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Shigellosis: An Old Disease in New Clothes?
Philippe J. Sansonetti

A new study published in *PLoS Medicine* by von Seidlein and colleagues is a landmark in research on shigellosis [1]. von Seidlein and colleagues conducted a prospective, population-based, multi-centre study of *Shigella* diarrhoea in six Asian countries, producing data on disease burden, clinical manifestations, and microbiology. The study provides, at the scale of a continent, critical epidemiological information regarding prevention strategies against a largely neglected disease that threatens to re-emerge due to its highly infectious potential and its ability to develop resistance to multiple drugs [2].

The Burden of Diarrhoeal Disease

There is no sign that the incidence of diarrhoeal diseases, which are diseases of the poorest, is currently decreasing. Morbidity remains high, particularly in children younger than the age of five years (3.2 diarrhoea episodes per child per year), according to active surveillance studies carried out between 1992 and 2000 [3]. With 2.5 million annual deaths, diarrhoea remains a leading public health concern, even though the attributed mortality has steadily declined in endemic areas, from 13.6 children per 1,000 per year in the period 1954–1979 to 4.9 children per 1,000 per year in the period 1992–2000 [3]. In other words, mortality has roughly halved in the past 20 years. Better primary care, education of mothers, and widespread implementation of oral rehydration therapy are probably the factors that significantly contributed to the decreasing trends in mortality.

Evaluating the health impact of diarrhoea and implementing therapeutic and preventive measures is a headache for national and international health authorities. Unlike other infectious diseases, such as tuberculosis, HIV/AIDS, and malaria, which are all caused by a single etiological agent, diarrhoea is etiologically diverse. Setting priorities for tackling diarrhoeal disease is a complex endeavour, and this complexity largely accounts for its status as a neglected disease. Priorities nonetheless emerge, such as the need to tackle cholera and cholera-like infections caused by enterotoxigenic *Escherichia coli*, rotavirus infection, and shigellosis. Another priority is vaccine development. Rotavirus vaccines are currently appearing on the market, and promising vaccines against the other pathogens that cause diarrhoea are in the pipeline [4].

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The time has come to update epidemiological and disease burden data on diarrhoeal diseases. For instance, a recent population-based study conducted in Thailand during a period of 36 months showed that estimates of incidence are 10- to 100-fold higher than those found by routine, health ministry–based surveillance [6]. Such studies confirm that shigellosis is generally largely underestimated.

There are three major reasons for this underestimation. First, published studies are often based upon passive surveillance carried out in medical institutions, and, therefore, many cases are missed, particularly those devoid of dysenteric symptoms that do not justify medical attention. Whether what counts in public health decisions are exhaustive figures on the incidence across the entire population or simply data on the cases that come to medical attention and bear medical costs is, of course, an important issue. Nevertheless, accurate appreciation of circulating strains in the population is important for decision makers, particularly for a disease that has no significant reservoir other than humans, making it a good target for eradication by a vaccine.

Second, *Shigella* is a very fastidious microorganism that “dislikes” transport, and for which no enrichment medium exists [7]. There is, therefore, a clear need for improved, quick, and robust methods of straight detection from faecal samples. Last but not least, significant numbers of cases occur in adults, with a second disease peak after the age of 40 years. These cases are necessarily considered in studies that are often focused on young children.

One major issue is at stake here: do we still need a vaccine against shigellosis [8]? If the morbidity and

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Abbreviations: *ipath*, invasion plasmid antigen H; *PCR*, polymerase chain reaction.

Philippe J. Sansonetti is at Unité de Pathogénie Microbienne Moléculaire, Unité INSERM 786, Institut Pasteur, Paris, France. E-mail: psanson@pasteur.fr
mortality from shigellosis turn out to be declining, one could seriously question the relevance of continued efforts towards developing a vaccine. Such efforts have not, so far, attracted significant interest from vaccine companies, and the idea of developing such a vaccine may become even less appealing if its cost–benefit ratio were to further decline. On the other hand, if the burden of shigellosis is not falling, epidemiological studies would be crucial in deciding which type of vaccine should be developed, particularly with respect to the number of serotypic valences represented (protection against *Shigella* infection is generally considered serotype specific).

### A Landmark Study

von Seidlein and colleagues' study of the epidemiology and microbiology of shigellosis was conducted in study sites in three rural or semi-rural areas (China, Vietnam, and Thailand) and three urban slums (Bangladesh, Pakistan, and Indonesia). The authors used passive surveillance for case detection, which depends on the health care–seeking behaviour of individual patients, and which risks missing a significant number of cases. Nevertheless, the authors included more than 600,000 people of all ages, which is an impressive achievement. Five major points emerged from their study.

First, the researchers found that, overall, the incidence of diarrhoeal diseases remains high (40 per 1,000 per year in all age groups, and as high as 254 per 1,000 per year in children younger than five years). *Shigella* infection, diagnosed by classical microbiology procedures, accounted for five percent of these diarrhoeal episodes, a proportion very similar to for five percent of these diarrhoeal episodes, a proportion very similar to the exception of Thailand, in which, as is already known, *S. sonnei* prevails, in other areas the authors found a large diversity of serotypes. A serogroup such as *S. boydii* that was considered rare and limited to the Indian subcontinent has now expanded its “zone of activity”. This makes the aim of developing a serotype-based *Shigella* vaccine a difficult endeavour, and emphasises the need for a switch in paradigm and investment in renewed research efforts to develop cross-protective vaccine candidates.

A last, but essential, point is the demonstration of the high incidence of multiple drug resistance, including all first-line antibiotics (chloramphenicol, tetracycline, sulfonamides, ampicillin, sulfamethoxazole-trimethoprim, and nalidixic acid). This is not a new finding, but what is important is the demonstration that in some areas a significant percentage of strains (about five percent) is also resistant to fluoroquinolones, leaving little, if any, therapeutic alternative. Large, uncontrolled use of antibiotics in these areas is likely to provoke a major crisis, which may change the profile of shigellosis once again, but for the worse.

### Conclusion

von Seidlein and colleagues found that the incidence of shigellosis is unchanged, but that there has been a trend towards a more benign disease. Is this sufficient to reconsider the relevance of developing a *Shigella* vaccine? The answer is likely to be no. We still do not know the reasons why the disease has become less deadly, and it is possible that the disease could become more deadly in the future, especially with the rapid spread of multi-drug resistance and the return of *S. dysenteriae* type 1. Three-quarters of a century ago, Charles Nicolle had already warned us against the “génie évolutif” of infectious diseases. Remember also that a “giant” is absent from this large-scale study and from others: Africa.

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3. Kosek M, Bern C, hand, if the burden of shigellosis is not falling, epidemiological studies would be crucial in deciding which type of vaccine should be developed, particularly with respect to the number of serotypic valences represented (protection against *Shigella* infection is generally considered serotype specific).

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