarbakır which are known as socioeconomically low cities of Turkey, were determined as extreme rates with typhoid fever and there was a high trend towards to the South East region of Turkey. The spread of the bacteria is via water in some seasons. If there are so many patients diagnosed as typhoid fever in a region like our results, possibility of contaminated water should be kept in mind. This condition can be explained by possible low sanitation of water and high number of uneducated people about the hygene. A typhoid fever outbreak in Ahmetli village, Ergani-Diyarbakir, in the period of December 25, 2001-January 4, 2002 was occurred and a total of 181 suspicious cases were admitted to different health care centers and 71 (39.2%) of them were hospitalized. It was shown that the village-drinking water was contaminated with sewage (Ceylan et al,, 2003).

The disease is common in our country (Tekeli, 2008). The similar high prevalence of the disease was seen in other developing countries. Typhoid fever is still common in the developing world, where it affects about 21.5 million persons each year (CDC, 2008).

People are typically infected with *S typhi* and *S paratyphi* through food and beverages contaminated by a chronic stool carrier. Less commonly, carriers may shed the bacteria in urine. Individuals may also be infected by drinking sewage-contaminated water or by eating contaminated shellfish or faultily canned meat. But we think that another important public health measure is fly control which is still a problem especially in those cities with high *S typhi* prevalences. Currently, fly is recognized as an important mechanical vector of the disease especially in summers in these regions. (Tekeli, 2008)

In our study, there are some sporadic cases in other parts of Turkey. Like our country sporadic outbreaks occur in developed nations, which are explained with the individuals who have recently returned from travel to an endemic region. In the United States about 400 cases occur each year, and 75% of these are acquired while traveling internationally .(cdc, 2008) With the limited efficacy of the current typhoid vaccinations and the increase in multidrug-resistant strains, cases among travellers are expected to continue to increase and become ever challenging to treat (Meltzer et al., 2007).

Early antibiotic therapy has transformed a previously life-threatening illness of several weeks' duration with an overall mortality rate approaching 20% into a short-term febrile illness with negligible mortality. Case fatality rates of 10-50% have been reported from endemic countries when diagnosis is delayed (Brusch, et al., 2008) According to our study, the other reason of high prevalence of some regions can be the poor health service conditions or delayed apply of patients which cause the spread of the bacteria and increase the morbidity rate.

But on the other hand if antimicrobials are used in unnecessary conditions the risk of infection also increases (Mermin, 1999; Srikantiah, 2007). Measures to decrease the unnecessary use of antimicrobials would be expected to reduce the risk of typhoid fever and decrease the spread of multiple drug-resistant Salmonella Typhi.

From 1900-1960, the incidence of typhoid fever declined steadily and has remained low in the United States. Improved sanitation and successful antibiotic treatment led to this decline. An average of 245 cases has been reported annually, with an incidence of 0.2 per 100,000 populations since 1985 compared with 35,994 reported cases in 1920. More than 70% of cases occurred within 30 days of returning from international travel, mostly to the Indian subcontinent and Latin America (Brusch et al., 2008). The rare outbreaks of typhoid fever due to transmission within the United States are generally traceable to imported food or a food handler from an endemic region. This condition is also being considered for our country as transmission of the bacteria.

In endemic areas, children aged 1-5 years are at the highest risk of infection, morbidity, and mortality because of waning passively acquired maternal antibody and a lack of acquired immunity. Also, in young children, the clinical syndrome is often a nonspecific febrile illness that is not recognized as typhoid fever which causes the delayed diagnosis of the disease and the spread of the bacteria till beginning of the treatment.

5. CONCLUSION

To provide clean water, food hygene, environmental conditions are essential to control the typhoid fever. With this provision and other control measures including health education activities, the number of cases can be declined.

The Ministry of Health has important roles to control the epidemic, including: sampling water points, establishing mobile clinics, laboratory testing of cases, providing health education, and organizing the response at the local level.

Spatial analyses and statistic significantly contribute to the understanding the epidemiology of diseases. With the aid of these analyses it will be effective to monitor and identify high rate disease locations or regions and to implement precautionary measures and provisions. In this study, it was demonstrated that spatial analysis and spatial statistic can be applied to study the distribution of typhoid fever infection. Specifically, the distributions of typhoid fever reports belong the 1996-2006 periods were mapped and eight significant clusters were identified with spatial clustering methods. Each cluster had a high rate of typhoid fever reports after smoothing. The smoothed data provided more accurate visual representation of the overall distribution of the standardized rates compared with the original map of observed incidence rates, whereas the cluster analysis pinpoints statistically significant geographical areas generating reports of typhoid fever.

REFERENCES

Anselin, L., 1995. Local indicators of spatial association-LISA. *Geographical Analysis*. 27, pp. 93-115.

Anselin, L., 2004. GeoDa 0.95i Release Notes. Urbana-Champaign, IL: Spatial Analysis Laboratory (SAL), Department of Agricultural and Consumer Economics, University of Illinois, USA.

Anselin, L., Lozano, L., Koschinsky, J., 2006. Rate Transformations and Smoothing. Spatial Analysis Laboratory Department of Geography University of Illinois, Urbana-Champaign, pp. 85, USA.

Bailey, T.C., Gatrell, A.C., 1995. *Interactive Spatial Data Analysis.* Essex: Addison, Wesley Longman Limited

Bailey, T.C., 2001. Spatial statistical methods in health. *Cad Saude Publica*, 5, pp. 1083-1098.

Booth, A.J., 2004. Spatial statistic and aquatic geographic information systems, In: Nishida T, Kailola PJ, Hollingworth CE (eds), Fishery-Aquatic GIS Research Group In: Proceedings of the Second International Symposium on GIS/Spatial Analysis in the Aquatic Sciences. Kawagoe-city, Japan, pp. 3–44.

Brusch, J. L., Garvey, T., Typhoid Fever. http://www.emedicine.com/MED/topic2331.htm (accessed 28 April 2008).

CDC, 2008. Centers for Disease Control and Prevention. http://www.cdc.gov/ncidod/dbmd/diseaseinfo/typhoidfever_g.htm (accessed 28 April 2008)

Ceylan, A., Acemoğlu, H., Hoşoğlu, S., Gül, K., Ilçin, E., Efe, M., 2003. Typhoid fever epidemic in Ahmetli village, Diyarbakir-Ergani. *Mikrobiyol Bul.* Jan; 37(1), pp. 41-7. [Article in Turkish]

Erdem, B., Hasçelik, G., Gedikocğlu, S., Gür, D., Ercis, S., Sümerkan, B., Aysev, A.D., Tuncer, I., Tuğrul, M., Tatman, Otkun, M., Tünger, A., Akgün, Y., Acar, N., Köksal, I., Gültekin, M., Söyletir, G., Elhan, A., 2004. Salmonella enterica serotypes and Salmonella infections: a multicenter study covering ten provinces in Turkey. *Mikrobiyol Bul.* Jul;38(3), pp.173-86. [Article in Turkish].

Erdogan, S., Yılmaz, İ., Baybura, T., Güllü, M., 2008. Geographical information systems aided traffic accident analysis system case study: city of Afyonkarahisar. *Accident Analysis and Preventation*, 40, pp. 174-181.

Gotuzzo, E., Guerra, J.G., Benavente, L., et al., 1988. Use of norfloxacin to treat chronic typhoid carriers. *J Infect Dis,* Jun; 157(6), pp. 1221-5.

Hornick, R.B. 1991. Typhoid fever, *In* A. S. Evans and P. S. Brachman (ed.), Bacterial infections of human epidemiology and control, 2nd ed. Plenum Medical Book Company, New York, N.Y, p. 803-818.

Meltzer, E., Schwartz, E., 2007. Enteric fever: an Israeli perspective. *Isr Med Assoc J*., Oct; 9(10), pp. 736-41

Mermin, J.H., Villar, R., Carpenter, J, Roberts, L., Samaridden, A., Gasanova, L., Lomakina, S., Bopp, C., Hutwagner, L., Mead, P., Ross, B., Mintz ED., 1999. A massive epidemic of multidrug-resistant typhoid fever in Tajikistan associated with consumption of municipal water. *J Infect Dis.* Jun; 179(6), pp. 1416-22.

Pang, T., Bhutta, Z.A., Finlay, B.B. and Altwegg., M. 1995. Typhoid fever and other salmonellosis: a continuing challenge. *Trends Microbiol*. 3**,** pp. 253-255.

Republic of Turkey Ministry of Health. 1995. Health Statistics. Republic of Turkey, Ministry of Health. Ankara, Turkey.

Shi, H., Zhang, L., Liu, J., 2006. A new spatial-attribute weighting function for geographically weighted regression. *Can. J. For. Res*, 36, pp. 996–1005.

Srikantiah, P., Vafokulov, S., Luby, S.P, Ishmail, T., Earhart, K., Khodjaev, N., Jennings, G., Crump, J.A., Mahoney, F.J., 2007. Epidemiology and risk factors for endemic typhoid fever in Uzbekistan**.** *Trop Med Int Health*. Jul;12(7), pp. 838-47.

Tekeli, E., 2008. Typhoid fever. http://www.infeksiyon.org/detail.asp?ctg=12&Article=209 (accessed 28 April 2008).

Willke, A., Ergonul, O., Bayar, B., 2002. Widal test in diagnosis of typhoid fever in Turkey. *Clin Diagn Lab Immunol*. Jul;9(4), pp. 938-41.