Typhoid fever : aspects of environment, host and pathogen interaction

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I General introduction

Typhoid fever is caused by infection of humans with the microorganism *Salmonella enterica* subspecies *enterica* serotype Typhi (*S. typhi* for short). It is a systemic disease characterized by a prolonged fever, malaise and weight loss. On physical examination, characteristic skin lesions, rose spots, usually accompany a hepatosplenomegaly. Without antibiotic treatment the fever may persist for several weeks, and the disease will be fatal in about 15 percent of those affected. The bacterium is transmitted by faecal-oral route, through contaminated water or food.
S. typhi is highly adapted to its human host; there is no reservoir but man. Therefore, every case of typhoid fever means an infection from a previous one. The immunopathogenesis is characterized by a sustained low-grade bacteremia with microbial invasion of and multiplication within the mononuclear phagocytes lining the sinoids of the liver, spleen, bone marrow, lymph nodes, and Peyer's patches. Bacterial multiplication at the latter sites, with necrosis and sloughing of the overlaying mucosal epithelium produces the characteristic ulcerations of Peyer's patches in the terminal ileum, a long recognized pathological entity that proved invaluable to distinguish typhoid fever from typhus.
Paratyphoid fever is clinically and pathologically a highly similar disease, but caused by *Salmonella enterica* subspecies *enterica* serotypes Paratyphi A, B or C (*S. paratyphi* for short). Enteric fever refers to both typhoid fever and paratyphoid fever (1).
P. Louis described typhoid fever in 1829 as distinct clinical entity, apart from typhus and other sustained fevers. It took another 60 years before the microbial etiological agent, *S. typhi*, was isolated by Gaffkey in Germany in 1884. By serendipity, T. Woodward discovered shortly after the second World War that chloramphenicol could be used to successfully treat typhoid fever patients and shortly after that the first clinical fi eld studies were done in Malaysia (2).

Although practically eradicated from the developed Western countries, enteric fever remains a major global health problem due to its high incidence and significant morbidity and mortality in developing countries. For the year 2000, it was estimated that 21.650.974 patients contracted typhoid fever, and that 216.510 died due to the disease, whereas paratyphoid fever was responsible for about 25 percent of all enteric fever cases and was estimated to infect 5.412.744 individuals (3). In Indonesia, the annual costs of treatment of typhoid fever cases has been estimated at approximately US$ 60 million, with an additional US$ 65 million loss of income, and typhoid is cause of deaths of about 20.000 individuals (4). In Jakarta, clinicians and public health experts believe that typhoid fever still is one of the fi ve most common febrile illnesses causing the highest mortality among hospitalized patients.

Pathogenesis of typhoid fever

Salmonella enterica subspecies *enterica* serotype typhi is a member of the family Enterobacteriaceae. The bacterium is serologically characterized by the lipopolysaccharide antigens O9 and O12, the flagellar protein antigen Hd, and a polysaccharide capsular antigen Vi. The Vi capsular antigen is largely restricted to *S. typhi*, although it is shared by some strains of *S. enterica hirschfeldii* (Paratyphi C) and *dublin*, and *Citrobacter freundii* (5). The bacterium is strictly confined to the human species and there is no other reservoir of *S. typhi* but man.

The infectious dose of*S. typhi* in volunteers varies between 1000 and 1 million organisms (6). In real life, the infectious dose may well be much lower, because of the limited number of volunteers that participated in experimental infection studies. Although the Vi-antigen may not be responsible for virulence, Vi-negative strains of *S. typhi* appear to be less infectious than Vi-positive strains. After ingestion by drinks or food, *S. typhi* must survive the gastric acid barrier and reach the small intestine. As proven for non-typhoidal *Salmonellae*, individuals with a reduced gastric acid barrier are likely more susceptible to disease, because they fail to reduce the inoculum. In the small bowel, the bacteria adhere to the mucosa and next orchestrate their ingestion by mucosal cells. The so-called M cells, specialized epithelial cells overlying Peyer's lymphoid patches, are probably the primary sites of internalization of *S. typhi*. After passing these cells, the bacterium is presented to the underlying lymphoid tissue. Invading microorganisms translocate to intestinal lymphoid follicles and are transported to draining mesenteric lymph nodes. From there on, some pass into the circulation ('primary bacteremia') and are cleared by the mononuclear phagocyte system (previously designated as reticuloendothelial cells) of liver and spleen (7).

Just like other intracellular bacterial pathogens, *Salmonellae* manage to survive, persist and multiply within the mononuclear phagocytes of the lymphoid follicles, liver and spleen (8). At a critical point– which is probably determined by the number of bacteria, their virulence, and the host response– bacteria are released or spill over from this sequestered intracellular habitat into the bloodstream and cause a low-grade bacteremia. Until the (second) bacteremia, the patient does not have manifestations of disease and is in the incubation period that depending on the inoculum usually takes between 7 and 14 days.

In the bacteremic phase, the organism becomes widely disseminated. The most common sites of dissemination are the liver, spleen, bone marrow, gallbladder, and lymphoid tissues including the Peyer's patches of the terminal ileum. Gallbladder invasion occurs either directly from the blood or by retrograde spread from bile. Microorganisms excreted in the bile may re-invade the intestinal lining or are excreted in the faeces. It has been estimated that in patients with typhoid fever the total bacterial count in the bone marrow amounts to approximately 9 bacteria per millilitre, and in the blood to 0.9 per millilitre (9). Because of this difference, bone marrow cultures may still become positive when blood cultures are negative, as may be the case in patients just started on empirical treatment.

Clinical manifestations of typhoid fever

The clinical manifestations and severity of disease in typhoid fever may vary widely, largely depending on the patient population, e.g., adults versus infants, studied. Typhoid fever is a disease of children and young adults, and most patients who present to hospitals with typhoid fever are in the age class of 5 to 25 years. However, community-based surveillance in high-endemic regions demonstrate that many cases of typhoid, in particular in children under five years of age, may have a non-specific less severe illness that is not recognized clinically as typhoid (10). In most developing countries, many patients with typhoid fever do not receive appropriate medical attention or are treated as outpatients (11, 12).
The disease typically presents with a step-like, daily increase in temperature (finally reaching up to 40-41°C) combined with headache, malaise and chills. The hallmark of typhoid fever is a prolonged fever that may persist up to 4 to 8 weeks in untreated cases. Even though the illness may be mild and brief, in rare cases an acute severe infection progresses into multiple organ failure, disseminated intravascular coagulation and central nervous system involvement ('typhoid', i.e., 'in the clouds') and may results in early death. In other instances, necrotising cholecystitis or intestinal bleeding and perforation of the necrotic Peyer's patches can occur in the third or fourth week of illness, and result in late death. In most cases, the onset of these late complications is dramatic and clinically obvious. Other gastrointestinal manifestations include constipation (especially in adults) rather than diarrhoea (in children) and often is accompanied by abdominal tenderness. After the first week, mild hepatosplenomegaly is detectable in the majority of patients. A bradycardia relative to height of the fever may be a clinical clue to typhoid but is found in only a minority of patients. Epistaxis may be noted in the early stages of illness. "Rose spots," appearing as small, pale red, blanching, slightly raised maculae, are occasionally seen on the chest and abdomen during the first week. They can evolve into non-blanching small haemorrhages and may be difficult to see in dark skinned patients (13).

Like many infectious diseases, typhoid fever is the manifestation of the outcome of a complex crosstalk between the human host, its environment and the microbe, with many acquired, random and genetic factors coming into play. Somewhat oversimplified, it may be said that the severity of a case of typhoid fever depends on genetic properties of the pathogen (e.g., expression of Vi-antigen, other virulence factors, multi-drug resistance), the bacterial inoculum that effectively reaches its site of entry into the body (influenced by many environmental, social and host-specific factors, such as population density, food and personal hygiene, but also gastric acid, competing microorganisms in the gut, etc), and specific resistance mechanisms of the host (influenced by environmental factors like nutrition, as well as its genetic make-up, age, immune status, etc). Host genetic factors are therefore one among many determinants of susceptibility and outcome of infectious disease (14).

Considering the importance of typhoid fever to public health in Indonesia, there is a need for a comprehensive study describing environmental, host genetic and bacterial-specific characteristics as interactive aspects resulting in the clinical entity of typhoid and paratyphoid fever. The present thesis makes a start with such an analysis by focusing on these contributing elements.

Environmental factors in typhoid fever

The basic route of transmission of typhoid and paratyphoid fever is well known. Worldwide experience has demonstrated that improvement of environmental sanitation, including adequate sewage disposal and provision of safe water, sharply reduces the incidence of typhoid fever (13). However, such large infrastructural works that took decades to realise in Western countries about a century ago, cannot be realised overnight in the developing countries of today. Therefore, in these countries it is still useful to identify risk factors for disease and the most critical routes of transmission of disease linked to their particular situation, to enable the design of rational, 'individualized' public health control strategies. Risk factors for typhoid fever have been identified in several epidemiologic studies indicating a role for either waterborne (15-17) or foodborne (18,19) transmission. The risk factors for paratyphoid fever have not been determined in similar detail. The comparison of routes of transmission of both diseases is becoming increasingly relevant, however, since recent reports indicate a relative increase in cases of paratyphoid fever (20,21). It is not clear whether this change is due to incomplete reporting or to a downward trend in the incidence of typhoid fever (4) and by consequence a relative or absolute increase in incidence of paratyphoid fever. This is an important issue, for instance because of recent interest in mass immunization as a control strategy in regions of endemicity. This needs to be reconsidered if the incidence of typhoid fever is decreasing and paratyphoid fever is on the rise, because current typhoid fever vaccines do not provide protection against paratyphoid fever (22). Although the possible transmission routes of enteric pathogens like *Salmonella* are known, the relative importance of the various factors, i.e., the weak link in the transmission chain in a particular situation (rural vs. urban, Asia vs. South America, etc) is uncertain but of great importance to help focus the most relevant and cost-effective local health interventions. An additional complicating factor is the fact that *Salmonella* bacteria can multiply in food and easily reach infective dose after an initial insignificant contamination (23). Therefore, determinants for transmission of enteric pathogens into commercial food and handling of food were examined in a cross-sectional study.

Host genetic factors as determinants in typhoid fever

As abovementioned, host genetic factors may influence susceptibility to and outcome of infectious diseases. Also, studying host and bacterial genetic factors provides insight into

relevant pathophysiological mechanisms in typhoid, by identifying critical pathways and mechanisms of bacterial invasiveness, host resistance and immunity, or tolerance. On the population level, studying genetic variation in relation to environmental factors may help us understand the perceived variation between individuals in susceptibility and clinical outcome (14).

Typhoid induces systemic and local humeral and cellular immune responses, but these confer incomplete protection against relapse and reinfection (24). The multitude of host mechanisms involved leaves open the possibility that (failure of) effector systems at multiple levels of host defence culminate in a differential susceptibility to typhoid and paratyphoid fever. Also, *S. typhi* is highly adapted to its human host and for its transmission relies not only on reconvalescent patients who temporarily excrete the bacterium, but also on subjects that become chronic, sometimes life-long faecal carriers. About 3 to 5 percent of typhoid patients, with a preference for females, become long-term asymptomatic carriers, and can excrete the bacterium at very high numbers without showing any signs of carriership. Many carriers even cannot recall a history of a typhoid fever attack and probably have had an undiagnosed mild infection (13). Obviously, typhoid carriers are of particular concern to the public health since they represent the reservoir for spread of typhoid in the situation that most typhoid patients are recognized, treated adequately and educated how by simple hygienic measures they can prevent passing on the disease as long as they excrete the bacterium. Chronic carriers of *S. typhi* have high levels of serum antibodies to Vi and flagellar antigens, which can be useful for diagnostic purposes (8). Investigating the cohabitation of host and pathogen in chronic carriers should provide a fascinating insight into bacterial survival and propagation strategies, as well as information that could be useful to develop new approaches for the treatment of typhoid and perhaps other persistent microbial infections. With respect to the analysis of host genetic factors, it can be said that functional polymorphisms in genes encoding pro- or anti-inflammatory cytokines and their association with infectious diseases had been studied extensively. In some cases, an association of a particular polymorphism and an infection seemed clear, whereas in other diseases, no significant influence of genetic variation was evident. In most studies, it is not so clear whether susceptibility to disease per se was studied, or an association of genetic variability and severity of disease manifestation.

The activation of infected macrophages by interferon–γ in synergy with TNF–α is a major effector mechanism of cell-mediated immunity to intracellular pathogens like *S. typhi* (25). TNF–α is synthesized by macrophages and T cells as a membrane protein, which is cleaved to produce its soluble 17 Kd form. Soluble TNF–α exerts a range of inflammatory and immunomodulatory activities that are of importance to host defence (26).

The gene for TNF–α is located within the MHC region on chromosome 6p21.3. This is a highly polymorphic region and the location of multiple genes involved in host defense. The TNF–α gene contains a large number of polymorphisms. Of these, single nucleotide polymorphisms (SNP) at position –238 and –308 are the most extensively studied. The role of TNF–α SNPs had been studied in viral infections, i.e., hepatitis B (27) and hepatitis C (28), in parasitic infection, i.e., malaria (29) and leishmaniasis (30), as well as bacterial infection, i.e., meningococcal disease (31), sepsis due to various microorganisms (32-34), and in Vietnam among patients hospitalized for typhoid fever (35). Interestingly, an ex-vivo whole blood study of the cytokine response to lipopolysaccharide (LPS) in patients with typhoid fever found no association between the *TNFA–308* promoter polymorphism and LPS induced TNF–α release, neither during active infection nor after treatment (36). Polymorphism of *TNFRSF1A +36*, a gene that encodes TNF receptor 1 has been associated with Crohn's disease (37).

In the scope of the present study, other genetic variation of interest involves polymorphisms in *IFNG SNP+874* and an allele characterized on the basis of CA repeat polymorphism in intron 5 of *IFNGR1* that have been associated with susceptibility to *Mycobacterium tuberculosis* infection, an intracellular pathogen like *S. typhi* (38-41).

The cytokine IL-1 has been implicated in many inflammatory diseases and the *IL1A SNP-889*, for instance, has been associated with juvenile rheumatoid arthritis (42). Polymorphism in *IL1β SNP+3953* appears to have functional consequences, as it was associated with quantitative differences in expression levels of IL-1β (43). The second allele of *IL1B SNP-511* was decreased in seronegative Epstein-Barr virus culture-positive patients (44). The *IL1R1 SNPsA124G* and *R456R* are both in the coding region and have not been studied extensively.

Interleukin–12, a heterodimer composed of a p40 and p35 subunit, is produced by subsets of dendritic cells and macrophages and acts on natural killer (NK)-cells and T cells. It initiates their proliferative response that leads to the production of IFN-γ. Thus, IL-12 constitutes a major link between innate and adaptive immunity. The overall importance of this cytokine in the pathogenesis of salmonellosis was demonstrated in studies of humans with severe and recurrent infections caused by salmonellae and non-tuberculous mycobacteria: these subjects were found to have genetic defects in the interleukin–12/ interferon–γ mediated pathway of macrophage activation (45-47). A polymorphism in *IL12B SNP+1188* in the 3' untranslated region has been associated with levels of IL12B mRNA expression and IL-12p70 secretion (48).

Besides IL-12, the cytokine IL-18 plays a role in the activation of NK-cells and T-cells, likely by its co-stimulatory action on these cells to produce IFN–γ (49).

The IL-18 SNP in codon 35 has been identified as one of the genes that determines susceptibility to Crohn's disease (50).

Another candidate gene that may play a role in immunopathogenesis of typhoid fever is

CASP1, since genetic variation herein has been associated with *Salmonella enteritidis* infection in poultry (51). *CRP SNP+1444* was found to influence the basal, as well as the stimulated CRP levels (52) and previously, CRP levels were associated with typhoid fever (53). Studying the association of these polymorphisms with susceptibility to typhoid fever in cases identified in a population-based surveillance in an endemic area such as Jakarta, together with well-defined random community controls should help elucidate the role of many of these SNPs as risk factors for susceptibility to or severity of clinical manifestations of typhoid fever.

Besides the variation in genes that have been linked to the host immune response, some other candidate genes should be considered. Since both *Salmonella* and *Mycobacteria* are intracellular pathogens, some immunopathogenic pathways may be quite similar (25,45,46,54). Of interest then, study on leprosy patients revealed that polymorphisms on *PARK2* and *PACRG* were associated with susceptibility to *Mycobacterium leprae* infection (55). Mutations in *PARK2*, the gene encoding Parkin, on chromosome 6, have been identified to cause autosomal recessive juvenile Parkinsonism (56,57). Parkin is an E3 ubiquitin ligase that is required for poly-ubiquitination of proteins before degradation by the proteasome (58). Parkin Co-Regulated Gene or *PACRG* is a reverse strand gene located upstream of the Parkin gene. The gene product, termed Glup, together with Parkin may deal with cytotoxic intermediates by breaking them down or turning them into harmless molecules in the proteasome (59). The ubiquitin-proteasome pathway is important in protein processing and degradation, and contributes to quality control of proteins in cells and antigen-processing for cross-presentation (60). An essential feature of the bacterial pathogen *Salmonella spp.* is its ability to enter cells that are normally non-phagocytic, such as those of the intestinal epithelium. The bacterium achieves entry by delivering effector proteins that cause physiologic changes in mucosal cells. These bacterial proteins must be degraded in exactly the right way and sequence to keep the cells intact and to provide a sustainable environment for *Salmonella* to multiply. The possible role of the ubiquitin-proteasome pathway in effector protein degradation has been cited by several studies on *Salmonella* and host cell interaction (61-63). Mutations in *PARK2/PACRG* might influence the ubiquitin-proteasome pathway; therefore it is interesting to extend the association found with leprosy to that with typhoid fever.

Another gene of potential interest in susceptibility to typhoid fever concerns the cystic fibrosis transmembrane conductance regulator (CFTR) protein. *Salmonella* infection starts with the invasion of bacteria into the mucosa of the small intestine (13). It has been hypothesized that the CFTR protein is used by *Salmonella* Typhi as a docking station, necessary as the first step in entering epithelial cells. CFTR is a chloride ion channel

expressed on many secretory epithelial cells. Many deleterious homozygous mutations of the CFTR result in an almost absence of membrane expression and are the cause of cystic fibrosis. Consistent herewith, cells expressing wild-type CFTR RNA internalize more *S. typhi* than isogenic cells expressing the most common CFTR mutation, a phenylalanine deleted at residue 508 (Δ508). Antibodies against CFTR and synthetic peptides mimicking a domain of CFTR inhibited the uptake of *S. typhi* (64). Finally, yet another study found that *S. typhi* was bound to the CFTR by interaction of its prePilS protein with a 15-mer peptide representing the first extra cellular domain of CFTR (65). In one study, *S. typhi* was even found to induce intestinal epithelial cells to increase membrane expression of CFTR, resulting in enhanced bacterial ingestion and sub-mucosal translocation. In conclusion, CFTR could well play as essential role in the first step in the infectious process leading to typhoid fever, i.e., adhesion to the gut mucosa (66).

Pathogen factors as determinant in typhoid fever

Controlling infectious diseases such as typhoid fever depends on the ability to rapidly detect, identify and characterize the etiological microbial agent. In turn, this relies on an adequate surveillance system to monitor prevalence, detect outbreaks, and assess effects of control programs, so that appropriate intervention strategies can be implemented (67). To be able to interpret the epidemiology of infectious diseases, e.g., to distinguish an outbreak from an overall increase in endemicity, or establish a common link between scattered cases, genetic identification of the various clones of bacteria has become an essential tool. Molecular typing has been used as a tool to identify different *Salmonella* strains. Distinction based on different plasmid profiles of *S. typhi* and *S. paratyphi* A is unsuitable, because only a small proportion of strains (10%) contain plasmids (68). Vi phage typing is technically demanding, and the analysis of envelope proteins detected only minor differences between strains (69). In recent years, macro restriction analysis using Pulsed Field Gel Electrophoresis (PFGE) methods has been used to analyze *Salmonella typhi* isolates in outbreaks (70-77).

Selective amplification of fragment length restriction (AFLP), a technique developed for DNA fingerprinting based on the selective PCR amplification of restriction fragments from a total digest of genomic DNA (78), has been used in the genotypic analysis of several species of bacteria which were highly related or identical using other typing methods (79-81). AFLP has the advantage of being more efficient and readily adapted for automation compared to PFGE (82). Recently, AFLP also has been used for genotypic characterization of *S. typhi* (83). A study comparing characterization of isolated *S. typhi* and *S. paratyphi* A using genomic typing by AFLP and phenotypic typing by biochemical and antibiotic sensitivity profiles and in combination with the data from our epidemiology study will give insight of how many genotypically-distinct *Salmonella* strains might circulate.

Besides the molecular typing methods, also phenotypic typing can be applied, for instance by looking at certain biochemical characteristics or resistance to multiple antibiotics. With respect to *S. typhi*, there is a lack of comparison between these phenotypic and genotypic methods.

Moreover, surveillance for antibiotic resistance is important also from the point of view of patient treatment. Especially so, as blood cultures supplemented by antibiotic sensitivity testing are rarely performed in Jakarta. For the treatment of patients, one has to rely on knowledge of the prevalence of antibiotic resistance of microorganisms in the population, but little data is available for Jakarta or Indonesia. Resistance to chloramphenicol in *S. typhi* was reported already in 1950, but it was not until 22 years later that the first large outbreaks of chloramphenicol-resistant typhoid fever occurred (84). Since 1992, multiple antibiotic resistance (MDR) among isolates of *S. typhi* has become an increasingly important and serious problem (4). In Asia, outbreaks of infections with these strains occurred in India (75,85), Pakistan (86,87), Bangladesh (88), Tajikistan (17) and in Vietnam (89). In Vietnam, MDR *S. typhi* were present in higher numbers in the blood of patients than the sensitive strains (9), in accordance with a previous notion that MDR strains of *S. typhi* are somehow more virulent (90). Little is known on antibiotic resistance of *S. typhi* and *S. paratyphi* in Indonesia. Trends in antibiotic resistance of *S. typhi* and *S. paratyphi* A in Europe are monitored by the Enter-net surveillance hub (91).

Outline of the thesis

In **Chapter 1** a general introduction to typhoid and paratyphoid fever is given.
In the introduction, the burden of disease by typhoid and paratyphoid fever, and clinical aspects are reviewed. Attention is given to the interaction between environment, host and pathogen. Environmental factors, such as personal hygiene and behaviour, contaminated food and water, and host genetic background as risk factors for contracting and defining clinical outcome of typhoid or paratyphoid fever are discussed, as are *Salmonella*-related factors.
In **Chapter 2** risk factors for typhoid and paratyphoid fever in Jakarta are discussed (12). The chapter deals with the influence of personal hygiene, water supply and quality, and eating habits as risk factors for typhoid and paratyphoid fever. Knowledge of the relative contribution of each of these risk factors will be essential to be able to design effective control strategies.
In **Chapter 3** risk factors for transmission of foodborne illness in restaurants and by street vendors in Jakarta are discussed (92). The chapter describes the identification of determinants of transmission of foodborne diseases such as typhoid and paratyphoid fever, in commercial food handling in restaurants, food stalls and pushcarts.
In **Chapter 4** the analysis of environmental determinants is replaced by an evaluation of genetic determinants of disease, by discussing polymorphisms in pro-inflammatory (cytokine) genes in relation to susceptibility to and severity of typhoid fever and paratyphoid fever (93).
In **Chapter 5** an interesting typhoid-susceptibility related candidate gene, i.e., *PARK2/PACRG*, and its polymorphisms in relation to susceptibility to typhoid and paratyphoid fever is discussed (94). Specifically, the chapter explores the association of *PARK2/PACRG* polymorphisms, genes that play a role in ubiquitin-proteasome pathway and were found to be associated with leprosy, with susceptibility to typhoid and paratyphoid fever.
In **Chapter 6** the hypothesis is tested that expression of the cystic fibrosis CFTR protein might be related to susceptibility to typhoid fever (95).
In **Chapter 7** a phenotypic analysis and molecular typing of *S. typhi* by AFLP is applied to assess which method is useful and contributes to the understanding of the epidemiology of typhoid fever and paratyphoid fever in Jakarta (96). To this end, the molecular method for strain typing, AFLP, is compared with conventional methods such as biochemical and antibiotic sensitivity profiles.
Chapter 8 concludes with a general discussion and a summary of the findings of this thesis.

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