PERSPECTIVE

Opportunities for Typhoid Vaccination in India

MANIKANDAN SRINIVASAN[1], KULANDAIPALAYAM NATARAJAN SINDHU[1], JACOB JOHN[2] AND GAGANDEEP KANG[1]

From [1]Division of Gastrointestinal Sciences and [2]Department of Community Health, Christian Medical College, Vellore, India. Correspondence to: Dr Gagandeep Kang, The Wellcome Trust Research Laboratory, Division of Gastrointestinal Sciences, Christian Medical College, Vellore 632 002, Tamil Nadu, India. gkang@cmcvellore.ac.in

Typhoid fever, an infection with potentially life threatening complications, is responsible for 11 to 21 million illness episodes and 145,000 to 161,000 deaths each year globally. India is a high burden country and also faces the challenge of antimicrobial resistance, which further narrows treatment options. This review analyzes the need for typhoid vaccination in India, and appraises the evidence on efficacy, immunogenicity and cost-effectiveness of currently available typhoid vaccines. In 2018, WHO prequalified the first typhoid conjugate vaccine Vi-TT and recommended it for children aged 6-23 months, along with measles vaccine at 9 or 15 months of age through the expanded programme on immunization. With the high endemicity of typhoid in India and the proven cost-effectiveness of the conjugate vaccine, a roll-out of typhoid vaccine should be considered at the earliest.

Keywords: *Community, Immunization, Implementation, Prevention.*

Typhoid fever is caused by *Salmonella enterica* serovar typhi or *Salmonella typhi*, which spreads by the feco-oral route of transmission, through a combination of short and long transmission cycles. The Joint Monitoring Programme 2017 update report has estimated that worldwide, two billion people use drinking water from a source contaminated with faeces and 2.3 billion people do not have access to safe sanitation [1]. Typhoid is endemic in low- and middle-income countries (LMIC) where the widespread implementation of well-engineered water and sewage systems is yet to be achieved. Globally 11 to 21 million cases of typhoid fever occur annually, resulting in 145,000 to 161,000 deaths, with a substantial burden in South Asia [2]. Modelled estimates have shown that 3.6 (1.5-9.4) million cases of typhoid fever occur annually in South Asia [3]. In India, the pooled incidence of typhoid fever was reported to be 377 (178-801) per 100,000 person-years, with highest incidence in children aged 2 to 4 years [4]. The Disease of the Most Impoverished (DOMI) program in Asian countries in 2001-04 reported a typhoid fever-related hospitalization rate of 8.8%, with most hospitalizations in children between 5 and 15 years [5]. Intestinal perforation, a serious complication in inadequately treated typhoid fevers, can have a case fatality rate of 15% [6].

The DOMI study highlighted the magnitude of Multi-drug resistance (MDR) to first-line antibiotics, namely, chloramphenicol, ampicillin and co-trimoxazole. Pakistan had a high proportion of resistance, with 65% of its *S. typhi* strains isolated being multidrug resistant, followed by Vietnam (22%) and India (7%) [5]. The H58 clade, a dominant, MDR haplotype of *S. typhi*, circulating in Asia and Africa over the last 25 years is a serious concern [7]. Since 2016, extended drug resistance (XDR) typhoid cases (resistant to fluoroquinolones and third generation cephalosporins in addition to first line antibiotics) have been reported from Pakistan, and this is an impending threat for other countries [8].

Well-engineered water and sanitation systems, effective treatment of cases and carriers, food hygiene measures, and a pragmatic vaccination programme have demonstrated a decrease in burden of typhoid fever [9]. Water, sanitation and hygiene (WASH) interventions carry multiple benefits beyond typhoid prevention. However, their implementation is expensive and takes time, particularly in resource-constrained LMICs.

In the year 2000 and 2008, WHO recommended typhoid vaccination in high-burden countries, including India [10,11]. Further, in 2018, the Strategic advisory group of experts on immunisation (SAGE) upheld its view on programmatic implementation of typhoid vaccines in endemic countries [12], and WHO additionally prequalified one typhoid conjugate vaccine (TCV) which has the Vi polysaccharide conjugated to tetanus toxoid (Vi-TT) [13]. In this article we critically analyze the currently available options for typhoid vaccination in India and the need for the introduction of the vaccine into the National immunization program.

WHO-RECOMMENDED TYPHOID VACCINES

Three WHO prequalified typhoid vaccines are currently available: live attenuated Ty21a, Vi capsular polysaccharide (ViPS) and TCV vaccines.

Ty21a, Vi Capsular Polysaccharide Vaccines

Both Ty21a and ViPS vaccine have demonstrated efficacies of 50% in large field trials and possess a good safety profile as per Global Advisory Committee for Vaccine Safety (GACVS) (***Table* I**). The need for booster doses and the fact that these vaccines were not licensed for use in younger children, limits the potential for their use in national programs.

Typhoid Conjugate Vaccines (TCV)

TCV has a capsular polysaccharide (Vi) covalently linked to a protein conjugate such as recombinant exoprotein of *Pseudomonas aeruginosa* (rEPA), tetanus toxoid, diphtheria toxoid or cross reactive material 197 (CRM197). Linkage of a protein moiety results in T-cell dependent differentiation of B cells. Thus, TCVs are able to mount a robust immune response in children aged less than 2 years, rendering the vaccine highly immunogenic and suitable for use in this age group [14]. Currently, the Drug Controller General of India has licensed three Vi-conjugated vaccines. The features of Vi vaccines are detailed below:

Efficacy: Vi-TT and ViPS were evaluated in adults in a controlled human infection model and demonstrated a vaccine efficacy of 54% and 52%, respectively, with the end-point of persistent fever of ≥38ºC for 12 hours or longer or *S. typhi* bacteremia. Among those with fever of ≥38°C, preceding a *S. typhi* bacteremia, the efficacy of Vi-TT and ViPS was 87% and 52%, respectively [15]. An efficacy trial for Vi-TT vaccine in children aged 6 months to 12 years at Kolkata showed a vaccine efficacy of 100% [95% CI: 97.6 -100] when 2 doses of the vaccine were administered at a 6- week interval [16], although boosters are not now recommended.

Higher seroconversion and avidity: Vi-TT demonstrated higher seroconversion rate (100%) when compared to ViPS (88.6%), 28 days following vaccination [15]. In an Indian trial, in individuals aged between 2 and 45 years, Vi-TT had a significantly higher seroconversion rate than ViPS (97.3% *vs.* 93.1%; $P<0.01$) at six weeks post-vaccination [17]. A two year follow-up showed antibody titers to be significantly higher in Vi-TT group when compared to ViPS group (74.1% *vs.* 53.3%*;* $P<0.001$) [12]. The avidity of antibodies (Avidity Index >60) following a booster dose was superior in Vi-TT recipients (46%) compared to ViPS (16%) vaccines [12]. Conjugate vaccines not only demonstrate a better seroconversion rate and a longer antibody response when compared to ViPS, but also offer greater avidity (***Web Table* I**).

Higher immunogenicity of TCV in children aged <2 y: A Vi-TT trial in Indian children aged between 6 and 23 months demonstrated a seroconversion rate of 96.8% (95% CI: 92.1-99.1) and 65.1% (95% CI: 56.1-73.4) at 6 weeks and 2 years, respectively after vaccination. Even after 5 years, antibodies persisted in over 70% of Vi-TT vaccinees. Children of both age groups, 6-11 and 11-23 months, showed a robust immune response [12].

Sero-efficacy: The Vi-TT trial also determined the sero-efficacy, which was 85% (95% CI: 80-88%) [18].

Co-administration with EPI vaccines: Co-administration of Vi-TT and measles or measles-mumps-rubella (MMR) vaccines at 9 or 15 months of age showed no interference with antibody response to any antigen [12].

Safety: In 2018, SAGE acknowledged the safety profile of Vi-TT in children, but GACVS reports on post-marketing surveillance will provide more evidence on its safety [12].

Cost-effectiveness analysis of Vi-TT: Vaccination is 'cost saving' if cost of the vaccination program is lesser than the costs involved in treatment of cases. On the other hand, vaccination is 'very cost-effective' if cost-effectiveness (CE) ratio is less than the per capita gross national income (GNI) and 'cost-effective' if less than 3 times the per capita GNI.

CE of Vi-TT (priced at US$ 1 per dose) was analyzed in Delhi and Kolkata from a healthcare payer perspective under the following strategies: (*i*) Routine immunisation (RI) with TCV (9 months); (*ii*) RI + catch up vaccination (9 months–5 years); (*iii*) RI + catch up vaccination (9 months–15 years); (*iv*) RI + catch up vaccination (9 months–25 years); and (*v*) RI + catch up vaccination (all ages more than 9 months). In Delhi, compared to no vaccination, both RI with TCV (strategy1) and RI + catch up at all ages (strategy 5) were 'cost saving' strategies with a probability >99%. In Kolkata, compared with no vaccination, RI with TCV (strategy 1) was 'very cost effective' with >75% probability. On imputing the current market price of Vi-TT at a unit price of 1800 INR in the analysis, it was found that none of the above strategies were 'cost effective' at Kolkata. However, at Delhi, RI with TCV (strategy 1) was still 'cost effective' at the same unit price of the vaccine, and this may be due to higher costs incurred in treatment of cases [19].

Typhoid-endemic LMICs are classified based on annual incidence, as low (10-50 cases/100,000

TABLE I COMPARISON OF TY21A, VI POLYSACCHARIDE AND TYPHOID CONJUGATE VACCINES

Characteristics	*Ty21a*	*Vi Polysaccharide*	*Typhoid conjugate vaccine (Vi-TT)*[13]
Type of vaccine	Live attenuated	Polysaccharide subunit	Polysaccharide with a protein conjugate
Licensure, place and year	Europe in 1983	USA in 1994	India in 2013
Currently licensed formulation	Enteric capsule	Liquid	Liquid
Route and dose of administration	Oral; 3-4 doses on every second day	Intramuscular; single dose	Intramuscular; single dose
Common side effects	Transient fever and gastrointestinal symptoms	Transient fever, erythema and local pain	Fever, pain and swelling
Recommended age-group	Individuals older than 6 y	Individuals aged 2 y and above	Individuals aged 6 mo and above upto 45 y.
Cumulative efficacy at 3 y [28]	51% (95% CI: 36-62%)	55% (95% CI: 30-70%)	-
Herd effect	30%	44% (95% CI: 2-69%)	-
Time taken to demonstrate protective immunity	7 d from the last dose	7 d after vaccination	-
Correlate for protection	• Serum IgG anti-O seroconversion • Rise in IgA antibody titres: 7 d after the last dose	Serum IgG anti-Vi antibody level of at least 1 µg/mL	Serum IgG anti-Vi antibody level of 1000 Elisa Units and above [29]
Need of revaccination	• Highly endemic countries: every 3 -7 y • Travellers (from non-endemic to endemic area): every 1-7 y (as per the existing national policies)	Every 3 y	No sufficient evidence*
Precautions	• Not to be co-administered for individuals who are on antibiotics / anti- malarial therapy • Known hypersensitivity to the components of vaccine	Known hypersensitivity to the components of vaccine	Known hypersensitivity to the components of vaccine

**Not presently recommended.*

population), moderate (50-200 cases/100,000 population), and high (>200 cases/100,000 population). Considering the annual incidence of typhoid, CE of Vi-TT in LMICs was analyzed using two strategies: (*i*) RI in infants through EPI, and (*ii*) RI through EPI + one time catch-up campaign in school-aged children (5-14 years). Results showed that RI of infants through EPI (strategy 1) would be 'cost effective', if annual incidence is >50/100,000 population, and the second strategy of RI + one time catch up would be 'cost effective', if annual incidence of typhoid is >130/100,000 population [20]. These analyses thereby show that use of typhoid vaccines is indeed 'cost effective', provided vaccine delivery is strategically planned as per the geographic heterogeneity of disease distribution across different age groups.

BEYOND TYPHOID FEVER CONTROL?

In South-East Asia, considering the significant burden of typhoid, clinicians perceive undifferentiated acute febrile illness as suspected typhoid fever, and treat it empirically with antibiotics. It is estimated that, for every case of blood culture confirmed typhoid fever, three to 25 febrile patients without typhoid illness receive antibiotics, which could have been potentially avoided. This over-treatment with antibiotics can result in antimicrobial resistance (AMR) towards commonly used antibiotics, thereby compelling the use of higher antibiotics. Routine CEA involving vaccines, while considering the costs of illness from both societal as well as health care payer's perspective, leaves out potential benefits of avoiding overtreatment with antibiotics. Thus, using TCV to reduce typhoid burden can eventually bring down the prescription rates of antibiotics attributed for treating suspected typhoid fever cases [21], and potentially prevent emergence of antibiotic resistance.

RECENT RECOMMENDATIONS

In 2018, SAGE recommended a single dose of Vi-TT for children aged less than 2 years, either, along with initial dose of measles vaccine at 9-12 months of age or with the second dose of measles vaccine at 15-18 months. For children aged more than 2 years, SAGE continued its prior recommendation of either ViPS or Ty21a according to the country's immunization policy: although, Vi-TT likely offers longer duration of protection when compared to ViPS or Ty21a and hence, can be potentially considered for use in older children as well [13]. Further, in 2018, the Indian Academy of Pediatrics recommended a single dose of TCV for children from 6 months onwards, without any subsequent booster dose [22].

Following WHO's prequalification of Vi-TT in 2018, the GAVI Alliance agreed to provide a support of US$ 85 million towards introduction of TCV in 2019 in developing countries [23]. Following this, the manufacturer of Vi-TT vaccine has stated its willingness to reduce the price of Vi-TT from US$ 26 (1800 INR) per dose to US$ 1.5 (100 INR) per dose for GAVI eligible countries [24]. This significant cost reduction of Vi-TT will be an important factor to be considered by policymakers in India.

What Comes Next?

Country-level data in the Indian context on burden of typhoid fever among children is likely to be available from an ongoing Surveillance for enteric fever in India (SEFI) by 2020 [25]. In addition, the Typhoid Vaccine Acceleration Consortium (TyVAC) has begun a trial to study the effectiveness of TCV among children in Bangladesh, Malawi and Nepal [26]. The Navi Mumbai municipality has begun a campaign of TCV immunization in two rounds in July 2018, and vaccine effectiveness will be evaluated by a consortium including the Indian Council of Medical Research [27]. Thus, data on typhoid disease burden and effectiveness of TCVs are awaited, which will serve as strong evidence to aid the government to consider typhoid vaccine.

CONCLUSION

Typhoid burden is associated with considerable heterogeneity in distribution, and hence the decision on vaccination and its strategies for delivery should be based on local epidemiology. Vi-TT, with its unique advantage of being amenable for use in children, aged less than two years through routine immunization can decrease disease burden. With antimicrobial resistance looming large in Asia, this is a crucial time for India to consider introduction of typhoid vaccine into the national immunization programme at the earliest.

Contributors: JJ, MS: conceptualized the article; MS, KNS: reviewed the literature, drafted and revised the manuscript under the overall support and supervision of JJ and GK. All authors approved the manuscript for publication.
Funding: None; *Competing interest*: None stated.

REFERENCES

1. World Health Organization. Progress on drinking water, sanitation and hygiene: 2017 update and SDG baselines. Available from: *http://www.who.int/water_sanitation_health/ publications/jmp-2017/en/*. Accessed June 29, 2018.
2. Mogasale V, Maskery B, Ochiai RL, Lee JS, Mogasale VV, Ramani E, *et al*. Burden of typhoid fever in low-income and middle-income countries: A systematic, literature-based update with risk-factor adjustment. Lancet Glob Health. 2014;2:e570-80.
3. Antillón M, Warren JL, Crawford FW, Weinberger DM,

Kurum E, Pak GD, *et al*. The burden of typhoid fever in low- and middle-income countries: A meta-regression approach. PLoS Negl Trop Dis. 2017;11:e0005376.
4. John J, Van Aart CJ, Grassly NC. The burden of typhoid and paratyphoid in India: systematic review and meta-analysis. PLoS Negl Trop Dis. 2016;10:e0004616.
5. Ochiai RL. A study of typhoid fever in five Asian countries: disease burden and implications for controls. Bull World Health Organ. 2008;86:260-8.
6. Mogasale V, Desai SN, Mogasale VV, Park JK, Ochiai RL, Wierzba TF. Case fatality rate and length of hospital stay among patients with typhoid intestinal perforation in developing countries: A systematic literature review. PLoS One. 2014;9:e93784.
7. Wong VK, Baker S, Pickard DJ, Parkhill J, Page AJ, Feasey NA, *et al*. Phylogeographical analysis of the dominant multidrug-resistant H58 clade of Salmonella Typhi identifies inter- and intracontinental transmission events. Nat Genet. 2015;47:632-9.
8. 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:e00105-18.
9. Steele AD, Hay Burgess DC, Diaz Z, Carey ME, Zaidi AKM. Challenges and opportunities for typhoid fever control: A call for coordinated action. Clin Infect Dis. 2016;62:S4-8.
10. Typhoid vaccines: WHO position paper – August 2000. Wkly Epidemiol Recd. 2000;75:257-64.
11. Typhoid vaccines: WHO position paper – February 2008. Wkly Epidemiol Recd. 2008;83:49-59.
12. World Health Organisation. Background Paper to SAGE on Typhoid Vaccine Policy Recommendations, 2017. Available from *http://www.who.int/immunization/ sage/ meetings/2017/october/1_Typhoid_SAGE_background_ paper _Final_v3B.pdf*. Accessed August 12, 2018.
13. Typhoid vaccines: WHO position paper–March 2018. Wkly Epidemiol Recd. 2018; 93:153-72.
14. World Health Organization. The immunological basis for immunization series: module 20: salmonella enterica serovar Typhi (typhoid) vaccines. 2011. Available from: *http://www.who.int/iris/handle/10665/44752*. Accessed August 12, 2018.
15. Jin C, Gibani MM, Moore M, Juel HB, Jones E, Meiring J, *et al*. Efficacy and immunogenicity of a Vi-tetanus toxoid conjugate vaccine in the prevention of typhoid fever using a controlled human infection model of Salmonella Typhi: a randomised controlled, phase 2b trial. Lancet. 2017;390:2472-80.
16. Mitra M, Shah N, Ghosh A, Chatterjee S, Kaur I, Bhattacharya N, *et al*. Efficacy and safety of Vi-tetanus toxoid conjugated typhoid vaccine (PedaTyph™) in Indian children: School based cluster randomized study. Hum Vaccines Immunother. 2016;12:939-45.
17. Mohan VK, Varanasi V, Singh A, Pasetti MF, Levine MM, Venkatesan R, *et al*. Safety and immunogenicity of a Vi polysaccharide–tetanus toxoid conjugate vaccine (Typbar-TCV) in healthy infants, children, and adults in typhoid endemic areas: A multicenter, 2-cohort, open-label, double-blind, randomized controlled phase 3 study. Clin Infect Dis. 2015;61:393-402.
18. Voysey M, Pollard AJ. Sero-efficacy of Vi-polysaccharide tetanus-toxoid typhoid conjugate vaccine (Typbar-TCV). Clin Infect Dis. 2018;67:18-24.
19. Antillón M, Bilcke J, Paltiel AD, Pitzer VE. Cost-effectiveness analysis of typhoid conjugate vaccines in five endemic low- and middle-income settings. Vaccine. 2017;35:3506-14.
20. Lo NC, Gupta R, Stanaway JD, Garrett DO, Bogoch II, Luby SP, *et al*. Comparison of strategies and incidence thresholds for vi conjugate vaccines against typhoid fever: A cost-effectiveness modeling study. J Infect Dis. 2018;218:S232-42.
21. Andrews JR, Baker S, Marks F, Alsan M, Garrett D, Gellin BG, *et al*. Typhoid conjugate vaccines: A new tool in the fight against antimicrobial resistance. Lancet Infect Dis. 2019;19:e26-30.
22. Balasubramanian S, Shah A, Pemde HK, Chatterjee P, Shivananda S, Guduru VK, *et al*. Indian Academy of Pediatrics (IAP) Advisory Committee on Vaccines And Immunization Practices (ACVIP) Recommended Immunization Schedule (2018-19) and Update on Immunization for Children Aged 0 Through 18 Years. Indian Pediatr. 2018; 55:1066-74.
23. GAVI 2018. New Typhoid Vaccine to Receive GAVI Support. Available from: *https://www.gavi.org/library/ news/statements/2018/new-typhoid-vaccine-to-receive-gavi-support/*. Accessed August 12, 2018.
24. World Health Organizationý. Typbar TCV® from Bharat Biotech, world's first typhoid conjugate vaccine prequalified by WHO. 2018. Available from: *http:// www.who.int/ medicines/news/2017/Bharat-Biotech-TypbarTCV-WHO-PQ-Press-Release-Global-Final.pdf*. Accessed August 12, 2018.
25. NSSEFI Collaborators, John J, Bavdekar A, Rongsen-Chandola T, Dutta S, Kang G. Estimating the incidence of enteric fever in children in India: A multi-site, active fever surveillance of pediatric cohorts. BMC Public Health. 2018;18:594.
26. Meiring JE, Gibani M, Basnyat B, Bentsi-Enchill AD, Clemens J, Darton TC, *et al*. The Typhoid Vaccine Acceleration Consortium (TyVAC): Vaccine effectiveness study designs: Accelerating the introduction of typhoid conjugate vaccines and reducing the global burden of enteric fever. Report from a meeting held on 26–27 October 2016, Oxford, UK. Vaccine. 2017;35:5081-8.
27. Coalition against typhoid. Navi Mumbai Municipal Corporation launches the world's first public-sector typhoid conjugate vaccine campaign. 2018. Available from: http:// *www.coalitionagainsttyphoid.org/navi-mumbai-municipal-corporation-launches-the-worlds-first-public-sector-typhoid-conjugate-vaccine-campaign/*. Accessed December 22, 2018.
28. Milligan R, Paul M, Richardson M, Neuberger A. Vaccines for preventing typhoid fever. Cochrane Database Syst Rev. 2018;CD001261.

29. Klugman KP. Usefulness of the serial measurement of Vi antibodies. Clin Infect Dis. 2018;67:25-6.
30. Lin FYC, Ho VA, Khiem HB, Trach DD, Bay PV, Thanh TC, *et al*. The efficacy of a Salmonella typhi Vi conjugate vaccine in two-to-five-year-old children. N Engl J Med. 2001;344:1263-9.
31. Lanh MN, Van Bay P, Ho VA, Thanh TC, Lin FYC, Bryla DA, *et al*. Persistent efficacy of Vi conjugate vaccine against typhoid fever in young children. N Engl J Med. 2003;349:1390-1.

WEB TABLE I TRIALS EVALUATING THE IMMUNOGENICITY AND PROTECTIVE EFFICACY OF TYPHOID CONJUGATE VACCINES

Type of typhoid conjugate vaccine	*Author (y) [Ref.]*	*Country of study*	*Year of study*	*Age of the subjects*	*Sample size*		*Follow-up duration*	*Seroconversion rate/protective efficacy at the end of follow-up period (%)*
					Vaccine	*Placebo*		
Seroconversion rate								
Vi-CRM197	Bhutta, *et al.* (2014)[30]	India, Pakistan, Philippines	2011-12	Infants: 6 to 8 weeks Older infants: 9 to 12 mo Children: 24 to 59 mo Adults: 18 to 45 y	40 (in each age group)	40 (in each age group)	6 mo	Infants: 25-70* Older Infants: 70-89* Children: 90-95* Adults: 85-95*
Vi-TT	Mohan, *et al.* (2015)[17]	India	2011-12	Open label cohort: 6 mo to 23 mo	Open label cohort (no controls) 327		2 y 5 y	65.1 (56.1-73.4) 84.1 (76.6-90)[#]
	WHO (2017)[12]			Double blinded, RCT 2 to 45 y	Double blinded, RCT 340	 314	2 y 5 y	79.8 (69.6-87.8) 92.9 (85.1-97.3)[#]
	Mitra, *et al.* (2015)[16]	India	2012	6 mo to 12 y	905	860	1 y	6 months to 2 years: 100 2 years to 5 years: 88.9 5 years to 12 years: 81.6
	Jin, *et al.* (2017)[15]	UK	2015-16	18 to 60 y	41	34	1 mo	100
Protective efficacy								
Vi-rEPA	Lin, *et al.* (2001) [30]	Vietnam	1998 -2002	2 to 5 y	5991	6017	27 mo	91.5 (77.1-96.6)
	Lanh, *et al.* (2003)[31]						46 mo	89 (76-96.9)
Vi-TT	Mitra, *et al.* (2016) [16]	India	2012	6 mo to 12 y	905	860	1 y	100 (97.6-100)
	Jin, *et al.* (2017)[15]	UK	2015-16	18 to 60 y	41	34	1 mo	54.6 (26.7-71.8)

**Seroconversion rates are presented as range; [#]5 year seroconversion rates observed after a booster dose at 720 days; RCT: randomized controlled trial.*