



# Outer Membrane Protein of *Salmonella typhi* as a Diagnostic Kit for Typhoid Fever: A Bibliography Study

Yunita Aldirahayu<sup>1</sup>, Ana Hidayati Mukaromah<sup>2</sup>, Sri Darmawati<sup>3</sup>

<sup>1,2,3</sup>Universitas Muhammadiyah Semarang, Semarang, Central Java 50273, Indonesia  
ciciekdarma@gmail.com

**Abstract.** Typhoid fever is an infectious disease, the main cause of typhoid fever is *Salmonella typhi*. *S. typhi* bacteria have characteristics such as being rod-shaped, Gram negative, motile, able to ferment lactose quickly, and are facultative anaerobes. The entry of *S. typhi* bacteria into the body can be influenced by several factors, namely household waste contamination and exposure to food or drinks that have been contaminated with *S. typhi* bacteria. Outer membrane protein (OMP), which is one of the envelope components of *S. typhi* bacteria, makes up almost half part of the outer membrane of bacteria. Several researchers have proven that this specific OMP protein is a good immunogen in inducing a person's immunity against *S. typhi*. The literature search first collected databases such as PubMed, Medrxiv, and Google Scholar. Articles published in the 2014-2023 period were related to Outer Membrane Protein *Salmonella typhi*, so the article search used Medical Subject Title Headings (MeSH) with several combinations of keywords including Outer membrane protein, *Salmonella typhi*, typhoid fever, and diagnostic kit. The search was conducted using the database <https://app.dimensions.ai/> which was published in the 2014-2023 data range and produced 8,458 publications or proceedings of scientific articles. Number of publications about "Outer Membrane Protein *Salmonella typhi* for diagnostic kit" per year. Based on search results in the dimension database, research development from 2014 - 2023 experienced changing conditions, and increased significantly in 2016, namely 876 publications. In this way, it facilitates researchers' opportunities to determine the latest research trends at this time so they can obtain the required data. Based on the findings from the results of this bibliography study, it is important to review the Outer Membrane Protein of *S. typhi* in strengthening the manufacture of diagnostic kits.

**Keywords:** Outer Membrane Protein, *Salmonella Typhi*, Diagnostic Kit, Typhoid Fever.

## 1. Introduction

Typhoid fever is a potentially dangerous and life-threatening systemic infectious disease. The main causative bacteria of typhoid fever is *Salmonella typhi* [1]. *S. typhi* bacteria have

characteristics such as rod-shaped, Gram negative, motile, able to ferment lactose quickly, and are facultatively anaerobic [2].

The entry of *S. typhi* bacteria into the body can be influenced by several factors, namely household waste contaminated with *S. typhi* bacteria [3]. The diagnosis of typhoid fever becomes quite difficult when there are no specific symptoms or signs. In endemic areas, fever for more than 1 week with no known cause should be considered as typhoid fever until the cause is proven. Some supporting examinations that are often used to diagnose typhoid fever consist of peripheral blood tests, identification of bacteria through isolation or culture, identification of bacteria through serological tests, and molecular identification of bacteria. A definitive diagnosis of typhoid fever can be made when *S. typhi* bacteria are found in blood, urine, feces, or bone marrow cultures [4].

Outer Membrane Protein (OMP), which is one component of the *S. typhi* bacterial envelope that fills almost half of the bacterial outer membrane. Some researchers have proven that this specific OMP protein is a good immunogen in inducing immunity against *S. typhi*.

Outer Membrane Protein (OMP) is an antigen that consists of part of the cell wall. Located outside the cytoplasmic membrane and peptidoglycan layer that separates the cell from the surrounding environment, so it is considered an important antigen in inducing immunity against *S. typhi* [5].

From several studies that have identified proteins from *S. typhi* OMP, among them are *S. typhi* OMP which have very strong immunogenic potential and have been involved as typhoid fever vaccine candidates and also have potential as antigens used in diagnostic kits.

The Outer Membrane Protein of *S. typhi* bacteria is considered as a potential target candidate because it has good antigen specificity and is immunogenic. Diagnostic test kits to detect antigens or antibodies (markers of a person's immune response to antigens). Based on the target diagnostic tests are divided into several types, namely diagnostic kits that detect antibodies (IgG, IgM, or both) and antigen detection [6].

The advantages of kit diagnostic methods are simple and relatively fast [7]. The development of RDT methods requires specific antigens, the antigens used are usually proteins and lipopolysaccharides [8]. In the development of diagnostic kits in the form of antigens that are specific for detecting typhoid fever and are antigenic or able to stimulate the formation of specific antibodies. Some types of candidate antigens that can be used are Outer Membrane Protein, LPS, and heat shock protein (HSP) [9].

Dot-Enzyme-Immunoassay Outer Membrane Protein (DOT-EIA-OMP) is a frequently used laboratory test to trace the OMP antigen of *S. typhi*. This test is practical at a lower cost, using polyclonal antibodies. Thus, this test shows a diagnostic sensitivity of 93% (with gold standard PCR assay). The diagnostic specificity is only 77% and the examina-

tion time is 5 hours, if this polyclonal antibody is replaced with a monoclonal antibody, it is hoped that the diagnostic specificity will be significantly improved [10].

The diagnostic kit to be developed also has a low risk of bias, is easy to use, and provides fast results without the need for laboratory tests such as blood cultures. The cost of this typhoid fever diagnostic test will be much lower than blood culture, and requires less training, equipment and materials to perform [7].

Some studies that have identified the OMP of *S. typhi* also play a role, namely: [11] The 31 kDa *S. typhi* OMP isolate is immunogenic and can be used as a vaccine candidate [12]. Produced a 36 kDa *S. typhi* OMP protein that is immunogenic in diagnosing typhoid fever, whereas [13]. Immuno-blotting using 35 kDa *S. typhi* OMP samples has a higher specificity value. Therefore, it is necessary to characterize the immunogenicity of *S. typhi* OMP as a candidate for the manufacture of typhoid fever diagnostic reagents. [7].

## 2. Materials and Method

The literature search first collected databases such as PubMed, Medrxiv, and Google Scholar. Articles published between 2014 -2023 related to Outer Membrane Protein *Salmonella typhi*, so the article search used Medical Subject Title Headings (MeSH) with several keyword combinations including "Outer membrane protein", "*Salmonella typhi*", "typhoid fever", and "diagnostic kit".

Journal reviews have the aim of knowing an overview of the research to be studied, so that it can be continued when working in the research laboratory. Complete article data is then extracted with advanced searches using manual searches such as PubMed, Medrxiv, and Google Scholar. Studies excluded from this study were: (i) Studies reported before 2014, (ii). Studies on the type of outer membrane protein from bacteria other than *S. typhi*; (iii) review; (iv) review.

### 2.1. Journal Eligibility Criteria

Screening of studies based on journal eligibility had the following inclusion criteria: (i). subjects related to outer membrane protein of *S. typhi*; (ii). Diagnostic test for typhoid fever; (iii) dot blotting; (iv) reported in English or Indonesian; (v) observational study as the search plan with the publication data range set at the last 10 years. Regardless of the publication date, a manual search was performed using the predefined MeSH. Using this strategy, there were 65 relevant references, but only 1 was retained.

**Dimensions.** Review using dimensions <http://app.dimensions.ai/>. to see the development of research related to the search for "Outer Membrane Protein *Salmonella typhi*" in the development of diagnostic tests published in the 2014-2023 range and have searched for

titles and abstracts. Journals included in the dimension category are the types of journals that have been standardized by DOI, so that they can be sorted by keywords and can be seen in the overview, journal publication charts from 2014 to 2023. Furthermore, the results of data collection that have been obtained from dimensions can be visualized networks and visualization maps related to research will be illustrated using the VOSviewer application.

**VOSviewer.** Journals that are in accordance with the keywords of the dimensions, namely "Outer membrane protein *Salmonella typhi*" can be downloaded using the RIS format. The RIS data that has been obtained is then analyzed using the VOSviewer algorithm software. This aims to determine the bibliography map and the current trend of scientific publications on the outer membrane protein of *S. typhi* in the development of diagnostic tests globally for the last ten years, namely 2014 - 2023.

## 2.2. Journal Selections

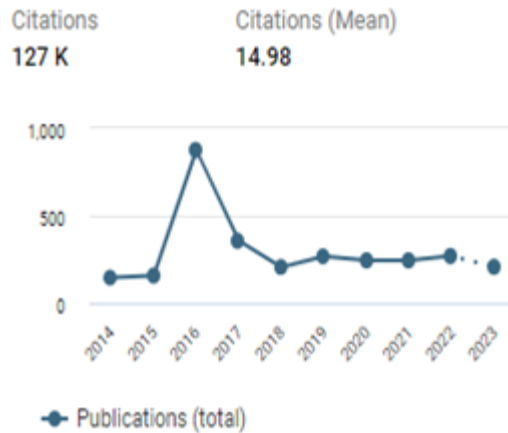
Based on the guidebook of Sid-daway [14], journal selection has been done to facilitate the identification of journals that have met the standard inclusion criteria applied in this journal review. Titles and abstracts obtained from the search were carefully analyzed to determine which inappropriate references should be excluded. Journals from the search that have been selected also need to be evaluated whether they have met the inclusion criteria or not.

## 2.3. Research Bias Control

Things that need to be included in the risk of bias or judgment in the quality of the review in this journal are: (i) information that has been reported, (ii) selective reporting information of result and innovation. When the overall criteria are met, the overall risk of bias for a reasonable journal will be considered small.

## 3. Result and Discussion

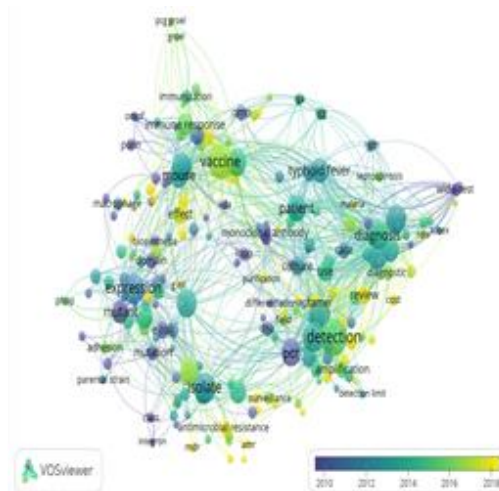
The search through the <http://app.dimensions.ai/> database search published in the 2014-2023 data range and resulted in 8,458 publications or proceedings of scientific articles. The number of publications on "Outer Membrane Protein *Salmonella typhi* for diagnostic kit" per year has been presented in Figure 1.



**Fig. 1.** Number of publications of "Outer mem-brane protein of *S. typhi* as diagnostic kit" from 2014-2023. (Source: <https://app.dimensions.ai/>)

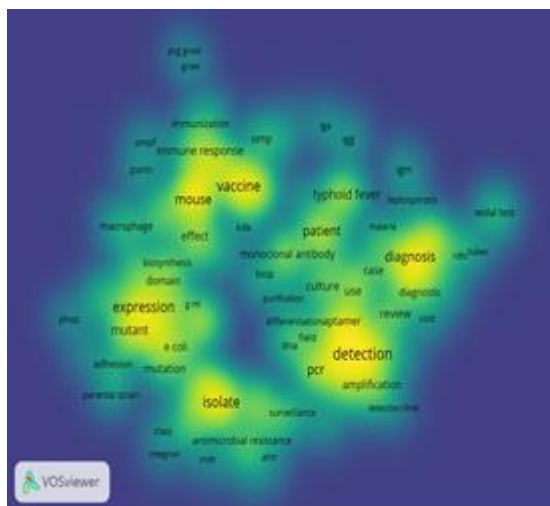
Figure 1 explains that the search for research on Outer Membrane Protein *Salmonella typhi* is still little researched from 2014 to 2023. Based on the search results in the dimension database, the development of re-search from 2014 - 2023 experienced changing conditions, and increased significantly in 2016, which was as many as 876 publications.

Figure 2. VOSviewer provides an overlay visualization map for concurrent events. Based on Figure 2, it can be seen that "Outer Membrane Protein *S. typhi* for Diagnostic kit" connected 50 research links in 3 groups. Some important links also fall into the category of "diagnostic, diagnosis, typhoid fever, vaccine, porin, outer membrane protein, and immunization". Meanwhile, there were strong links to patient cases, malaria, leptospirosis, and mouse. Links that are not strongly associated with the spread of 3 groups are indicated by the small circle. As little research has been done on these small circles, there may be opportunities for new research to be conducted.



**Fig. 2.** Overlay visualization for co-occurrence (Source: VOSviewer and dimensions <https://app.dimensions.ai/>).

Furthermore, VOSviewer also provides a density visualization map of the co-occurrence. The density visualization, presented in Figure 3.



**Fig. 3.** Density visualization (Source: VOSviewer and dimensions <https://app.dimensions.ai/>)

The density visualization in Figure 3 shows that the most related to "Outer Membrane Protein *S. typhi* as a diagnostic kit" are detection, diagnosis, vaccine, typhoid fever, isolate, expression, mouse, and OMP which are marked in yellow, the lighter the color, the more research has been done. In this way, it facilitates the opportunity for researchers to determine the latest current research trends so that they can obtain the data needed.

#### 4. Conclusion

Based on the findings of this bibliographic study, it is important to review the Outer Membrane Protein of *S. typhi* in strengthening the manufacture of diagnostic kits. Based on the bibliography reported that the Outer Membrane Protein of *S. typhi* has several properties/characteristics that need to be considered, the selection of *S. typhi* parts to be used also has a big influence in the success of making diagnostic kits. Furthermore, dimensions are used as a database to get a bibliography map by VOSviewer in identifying research trends, authors, publications that are widely cited, and research areas.

**Authors' Contributions.** All authors contributed equally to this work.

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