10-21-2020

An optimal typhoid conjugate vaccine coverage complemented with WASH is imperative for the control of antimicrobial resistance in Pakistan

M. Imran Khan

Saher Aijaz

Farzeen Fatma Syed

Linda M. Kaljee

Vaccine 38 (2020) 6969–6970

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Commentary

An optimal typhoid conjugate vaccine coverage complemented with WASH is imperative for the control of antimicrobial resistance in Pakistan

M. Imran Khan [a,*], Saher Aijaz [b], Farzeen Fatma Syed [c], Linda Kaljee [d]

[a] PHC Global (pvt) Ltd., 241 Bahadur Shah Zafar Road, Bahadurabad, Karachi 74800, Pakistan
[b] School of Nursing and Midwifery, The Aga Khan University, Karachi 74800, Pakistan
[c] Medical College, The Aga Khan University, Karachi 74800, Pakistan
[d] Global Health Initiative, Henry Ford Health Systems, Detroit Michigan, United States of America

ARTICLE INFO

Article history:
Received 10 May 2020
Received in revised form 25 August 2020
Accepted 14 September 2020
Available online 30 September 2020

Keywords:
Salmonella typhi
Typhoid conjugate vaccine
Enteric fever
Pakistan
Developing countries
Immunisation

1. Background

Typhoid fever, a systemic illness, is caused by Salmonella Typhi (*S.* Typhi), a Gram-negative bacterium [1]. Typhoid fever varies in its clinical presentation depending on the time and stage of infection. Patients may present with mild illness of low-grade fever, malaise, and slight dry cough. The more severe clinical presentation may include abdominal discomfort and complications such as gastrointestinal bleeding resulting to shock. If untreated, typhoid fever may result to intestinal perforation and in many cases death. Factors such as duration of illness before the initiation of appropriate therapy, the choice of antimicrobial treatment, age, the previous exposure or vaccination history influence the severity and overall clinical outcome of typhoid fever.

Multidrug resistant strains including extensively drug-resistant (XDR) *S.* Typhi are decreasing effectiveness of lifesaving antibiotics [2]. The XDR isolates from Pakistan showed an array of genetic modifications, conferring resistance to first-line antibiotics as well as fluoroquinolones and third generation cephalosporins. This may be referred to as the biosocial footprints of intensive global antibiotic use and neglect of typhoid in LMIC (low- and middle-income countries) for more than half a century [3]. Between November 2016 and December 2019, a total of 15,238 XDR S. Typhi have been reported in Sindh province (in the south-east of Pakistan) alone [4]. This XDR outbreak is declared the largest drug-resistant typhoid outbreak to date. While not the first time, *S.* Typhi has challenged the global public health community, the current episode has highlighted the need for comprehensive typhoid fever prevention measures.

2. Disease burden

Estimates indicate an annual 14·3 million cases of typhoid and 116,000 deaths [5]. South Asia exhibits 75% of global case count and the highest age adjusted incidence of 1506 per 100,000 person-years [5]. Globally in 2017, S. Typhi attributed to 8.3 million years of life lost (YLLs) and 8.4 million disability-adjusted life-years (DALYs) [5]. Typhoid continues to undermine healthcare systems in LMIC by inculcating significant health service costs. Increasing urbanization has contributed to compromised water and sanitation conditions in cities, and in rural areas, where water and sanitation conditions remain inadequate. Global climate changes in temperatures, rainfall, and river levels are also contributing to increases in typhoid cases [6].

* Corresponding author.
E-mail address: imran@phcglobal.org (M. Imran Khan).

https://doi.org/10.1016/j.vaccine.2020.09.051

3. Typhoid fever and vaccination

Many LMIC do not have the resources and infrastructure to adopt and sustain water, sanitation, and hygiene (WASH) interventions. In conjunction with continued WASH programs, vaccine introduction is the most cost-effective public health measure to decrease the global burden of typhoid fever [7]. While typhoid fever has recently received attention due to multi-drug resistance, its concentration in LMICs and associated health, social, and economic burden have not been adequately acknowledged. A far-reaching global policy for implementation of vaccines in health systems is imperative to counteract the emergence of drug resistant *S.* typhi. Vaccine introduction will not only have a primary effect of reducing the incidence of Typhoid fever, it will also have a secondary effect through reduced empiric antibiotic treatment use and hence development of antimicrobial resistance [8]. Previous programs identified paucity of global policy, fragile health systems, and inadequate planning, funding, and decision-making procedures as the principal impediments to vaccine introduction [9]. Furthermore, a scan of WHO-UNICEF immunization uptake data for Pakistan indicates varying uptake levels less than 80% for many childhood vaccines [10]. As with the Pakistan's polio eradication program, an effective and sustainable TCV immunization program needs efforts to increase public and health sector engagement of the public and opinion leaders, innovative immunization program outreach strategies, public health case finding, promoting antibiotic stewardship, strengthened laboratory capacity and effective surveillance of vaccine safety and typhoid disease, to be able to evaluate the program, identify gaps and address deficiencies [11]. The multilateral organizations (e.g., GAVI, WHO) were only willing to invest in a conjugate vaccine, and international and national stakeholders only saw solution in WASH interventions. Investment by industry for improved diagnostics to support early detection did not yield a test that can address the delayed recognition of typhoid. The WHO recommendation of programmatic inclusion of typhoid vaccines (parenteral unconjugated Vi polysaccharide (ViPS) and oral live attenuated Ty21a) in high-risk countries was never implemented at scale [12]. Challenges in public health adoption of ty21a and ViPS were low levels of efficacy in younger children, repeat dose requirements, and vaccine costs. However, the global political commitment was the main reason since vaccines with similar obstacles for other diseases have been introduced in routine immunization programs. These challenges with typhoid fever vaccines could have been addressed if national support for vaccination and global financing was available.

More recently, the WHO Strategic Advisory Group of Experts (SAGE) recommended typhoid conjugate vaccines (TCV) and their inclusion in routine immunization programs. In the past two decades there are at least six TCV candidates at different development stages [13]. WHO has prequalified the ViPS tetanus-toxoid conjugate vaccine (Typbar-TCV®) which is safe for administration from 6 months of age and has high tolerability [14]. However, despite the prequalification of TCV, the increasing global drug resistant *S.* Typhi strains would require a larger number of TCV supply and manufacturer capacity in meeting the demand.

4. The future typhoid control

With the introduction of TCV into Pakistan's Expanded Program for Immunization (EPI) in 2019, doors have been opened for introduction in other endemic countries. The WHO recommends that 80% of the districts should have 80% completion rates for vaccines in the immunization schedule. The mathematical models on typhoid vaccine effectiveness have shown highest impact at least 80% TCV coverage. However, adherence to timely receipt of the TCV will be imperative as Pakistan and other LMIC continue to lag behind international benchmarks for completion of current EPI vaccines [15]. To address this issue proven effective strategies must be employed to gain stakeholders' confidence. Vaccine introduction is an iterative process which is both resource- and time-consuming. Advocacy and communication across a broad range of stakeholders is essential – not just prior to introduction but throughout the entire implementation process. With the risks for increasing mortality and morbidity from multi-drug resistant typhoid fever, now is the time for a global and local synergy to ensure adoption, implementation, and sustainability of comprehensive and integrated WASH and TCV programs [16].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Acosta C, Albert JM, Bhan MK. Background document: The diagnosis, treatment and prevention of typhoid fever. Geneva, Switzerland: World Health Organization 2003;7:2003.
[2] Klemm EJ, Shakoor S, Page AJ, Qamar FN, Judge K, Saeed DK, et al. Emergence of an extensively drug-resistant Salmonella enterica serovar Typhi clone harboring a promiscuous plasmid encoding resistance to fluoroquinolones and third generation cephalosporins. MBio. 2018;9(1):e00105–e118.
[3] Kirchhelle C, Dyson Z, Dougan G. A biohistorical perspective of typhoid and antimicrobial resistance. Clin Infect Dis 2019; 69(Supplement_5): S388–S394.
[4] National Institute of Health Pakistan Weekly epidemiological report https://www.nih.org.pk/wp-content/uploads/2020/03/07-FELTP-Pakistan-Weekly-Epidemiological-Report-Feb-03-Feb-09-2020.pdf accessed on March 15, 2020.
[5] GBD 2017 Typhoid and Paratyphoid Collaborators. The global burden of typhoid and paratyphoid fevers: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Infect Dis 2019 Apr; 19(4): 369–381.
[6] Dewan AM, Corner R, Hashizume M, Ongee ET. Typhoid Fever and its association with environmental factors in the Dhaka Metropolitan Area of Bangladesh: a spatial and time-series approach. PLoS Negl Trop Dis 2013;7(1): e1998.
[7] Guzman CA, Borsutzky S, Griot-Wenk M, Metcalfe IC, Pearman J, Collioud A, et al. Vaccines against typhoid fever. Vaccine 2006.
[8] Klugman B. Impact of existing vaccines in reducing antibiotic resistance: Primary and secondary effects. PNAS 2018;115(51):12896–901.
[9] Levine OS, Hajjeh R, Wecker J, Cherian T, O'Brien KL, Knoll MD, et al. A policy framework for accelerating adoption of new vaccines. Hum Vaccine 2010;6 (12):1021–4.
[10] Organization W. WHO vaccine-preventable diseases: monitoring system. 2019 global summary [Internet]. Apps.who.int. 2020 [cited 29 June 2020]. Available from: https://apps.who.int/immunization_monitoring/globalsummary/estimates?c=PAK.
[11] Hussain S, Boyle P, Patel P, Sullivan R. Eradicating polio in Pakistan: an analysis of the challenges and solutions to this security and health issue. Globaliz Health 2016;12(1).
[12] Khan MI, Franco-Paredes C, Sahastrabuddhe S, Ochiai RL, Mogasale V, Gessner BD. Barriers to typhoid fever vaccine access in endemic countries. Res Reports Tropical Med 2017;8:37–44.
[13] Sahastrabuddhe S, Saluja T. Overview of the typhoid conjugate vaccine pipeline: current status and future plans. Clin Infect Dis 2019;68 (Supplement_1):S22–6.
[14] Shakya M, Colin-Jones R, Theiss-Nyland K, Voysey M, Pant D, Smith N, et al. Phase 3 Efficacy Analysis of a Typhoid Conjugate Vaccine Trial in Nepal. The New England J Med 2019; 381(23): 2209–2218.
[15] Hosseinpoor AR, Bergen N, Schlotheuber A, Gacic-Dobo M, Hansen PM, Senouci K, et al. State of inequality in diphtheria-tetanus-pertussis immunisation coverage in low-income and middle-income countries: a multicountry study of household health surveys. The Lancet. Global Health 2016;4(9):e617–26.
[16] Gibani MM, Britto C, Pollard AJ. Typhoid and paratyphoid fever: a call to action. Curr Opinion Infect Dis 2018;31(5):440–8.