TYPHOID CARRIER TEST [redacted]

HEALTH TECHNOLOGY ASSESSMENT SECTION
MEDICAL DEVELOPMENT DIVISION
MINISTRY OF HEALTH MALAYSIA
008/2014

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DISCLOSURE

The author of this report has no competing interest in this subject and the preparation of this report is totally funded by the Ministry of Health, Malaysia.

EXECUTIVE SUMMARY

Introduction

Typhoid remains a public health challenge in developed and underdeveloped countries. Salmonella typhi is a human-restricted pathogen which are spread via ingestion of contaminated food and water and by food handlers who are carriers. Persistent infection by the organism results in chronic carrier status among the host which may last for decades and if untreated, remain for life. These chronic carriers are known to shed the bacteria in faeces and urine, and act as the crucial reservoir for the persistence of typhoid infection within the community. Typhoid carriers can be detected by rectal swabs and bile culture, Polymerase Chain Reaction (PCR) and Vi antigen serology with stool culture as the gold standard. However, stool or rectal swab culture has disadvantages of low carrier detection rate due to intermittent release of the organism, low culture isolation rate from stool, being tedious and costly tests. Bile culture for carrier status showed good sensitivity but is traumatic. PCR test depends on viable S. typhi or sufficient DNA concentration in the specimen tested. Typhoid carrier test [redacted] has been utilised for typhoid carrier detection merely in Kelantan State. Hence this review is requested by the Food Water Borne Disease Control Program Officer, Ministry of Health to review its evidence for the detection of typhoid carriers in an attempt to expand its use nationwide in the battle against typhoid.

Objective/aim

The objective of this systematic review was to assess the diagnostic accuracy and effectiveness, as well as the safety and cost-effectiveness of typhoid carrier test (previously known as [redacted]) in detecting typhoid carriers.

Results and conclusions

The search strategy yielded only one article on diagnostic accuracy of typhoid carrier detection test [redacted] in detecting typhoid carriers, which was a diagnostic study, with no evidence retrieved on its safety and cost-effectiveness.

There was limited retrievable evidence which was of fair level to support the use of typhoid carrier test [redacted] in the detection of typhoid carrier. However, the evidence showed that Typhidot-C appeared beneficial in the detection of typhoid carriers, following its good diagnostic value (100% sensitivity and specificity), compared to stool culture and PCR positive. It may have the potential benefit to be used as a feasible typhoid carrier detection tool due to the ease of performing compared to stool culture and PCR, as well as cheaper in price.

Methods

Systematic literature search was conducted. Electronic databases were searched through the Ovid interface: MEDLINE(R) In-process and other Non-Indexed

Citations and Ovid MEDLINE(R) 1948 to present. EBM Reviews - Cochrane Central Register of Controlled Trials – March 2014. EBM Reviews - Database of Abstracts of Review of Effects (1st Quarter 2014). EBM Reviews - Cochrane Database of Systematic Reviews - 2005 to March 2014. EBM Reviews - Health Technology Assessment – 1st Quarter 2014. NHS economic evaluation database – 1st Quarter 2014. EMBASE – 1988 to 2014 week 18. Searches were also run in PubMed. Google was used to search for additional web-based materials and information. The search was limited to publication year from 2009 to current. No other limits were applied. Additional articles were identified from reviewing the references of retrieved articles. Last search was conducted on 8 May 2014.

TYPHOID CARRIER TEST [redacted]

1. INTRODUCTION

Typhoid remains as a public health challenge in developed and underdeveloped countries with an estimated 16.6 million new infections and 600,000 deaths occur each year.[1] It is endemic in the Indian subcontinent including Bangladesh, South-East and Far-East Asia, Africa and South Central America. The annual incidence of typhoid fever has been reported as more than 13 million cases in Asia.[2] In Malaysia, typhoid incidence rate reported in Kelantan was 2.8 per 100,000 population in 2010.[3] The aetiologic agent, *Salmonella typhi* is a human-restricted pathogen. These enteric pathogens are spread via ingestion of contaminated food and water and by food handlers who are carriers.[4] Given that humans are the only reservoir of *S. typhi*, the detection of carriers is necessary for the control of typhoid fever.[5]

Accurate diagnosis of typhoid fever at an early stage is important not only for etiological diagnosis, but also to identify individuals that may serve as a potential carriers, who may be responsible for typhoid outbreaks.[6] The chronic typhoid carrier state can occur following symptomatic or subclinical infections of *S. typhi*.[4] Approximately, 2 to 5% of infected individuals become chronic biliary carriers[7] which increases with age and is greater among women and hence perpetuate the endemicity of the disease. Persistent infection by the organism results in chronic carrier status among the host which may last for decades and if not treated, remain for life.[8] Chronic carriers of *S. typhi* are known to shed the bacteria in feces and urine, and act as the crucial reservoir for the persistence of typhoid infection within the community.[1,8] These chronic carriers can persist for decades and continue to spread the disease while exhibiting no clinical symptoms, making detection difficult because of non-availability of sensitive detection tool and elimination of typhoid carriers.[8]

According to WHO, chronic carrier is defined as an individual who continues to excrete *S. typhi* in stools or urine for longer than one year after the onset of acute typhoid fever.[9] The continuous excretion of organism after one year after having had the disease is important to differentiate chronic from transient carrier that may harbour the organism for a short time such as after being vaccinated with typhoid vaccine.[8]

During the course of infection, the bacilli can be isolated from faeces, urine, bone marrow and blood. Specific agglutinins appear during the course of most of the attacks during the second week of infection.[6] The type of immunoglobulin detected could be either IgM, which is indicative of recent exposure, or IgG, which can indicate recent or previous exposure.[10] Detectable levels of IgM antibodies against S. typhi appear and persist for

four months, while IgG antibodies detected thereafter and remain in blood for two years.[6] Serological studies on carriers have shown that the predominant antibody is IgA and IgG. IgM is mainly among those with acute typhoid. IgA normally has a short half life of not more than 2 weeks. Due to defect in the hepatobilliary circuit, IgA is sustained at high levels in carriers.[4]

Gold standard in the diagnosis of typhoid fever is the isolation of the organism in fecal sample.[11] Other bacteriological culture, Polymerase Chain Reaction (PCR), serological test by Widal test, haemagglutination assay for Vi antibodies, counterimmunoelectrophoresis, solid phase radioimmunoassay and ELISA, typhidot-M and Tubex could also be done. The current gold standard for carrier detection is by means of stool culture.[12] Other methods to diagnose typhoid carriers include rectal swabs and bile culture, PCR and serology by means of Vi antigen (not available commercially).[8] However, carrier detection by means of stool or rectal swab culture is low (only one to five percent) due to intermittent release of the organism and low culture isolation rate from stool,[8] tedious and costly.[12] Bile culture for carrier status can deliver sensitivity of >90% but is traumatic. PCR test depends on viable *S. typhi* or sufficient concentration of DNA within detection limit present in the stool specimen tested.[8] Hence asymptomatic carriers continue to perpetuate the disease.[4]

[redacted] typhoid carrier test has been used in Kelantan since 2008 after major typhoid outbreaks, carried out in partnership between the Kelantan State Health Department and the Typhoid Research cluster under the Institute for Research in Molecular Medicine (INFORMM) at the USM Health Campus. This technology review was conducted following a request from the Food Water Borne Disease Control Program Officer, Disease Control Division, Ministry of Health to review the evidence on Typhidot-C typhoid carrier test in detecting typhoid carriers in an attempt to expand the use of Typhidot-C nationwide in the control of typhoid.

2. OBJECTIVE / AIM

The objective of this systematic review was to assess the diagnostic accuracy and effectiveness, as well as the safety and cost-effectiveness of typhoid carrier test (previously known as [redacted]) in detecting typhoid carriers.

3. TECHNICAL FEATURES

The original Typhidot is a qualitative rapid dot enzyme immunoassay (EIA) designed to detect the presence of IgM and IgG antibodies against specific 50 kDa outer membrane protein (OMP) antigen specific for *S.*

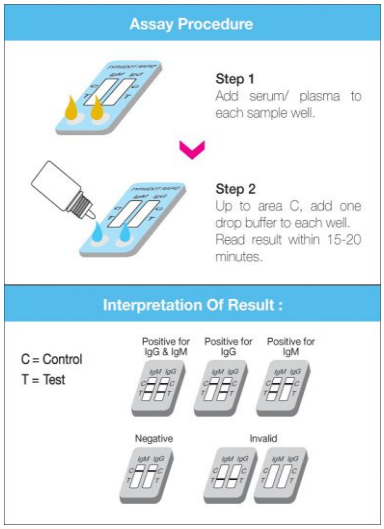
typhi which is impregnated on nitrocellulose strips in acute typhoid fever. It has been commercialised worldwide.[4,6] IgM shows recent infection whereas IgG signifies remote infection.

- Specimen used : Serum [13]
- Specimen volume : 5 µl (1 hour method); 20 µl (3 hours method)
- Assay time : 1 or 3 hour
- Shelf life : 12 months

Typhidot becomes positive as early as in the first week of fever.[2] It is simple to perform, result can be visually interpreted and requires approximately one hour to complete. It does not require any special equipment and hence is convenient to conduct the test in the field and in small hospitals where facilities are lacking.[11]

Typhidot M is a dot enzyme immunoassay for the detection of specific IgM to *S. typhi*. In this test IgG is inactivated before carrying out the assay as for the Typhidot.[11]

Figure 1: Steps in conducting Typhidot M assay with its result interpretation (left) and the Typhidot M kit (right)



Typhoid carrier test or previously known as Typhidot-C is a modification of the original Typhidot test and is used for detection of specific IgA and IgG antibodies to the 50kDa surface protein antigen.[8] OMP due to the location have been primed as important candidates to elicit host immune response. Only the 50 kDa protein has undergone a full scale multinational clinical trial in order to evaluate its diagnostic value, although several possible antigenic candidates have been elucidated from studies on the OMPs. The 50 kDa OMP was determined to be antigenic as well as specific for *S. typhi* since it only reacted immunologically with typhoid sera. [14]

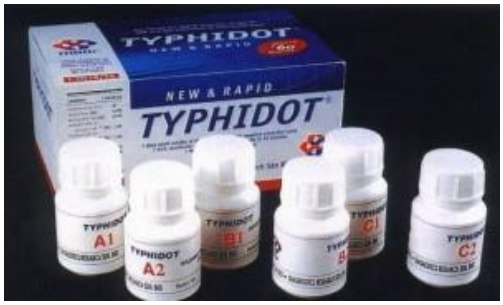
Typhoid carrier test [redacted] uses the immunoassay technique to detect the presence of specific IgG and IgA antibodies in human sera or plasma samples against the specific antigen from the outer membrane of *S. typhi*. The test is meant for the in vitro screening of suspected typhoid carriers among those who previously had typhoid, possible contacts of typhoid patients and among food handlers. Positive results attained with IgA or IgG alone or in combination by observing the colour intensity of the dots produced which is higher than the positive control produced is highly suggestive of typhoid carriers. The carrier test produces results in 3 hours.

Table 1: The difference in results interpretation between Typhidot and Typhidot-C [4]

Test	Result	Interpretation
Typhidot	IgM positive only	Acute typhoid fever
	IgM positive and IgG positive	Acute typhoid fever (middle stage of infection)
	IgG positive	Suggest convalescence case or carrier
Typhidot C	IgG positive and IgA positive	Suggest typhoid carrier
	IgA positive	Suggest typhoid carrier

[redacted] can be a useful serology tool to screen a large population which will cut down unnecessary stool sampling during outbreaks since stool culture and PCR can be cost prohibitive.[4]

Figure 2: The Typhidot-C kit



Other competing technology in the detection/identification of typhoid chronic carriers are serologic screening for Vi antigen or also known as anti-Vi antibody detection by means of either ELISA,[5] passive hemagglutination assay (PHA)[15] and counterimmunoelectrophoresis.[16]

4. METHODS

4.1. Searching

Electronic databases were searched through the Ovid interface:

- MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to present
- EBM Reviews - Cochrane Central Register of Controlled Trials – March 2014
- EBM Reviews - Database of Abstracts of Review of Effects (1st Quarter 2014)
- EBM Reviews - Cochrane Database of Systematic Reviews - 2005 to March 2014
- EBM Reviews - Health Technology Assessment – 1st Quarter 2014
- NHS economic evaluation database – 1st Quarter 2014
- EMBASE – 1988 to 2014 week 18.

Other databases:

- PubMed
- Horizon Scanning database (National Horizon Scanning Centre, Australia and New Zealand Horizon Scanning Network, National Horizon Scanning Birmingham)
- Other websites; INAHTA, ASERNIP-S, CADTH, FDA and MHRA.

General databases such as Google and Yahoo were used to search for additional web-based materials and information. Additional articles retrieved from reviewing the bibliographies of retrieved articles or contacting the authors. The search was limited to articles on human. There was no language limitation in the search. **Appendix 1** showed the detailed search strategies. The last search was conducted on 8 April 2014. The search was re-run in May 2014. The search strategy used search terms as in criteria of study inclusion/exclusion below.

4.2. Selection

A reviewer screened the titles and abstracts against the inclusion and exclusion criteria and then evaluated the selected full text articles for final article selection.

The inclusion and exclusion criteria were:

Inclusion criteria

Population	Patient who previously had typhoid, possible contacts of typhoid patients and food handlers
Interventions	[redacted] , typhoid carrier test, Typhoid carrier detection test
Comparators	No comparator or compared with S. Typhi isolation culture (stool, rectal swabs or bile), PCR, typhoid serological (antibody detection) test using Vi antigen
Outcomes	Diagnostic performance • Detection of typhoid carrier - IgG, IgA - Sensitivity and specificity - Positive and negative predictive value, area under curve, positive and negative likelihood ratio
Study design	Systematic reviews, comparative study, cohort study, cross sectional/diagnostic studies
	English full text articles

Exclusion criteria

Study design	Anecdotal, Case series/reports, animal and laboratory studies, narrative reviews
	Non English full text articles

Relevant literature were critically appraised using Critical Appraisal Skills Programme (CASP) checklist, diagnostic accuracy evidence were graded according to the NHS Centre for Reviews and Dissemination (CRD) University of York, Report Number 4 (2nd Edition) for diagnostic accuracy studies **(Appendix 2a)** while effectiveness evidence were graded according to the US/Canadian Preventive Services Task Force Level of Evidence (2001) **(Appendix 2b)**.

Data were extracted and summarised in evidence table as in **Appendix 3.**

5. RESULTS AND DISCUSSION

The search strategy yielded only one article related to typhoid carrier detection test [redacted] which was a diagnostic study. There was no systematic review, RCT, non-randomised controlled trial or cohort study retrieved on effectiveness / diagnostic accuracy, safety nor economic evaluation study of typhoid carrier test ([redacted]) in the detection of typhoid carrier retrieved from the electronic databases.

5.1. DIAGNOSTIC ACCURACY AND EFFECTIVENESS

Chua AL et al. in 2012 conducted a study on identification of carriers among individuals recruited in the typhoid registry in Malaysia using stool culture, polymerase chain reaction (PCR) and dot enzyme immunoassay ([redacted]) as detection tool. The study aimed to determine prevalence of carriers among previous typhoid patients and among food handlers from typhoid outbreak areas, and to establish diagnostic value of [redacted] as compared to Vi antigen ELISA test as a screening tool for typhoid carriers. They involved 110 subjects who previously had typhoid fever and 106 food handlers. The author first identified chronic carriers in Kelantan using culture and PCR from subjects with 3 stool samples (involving 110 typhoid convalescence and 106 food handlers), from the inital 607 confirmed typhoid patient one year before and 3847 food handlers from typhoid endemic area. It was followed by retrospective evaluation of the sera with [redacted] (a novel serological tool to detect ST50 antibody status) and Vi ELISA (to detect Vi antibody), using the detected carriers to determine its feasibility as screening tool for chronic carriers. The result demonstrated chronic carriers positive by the culture and PCR method were 3.6% among individuals who previously had acute typhoid fever more than a year ago and 9.4% among food handlers screened during outbreaks. Diagnostic performance of [redacted] was good as it showed sensitivity and specificity of 100% compared to stool culture and PCR positive in detecting typhoid carriers. Similarly, Vi ELISA compared to stool culture and PCR positive showed good sensitivity of 92.9% and specificity of 93.4% in the detection of typhoid carriers. They concluded that [redacted] assay was able to detect all positive carriers showing its potential as a viable carrier screening tool and can be used for efficient detection of typhoid carriers in endemic area. They however suggested a larger study involving confirmed carrier samples to effectively determine the true diagnostic value of Typhidot-C. [8, level 3]

Another unpublished typhoid carrier detection project was carried out by Kelantan State Health Department between 2008 to 2010. 637 previous typhoid patients underwent Typhidot (IgG/IgA) serology and they found that 9.3% (59) patients were IgA positive, 18.5% (118) were both IgA/IgG positive and 28.1%(179) were IgG positive. Likewise, 2651 food handlers and contact of typhoid patients who underwent Typhidot (IgG/IgA) serology showed that 12.0% (318) patients were IgA positive, 8.3%(220) were both IgA/IgG positive and 9.17% (243) were IgG positive.[17, level III]

5.2. SAFETY

There was no evidence retrieved from the electronic databases on its safety in the detection of typhoid carrier.

Typhidot-C has no CE mark, nor it being registered with the USFDA.[18]

5.3. COST EFFECTIVENESS

There was no retrievable scientific evidence on cost-effectiveness of typhoid carrier test ([redacted]) in the detection of typhoid carrier. However, its estimated direct cost is approximately [redacted] per test.

5.4. ORGANIZATIONAL

In Malaysia, [redacted] has been used to detect typhoid carrier only in Kelantan State (typhoid endemic area). Whilst, the original Typhidot is currently being used to detect acute typhoid fever cases only in Hospital Kuala Lumpur (personal communication with microbiologist and pathologist).

[redacted] can be a useful serology tool to screen a large population which will cut down unnecessary stool sampling during outbreaks since stool culture and PCR can be cost prohibitive.[4]

Serological test has been suggested as potential screening tools for chronic carriers of *S. typhi*, since the conduct of these tests are usually simple, cost-effective, able to produce rapid results, free from limitation of culture and other available methods, as the serum reflects the systemic status of a longer duration.[19] Serological screening for typhoid carriers among food handlers is more feasible than bacteriological culture from stool, blood, bone marrow or bile because large number of samples have to be screened and the need to know result promptly.[20] In areas of typhoid endemicity, screening for chronic typhoid carriers by serological means is of practical importance since bacteriological screening is expensive and logistically difficult to perform.[5]

The ideal carrier detection test should be easily used and interpreted in the field rather than in the laboratory to allow for immediate diagnosis. Ability of a test to detect typhoid carriers that is cheap, sensitive, specific and user friendly for field work would promote effective typhoid management. Further development of multi-test for simultaneous typhoid and typhoid carrier diagnosis will be able to have a greater impact on the control and management of typhoid fever.[14]

5.5. LIMITATIONS

This technology review has several limitations. The selection of studies was done by one reviewer. Although there was no restriction in language during the search, only English full text articles were included in this report. Any abstracts without full text articles were also excluded. Among the studies retrieved were cross sectional study and descriptive report. Hence, the assessment of the methodological quality of these studies using CASP assessment tool was not possible due to limitations in the CASP checklist itself.

6. CONCLUSION

The search strategy yielded only one article on diagnostic accuracy of typhoid carrier detection test [redacted] in detecting typhoid carriers, which was a diagnostic study, with no evidence retrieved on its safety and cost-effectiveness.

There was limited retrievable evidence which was of fair level to support the use of typhoid carrier test [redacted]) in the detection of typhoid carrier. However, the evidence showed that [redacted] appeared beneficial in the detection of typhoid carriers, following its good diagnostic value (100% sensitivity and specificity), compared to stool culture and PCR positive. It may have the potential benefit to be used as a feasible typhoid carrier detection tool due to the ease of performing compared to stool culture and PCR, as well as cheaper in price.

7. REFERENCES

1. Olsen SJ, Pruckler J, Bibb W, et al. Evaluation of Rapid Diagnostic Tests for Typhoid fever. J Clin Microbial 2004; 42:1885-1889.
2. Ivanoff B, Levine MM, Lambert PH. Vaccination against typhoid fever, present status. Bull WHO 1994:72(6).957-71
3. Wan Mansor H, Fauziah MN, Hani MH. Kelantan typhoid initiative: lesson learnt. Malaysian Journal of Public Health Medicine.2011; Vol.11;2;6.
4. Asma I. Early detection of cases and carriers of typhoid and other food borne disease. Malaysian Journal of Public Health Medicine.2011; Vol.11;2;4.
5. Losonsky GA, Ferreccio C, Kotloff KL, et al. Development and Evaluation of an Enzyme-Linked Immunosorbent Assay for Serum Vi Antibodies for Detection of Chronic Salmonella typhi Carriers. Journal Of Clinical Microbiology, Dec. 1987, p Vol. 25, No. 12.; p 2266-2269.
6. Sanjeev H 2013. A systematic evaluation of rapid dot-EIA, blood culture and widal test in the diagnosis of typhoid fever. NUJHS 2013. Vol. 3, No.1;1-4.
7. Tynes, BS., and. Utz JP. Factors influencing the cure of Salmonella carriers. Ann. Intern. Med. 1962;57: 871-882.
8. Chua AL, Aziah I, Balaram P, et al. Identification of carriers among individuals recruited in the typhoid registry in Malaysia using stool culture, polymerase chain reaction and Dot enzyme immunoassay as detection tools. Asia Pacific Journal of Public Health 2012. DOI:10.1177/1010539512458521
9. World Health Organization. Background document: the diagnosis, treatment and prevention of typhoid fever. Communicable disease surveillance and response vaccine and biological 2003.2003;7-18.
10. Wijedoru L, Donegan S, Parry C. Rapid Diagnostic Tests for Typhoid and Paratyphoid (Enteric) Fever (Protocol). Cochrane Database of Systematic Reviews 2010, Issue 12. Art. No.: CD008892. DOI: 10.1002/14651858.CD008892
11. Gopalakrishnan V, Sekhar WY, Soo EH. Typhoid Fever in Kuala Lumpur and a Comparative Evaluation of Two Commercial Diagnostic Kits for the Detection of Antibodies to Salmonella typhi. Singapore Med J 2002.Vol 43(7) : 354-358
12. Braddick, M.R., B. J. Crump, and M.L. Yee. How long should patients with *Salmonella typhi* or *Salmonella paratyphi* be followed-up? A comparison of published guidelines. *J Pub. Hlth Med.* 1991;**13**: 101-107.
13. Diagnostic product for typhoid fever. Available at http://www.reszonics.com/product.html accessed on 20 Apr 2014.
14. Asma I. New Advances In The Diagnosis Of Typhoid And Detection Of Typhoid Carriers. Malaysian Journal of Medical Sciences 2000. Vol.7; No.2; 3-8.
15. Gupta A, My Thanh NT, Olsen SJ, et al. Evaluation of community-based serologic screening for identification of chronic Salmonella Typhi carriers in Vietnam. International Journal of Infectious Diseases 2006. 10; 309-314
16. Chau PY and Tsang RSW. Vi serology in screening of typhoid carriers: improved specificity by detection of Vi antibodies by counterimmunoelectrophoresis. J. Hyg., Camb.1982. 89; 261-267.
17. Kelantan State Health Department. *Kajian Semula Garispanduan Pengesanan dan Pengurusan Pembawa Tifoid Menggunakan Ujian Serologi (Typhidot).* May 2011. Unpublished report.

18. US Food and Drug Administration. Available at http://www.fda.gov/ http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=892.1550 accessed online on 18 April 2014.
19. Baker S, Favorov M, Dougan G. Searching for the elusive typhoid diagnostic. BMC Infect Dis. 2010;10;45.
20. Ferreccio C, Levine M, Astroza L, et al. The detection of chronic Salmonella typhi carriers: a practical method applied to food handlers. Rev Med Chil.1990.118;33-37.

8. APPENDIX

8.1. Appendix 1: LITERATURE SEARCH STRATEGY

Ovid MEDLINE® In-process & other Non-Indexed citations and OvidMEDLINE® 1948 to present

1. “typhoid carrier”.tw
2. "food handler".tw.
3. "typhoid contact*".tw.
4. "previous typhoid patient".tw.
5. "typhoid case".tw.
6. "old typhoid".tw.
7. "risk of typhoid".tw.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. carrier state/ or disease reservoirs/ or disease transmission, infectious/ or public health practice/
10. "typhoid carrier test".tw.
11. "carrier detection".tw.
12. "typhoid carrier detection".tw.
13. "typhidot c".tw.
14. "typhoid carrier diagnostic".tw.
15. "carrier diagnostic".tw.
16. diagnostic*adj1typhoid carrier.tw.
17. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. 8 and 17

OTHER DATABASES	
EBM Reviews - Cochrane Central Register of Controlled Trials	Same MeSH, keywords, limits used as per MEDLINE search
EBM Reviews - Cochrane database of systematic reviews	
EBM Reviews - Health Technology Assessment	
EMBASE	

PubMeD

Search [(“food handler”[MeSH Terms]) OR “typhoid contact”[Title/Abstract]) OR (“typhoid carrier” [MeSH Terms]) OR (“previous typhoid patient”) OR (“typhoid case”) OR (“old typhoid”) OR (“risk of typhoid”)] AND [(“typhoid carrier test”[Title/Abstract]) OR (“carrier detection”[Title/Abstract]) OR “typhoid carrier detection”[Title/Abstract]) OR “typhidot c”[Title/Abstract]) OR “IgG ELISA OMP”[Title/Abstract]) OR (“ELISA OMP”[Title/Abstract]) OR (“typhoid carrier diagnostic”[Title/Abstract]) OR (“carrier diagnostic”[Title/Abstract]]

8.2. Appendix 2a

HIERARCHY OF EVIDENCE FOR DIAGNOSTIC TEST ACCURACY STUDIES

Level	Description	
1.	A blind comparison with reference standard among an appropriate sample of consecutive patients	
2.	Any one of the following	Narrow population spectrum
3.	Any two of the following	Differential use of reference standard
4.	Any three or more of the following	Reference standard not blind Case control study
5.	Expert opinion with no explicit critical appraisal, based on physiology, bench research or first principles.	

SOURCE: NHS Centre for Reviews and Dissemination (CRD) University of York, Report Number 4 (2nd Edition)

8.2. Appendix 2b

HIERARCHY OF EVIDENCE FOR EFFECTIVENESS STUDIES
DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomized controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris S 2001)

Appendix 3

TYPHOID CARRIER TEST
Evidence Table : Effectiveness / diagnostic accuracy
Question : Is Typhoid carrier test (Typhidot-C) effective in the detection of typhoid carrier?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
Chua AL, Aziah I, Balaram P, et al. Identification of carriers among individuals recruited in the typhoid registry in Malaysia using stool culture, polymerase chain reaction and dot enzyme immunoassay (Typhidot-C) as detection tool. Asia-Pacific Journal of Public Health.2012.xx(x).p1 9.DOI;10.1177/1010 539512458521	Diagnostic study (Malaysia) **Objective:** To determine prevalence of carriers among previous typhoid patients and among food handlers from typhoid outbreak areas, and to establish diagnostic value of Typhidot-C as compared to Vi antigen ELISA test as a screening tool for typhoid carriers. **Method:** The author first identified chronic carriers in Kelantan using culture and polymerase chain reaction from subjects with 3 stool samples (involving 110 typhoid convalescence and 106 food handlers), from the inital 607 confirmed typhoid patient one year before and 3847 food hadlers from typhoid endemic area. It was followed by retrospective evaluation of the sera with Typhidot-C (a novel serological tool to detect ST50 antibody status) and Vi ELISA (to	3	110 typhoid convalescence (confirmed typhoid patient one year before) and 106 food handlers and (from typhoid endemic area during typhoid outbreak)	Typhoid-C (serological tool to detect ST50 antibody status) and Vi ELISA (to detect Vi antibody)	Stool culture and PCR	-	• Prevalence of chronic carriers (by positive culture & PCR):- ➢ 3.6% among individuals who previously had acute typhoid fever one year before (4 out of 110) ➢ 9.4% among food handlers screened during outbreaks (10 out of 106) • Diagnostic performance:- ➢ PCR compared to stool culture ➢ Sensitivity : 100% ➢ Specificity : 100% ➢ Typhidot-C compared to stool culture and PCR ➢ Sensitivity : 100% ➢ Specificity : 100% ➢ Vi ELISA compared to stool culture and PCR ➢ Sensitivity : 92.9% ➢ Specificity : 93.4% **Conclusion by author:** Typhidot C assay was able to detect all positive carriers showing its potential as a viable carrier screening tool and can be used for efficient detection of typhoid carriers in endemic	Local study with sufficient sample size, gold standard comparator, good applicability.

	detect Vi antibody), to determine its feasibility as screening tool for chronic carriers.						area. They however suggested a larger study involving confirmed carrier to effectively determine the true diagnostic value of Typhidot-C.	