The Need for an Information Communication and Advocacy Strategy to Guide a Research Agenda to Address Burden of Invasive Nontyphoidal Salmonella Infections in Africa

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Invasive nontyphoidal salmonellosis (iNTS) is often not recognized clinically, and prevention of iNTS is largely ignored by policy planners and decision makers. During 2010, an estimated 3.4 million cases and 681,316 deaths occurred worldwide due to iNTS, with the largest estimated disease burden in resource-limited areas of sub-Saharan Africa. These figures likely underestimate global burden for several reasons, further complicating efforts to raise awareness of iNTS. To increase disease recognition and facilitate development of interventions, a communication and advocacy plan should be developed and implemented by actors in different sectors of global health, including researchers and scientists, funders, vaccine manufacturers, civil society organizations, and government officials from highly affected countries.

Keywords. iNTS disease; Africa; developing countries; advocacy; communication strategy.

Salmonella infections are a significant cause of the global burden of morbidity and mortality. Salmonellae are divided into typhoidal serotypes (Salmonella enterica serovar Typhi and Salmonella enterica serovar Paratyphi A) and nontyphoidal Salmonella (NTS) serotypes. In 2010, there were approximately 3.4 million cases of invasive nontyphoidal Salmonella (iNTS) disease worldwide, resulting in an estimated 681,316 deaths [1]. Invasive NTS caused 4,847,000 disability-adjusted life-years (DALYs) lost, or approximately 70 DALYs lost per 100,000 persons worldwide. Despite a substantial burden of disease, deaths, and DALYs lost, iNTS disease, in comparison with other major infectious diseases (Figure 1), has received little attention as a major public health problem.

Invasive NTS infections occur both in developed nations of North America and Europe and in developing countries in Africa and Asia. North America and European iNTS infections are mostly of zoonotic origin, with transmission to humans via contaminated food, and are infrequently fatal. In developing countries, the source of iNTS infections is not well understood, and iNTS infections are frequently fatal, especially among children <5 years of age [3].

A recent study modeled the annual number of iNTS cases occurring globally and by different geographic areas and estimated that annually, approximately 2 million iNTS cases, or 56% of global cases, are reported from Africa, equating to an incidence of 227 cases per 100,000 population [1]. In Africa, 68% of cases occur among children aged <5 years, with some geographic variability. Two recent studies based on confirmed cases reported an annual iNTS incidence in rural Kenya and Mozambique of 88 and 120 cases per 100,000, respectively, in children aged <5 years [3,4]. There are reports of iNTS case fatality ratios (CFRs) of 3%–47% in Africa, making iNTS a major cause of under-5 mortality in the region [1].
Antimicrobial drugs are important to treat iNTS and reduce CFRs, but strains resistant to these drugs have emerged. A distinct genotype of *Salmonella enterica* serovar Typhimurium, ST313, is resistant to ampicillin, chloramphenicol, and cotrimoxazole, and has caused epidemics in multiple African countries. Without proper treatment, the CFR for this strain of iNTS in sub-Saharan Africa has been reported to range between 20% and 25% [5].

Despite this high documented burden, the total reported number of cases and CFRs likely underestimate the burden [6]. Inadequate diagnostic facilities, poor healthcare access, failure of clinicians to suspect and test for iNTS, and iNTS-related death occurring outside the health systems are all major causes of underreporting from low-resource settings [7, 8].

In light of the significant burden of iNTS disease as a major cause of mortality and morbidity and the need for actions to prevent iNTS disease, here we outline an approach that could generate interest among stakeholders (academia, funding agencies, drug and vaccine manufacturers, and national and local governing bodies), catalyze momentum around the disease, accelerate prevention efforts, and potentially lead to policy changes at the local, regional, and global levels to reduce suffering of vulnerable populations by iNTS disease.

The global disease control decision-making processes are complex and involve many stakeholders with differing and sometimes conflicting priorities. Consequently, a systematic approach is necessary to productively inform policy decisions. Such an approach should consider the extent of the problem, factors that either positively or negatively impact disease, knowledge of interventions, availability of interventions, the cost and practicality of implementation in a public health delivery system, and evidence of impact of interventions in reducing burden. One of the critical components in this effort is an environment of political commitment at the local, regional, and global levels. An in-depth analysis of the impact of such decisions is needed through a multidisciplinary approach to identify research needs, guide and develop diagnostic and treatment options, and develop and introduce preventive measures such as vaccines. As stated by Gavi, the Vaccine Alliance, “Getting new and underused vaccines on the development agenda is the first obligatory step toward introducing life-saving antigens” (http://www.gavi.org/about/gavis-business-model/getting-vaccines-on-the-agenda/).

There are many examples of addressing major public health problems through such a comprehensive strategy, one recent example being that of rotavirus diarrhea. Rotavirus today is recognized as a leading cause of severe childhood diarrhea and death in the developing world, with 2 licensed vaccines available for global use (and more to follow), vaccine implementation in 77 countries [9], and reductions of 49%–92% in rotavirus-associated hospitalizations [10]. Yet, its burden and the potential for prevention were poorly recognized 2 decades ago [11]. The appreciation of rotavirus-associated disease burden arose through the commitment of global and regional public health leadership and the efforts of a coordinated advocacy and scientific leadership group—namely, the RotaADIP (Accelerated Development and Introduction Plans), a partnership of PATH, the US Centers for Disease Control and Prevention, and the World Health Organization (WHO), with key support from Gavi. This group established rotavirus surveillance in >40 countries, played a key role in establishing pivotal vaccine trials in the most affected countries of Africa and Asia, promoted the information sharing that led to vaccine adoption globally, and supported planning and communication efforts that continue to the present period [12]. Similar efforts have occurred for yellow fever (the Yellow Fever...
Table 1. Outlining the Objectives, Stakeholders, and Approaches to Creating an Environment for Reducing the Burden of Invasive Nontyphoidal *Salmonella* Infection Globally

<table>
<thead>
<tr>
<th>Action</th>
<th>Strategic goals</th>
<th>1. Research iNTS impact across multiple geographic locations</th>
<th>2. Circulate research in persuasive and digestible form</th>
<th>3. Create a coalition of all key stakeholders</th>
<th>4. Host meetings and conferences with key actors</th>
<th>5. Secure long-term financing for vaccine and diagnostics</th>
<th>6. Research and develop iNTS vaccine and diagnostics in endemic countries in Africa</th>
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<tr>
<td>Key actors involved</td>
<td>NGOs, academia, WHO/World Bank/CDC/Gavi</td>
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<td>NGOs, academia, WHO/World Bank/CDC/Gavi</td>
<td>NGOs, academia, WHO/World Bank/CDC/Gavi, pharmaceutical industry, healthcare providers, government representatives, civil society organizations</td>
</tr>
<tr>
<td>Goal-level indicators</td>
<td>Number of open-access articles published</td>
<td>Number of deliverables created</td>
<td>Number of actors active in coalition</td>
<td>Number of conferences and attendees</td>
<td>Amount of guaranteed funding</td>
<td>Number of vaccines deployed</td>
<td></td>
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<tr>
<td>Strategic objectives</td>
<td>Increasing body of knowledge of iNTS</td>
<td>Increase awareness of the impact of iNTS</td>
<td>Coordinate actions to combat iNTS</td>
<td>Determine steps to combat iNTS</td>
<td>Initializing research and development</td>
<td>Decrease of iNTS burden</td>
<td></td>
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</table>

Abbreviations: CDC, Centers for Disease Control and Prevention; CRF, case fatality ratio; iNTS, invasive nontyphoidal *Salmonella*; NGO, nongovernmental organization; WHO, World Health Organization.
Initiative), *Haemophilus influenzae* type b (the Hib Initiative), and *Streptococcus pneumoniae* (the PneumoADIP).

It will be important for the public health community to learn from these successful examples for future disease prevention strategies, including those to address iNTS. However, before developing a communication and advocacy strategy for iNTS disease research and prevention, it is imperative to define specific short-term and long-term goals that highlight the steps needed to reduce global iNTS burden.

**Short-term Goals**

1. Establish a research agenda that delineates priority areas for scientists at various levels of basic science and epidemiology to determine iNTS burden (incidence of all and severe disease, mortality, sequelae) across various groups.
2. Identify risk factors for infection and severe disease, define the disease transmission cycle, and find opportunities for intervention to affect disease spread patterns stratified by age, socioeconomic, and geographic variables.
3. Disseminate information related to iNTS using a strategic communications plan directed at groups such as healthcare providers, researchers (epidemiology, diagnosis, and treatment), professional bodies, and vaccine and intervention developers with the goal of encouraging these groups to work together on disease control and increasing awareness among decision makers.
4. Encourage vaccine development by highlighting the need and anticipated demand for vaccines.

**Long-term Goals**

1. Develop and support implementation of a plan to create a rapid diagnostic test for iNTS for better recognition of iNTS cases both for clinical management and more accurate determination of disease burden.
2. Develop evidence-based strategies for NTS vaccine use that would consider target age groups, schedules, vaccine presentation, and programmatic issues (eg, using vaccine outside of traditional infant age groups).
3. Design alternative or complementary intervention methods to reduce transmission and disease burden.

Stakeholder identification and engagement will be a key step to move forward. Stakeholders necessary for the control of iNTS include government officials from iNTS-endemic countries as well as industrialized countries; international organizations such as WHO, the World Bank, and Gavi; healthcare providers and professionals from the health system delivery workforce; donor organizations such as the Bill & Melinda Gates Foundation; the pharmaceutical industry; civil society organizations; local nongovernmental organizations; and the academic research community (Table 1). Once the key partners are mobilized, a plan of action needs to be developed for implementation. Below we highlight priority activity areas and their purpose. Specific actions by stakeholder category are provided in Table 1.

**DEFINE THE BURDEN AND RISK FACTORS**

This first step toward iNTS disease control will require closing the many knowledge gaps in disease epidemiology. The reasons for the age, socioeconomic, and geographic distribution of incidence and severity are not clear. Whereas environmental sources of NTS include water, soil, insects, factory surfaces, kitchen surfaces, animal feces, raw meat, and raw seafood, to name only a few [6], questions remain about the reservoirs of iNTS infection in endemic countries in Africa. Finally, and most critically, disease burden remains poorly defined and will require determining the incidence of iNTS cases, severe cases, and mortality; sequelae across various populations; and calculation of summary measures such as DALYs lost. This goal will require rigorous studies that incorporate improved diagnostics, specimen transport, and laboratory quality assurance; assessment of the impact of lack of hospital access for iNTS cases; healthcare provider training; and thorough evaluation and follow-up of severe iNTS cases.

**DIAGNOSIS**

A key factor in determining disease burden remains accurate diagnosis. However, the nonspecific clinical presentation of iNTS makes accurate diagnosis without microbiological facilities problematic. Fever, the most common symptom of iNTS, is also a symptom of malaria, which like iNTS is endemic in sub-Saharan Africa. Moreover, iNTS and malaria caseloads both peak seasonally near the rainy season, further complicating the diagnostic process and increasing the CFR due to coinfection [13, 14]. While blood, bone marrow, and stool cultures are

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**Table 2. Key Messages That Could Be Used for Communication to Facilitate Invasive Nontyphoidal *Salmonella* Control in Endemic Populations**

<table>
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<tr>
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<tr>
<td>1. iNTS is a major cause of mortality and morbidity in sub-Saharan Africa, yet remains poorly recognized as a disease of major public health concern.</td>
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<td>2. Existing information regarding the mortality, morbidity, and impact of iNTS shows the need for further research.</td>
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<tr>
<td>3. The necessary key stakeholders exist in various sectors but have no unified plan to combat iNTS.</td>
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<tr>
<td>4. Strategic communication and advocacy efforts are needed to organize a global coalition that can promote prevention and control interventions and public health research.</td>
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Abbreviation: iNTS, invasive nontyphoidal *Salmonella*. 

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DESIGNING INTERVENTIONS FOR CONTROL

A high-priority advocacy goal will be the scaling up of interventions for disease control. However, efficiently addressing this issue largely relies on understanding disease burden, transmission, and risk factors. Moreover, once these issues are understood, results must be communicated to groups specializing in development and implementation of prevention measures such as vaccine manufacturers and public health officials. An efficacious, safe, and reasonably priced vaccine could have an immediate impact. However, the development timelines for vaccines are lengthy, and this will be particularly true for iNTS given that only a few candidate vaccines are under development [16, 17]. This emphasizes the urgency of reaching consensus in this area. In addition, it will be critical to work on development and implementation of reasonably priced and effective nonvaccine interventions. Repeated outbreaks of iNTS disease in developed countries emphasize the challenges in rollout of nonvaccine interventions, as despite the availability of such interventions iNTS disease appears in outbreaks and causes economic and epidemiological losses. The low CFRs in developed countries highlight the large benefits that could be realized through improved access to care and case management in control of iNTS disease and should be the focus in developing countries as well.

CONCLUSIONS

Invasive NTS remains one of the most common causes of mortality globally and decreases health equity by affecting primarily resource-poor populations in Africa. Many key stakeholders contribute currently to iNTS management and research, but there is no coordinated effort to promote an iNTS agenda globally. Learning from other successful initiatives, it will be important to form a comprehensive disease control strategy with a focused coordination group. Such a group could reduce the clinical consequences of iNTS and advance the cause of disease prevention through advocating for and pursuing a research and public health agenda that includes improved understanding of iNTS epidemiology, improved diagnostics, and better treatment options in the short term in addition to the long-term development of vaccine and nonvaccine interventions.

Notes

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