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## Enhanced surveillance for adverse events following immunization during the 2019 typhoid conjugate vaccine campaign in Harare, Zimbabwe

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### Abstract

**Background:** During February 25–March 4, 2019, Zimbabwe’s Ministry of Health and Child Care conducted an emergency campaign using 342,000 doses of typhoid conjugate vaccine (TCV) targeting individuals 6 months–15 years of age in eight high-risk suburbs of Harare and up to 45 years of age in one suburb of Harare. The campaign represented the first use of TCV in Africa outside of clinical trials.

**Methods:** Three methods were used to capture adverse events during the campaign and for 42 days following the last dose administered: (1) active surveillance in two Harare hospitals, (2) national passive surveillance, and (3) a post-campaign coverage survey.

**Results:** Thirty-nine adverse events were identified during active surveillance, including 19 seizure cases (16 were febrile), 16 hypersensitivity cases, 1 thrombocytopenia case, 1 anaphylaxis case, and two cases with two conditions. Only 21 (54%) of 39 patients were hospitalized and 38 recovered without sequelae. Attack rates per 100,000 TCV doses administered were highest for

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#### Declaration of Competing Interest

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seizures (6.27) and hypersensitivity (5.02). Only 6 adverse events were reported through passive surveillance by facilities other than the two active surveillance hospitals. A total of 177 (10%) of 1,817 vaccinees surveyed reported experiencing an adverse event during the post-campaign coverage survey, of which 25 (14%) sought care.

**Conclusions:** In line with previous evaluations of TCV, enhanced adverse event monitoring during an emergency campaign supports the safety of TCV. The majority of reported events were minor or resulted in recovery without long-term sequelae. Attack rates for seizures and hypersensitivity were low compared with previous active surveillance studies conducted in Kenya and Burkina Faso. Strengthening adverse event monitoring in Zimbabwe and establishing background rates of conditions of interest in the general population may improve future safety monitoring during new vaccine introductions.

### Keywords

Typhoid vaccine; Typhoid outbreak; Adverse events following immunization; Vaccine safety; Vaccine campaign; Active surveillance

## 1. Background

Typhoid fever is endemic in Harare, Zimbabwe, with cases recorded year-round and annual seasonal outbreaks during October–March [1,2]. In 2017–2018, there was a dramatic increase in the number of reported typhoid cases compared with two previous outbreaks in 2015–2016 and 2016–2017. During October 2017–June 2018, over 4,330 cases of typhoid fever were reported, with an overall attack rate of 2.73 cases per 1,000 residents. In addition, drug-resistant *Salmonella* Typhi is emerging in Zimbabwe [3].

In January 2018, the World Health Organization (WHO) prequalified a new single-dose injectable vaccine for typhoid fever, the Tybar-TCV typhoid conjugate vaccine (TCV) [4]. Data from clinical trials indicate that TCV is well-tolerated with no serious safety concerns identified [5,6]. TCV safety was found to be comparable to earlier generations of oral and injectable typhoid vaccines [7]. TCV was also used in the private sector in India for more than five years, with the most commonly reported adverse events being fever, pain, and injection site swelling in 1–10% of vaccinees [7].

In July 2018, the Zimbabwean Ministry of Health and Child Care (MOHCC) requested 342,000 TCV doses for an emergency vaccination campaign in nine high-risk suburbs in Harare [8]. This campaign represented the first use of TCV in Africa outside of clinical trials and the second use for typhoid outbreak control globally, after use in Pakistan [9]. The campaign occurred February 25–March 4, 2019 and targeted individuals 6 months–15 years of age, and up to 45 years of age in one suburb (Mbare) with a high burden of adult typhoid cases. An Oral Cholera Vaccine (OCV) campaign was conducted prior to (November 2018) and following (March 2019) the TCV campaign.

The MOHCC requested an evaluation of the adverse events following immunization (AEFI) with TCV. WHO defines AEFI as any untoward medical occurrences that follow immunization and which do not necessarily have a causal relationship with the usage of the

vaccine [10]. The MOHCC and the Medicine and Control Authority of Zimbabwe (MCAZ) operate a passive national surveillance system to capture AEFI [11]. From 1997 to 2017, the Zimbabwe overall annual reporting rate, across all vaccines, was 0.58 per 100,000 vaccine doses and the AEFI reporting ratio ranged between 0 and 30.2 AEFI reports per 100,000 surviving infants (i.e., those surviving their first year of life) [12]. An evaluation of the AEFI surveillance system in 2017 found underreporting of AEFI in Harare [13]. Therefore, active surveillance was organized to document adverse events following TCV administration during the campaign, and to complement data collected through the passive national AEFI surveillance system.

## 2. Methods

We used three methods to capture adverse events during the TCV campaign and for 42 days following the last dose of TCV administered: (1) active surveillance for adverse events of special interest (AESI) in two hospitals in Harare, (2) passive national surveillance for AEFI, and (3) a household post-campaign coverage survey. The surveillance window was February 25–April 15, 2019.

### 2.1. Active surveillance for AESI in two hospitals in Harare

AESI Surveillance was conducted among patients 6 months–4 5 years of age at two public hospitals in Harare [14] identified as the referral hospitals serving the campaign target areas. Ten AESI conditions were pre-selected for surveillance based on previous experience and a similar evaluation conducted in India [15]: anaphylaxis, non-anaphylaxis hypersensitivity, Guillain-Barre syndrome (GBS), aseptic meningitis, encephalitis, myelitis, acute disseminated encephalomyelitis (ADEM), seizures (febrile and afebrile), thrombocytopenia, and unexpected or sudden death in a child less than two years of age. Trained nurses in the outpatient, accident and emergency, and pediatric and adult inpatient wards at each hospital identified patients with one or more AESI, whose onset of symptoms occurred during the surveillance window. For all AESI except non-anaphylaxis hypersensitivity, nurses used Brighton Collaboration case definitions [16–23] to determine the level of diagnostic certainty of the identified AESI. If a patient had more than one AESI, Brighton levels were determined for each condition separately. For those patients with an identified condition, the nurses assessed if the patient received TCV during the campaign or another vaccine during the 42 days before the onset of symptoms. The MOHCC provided joint OCV-TCV campaign cards which were used to verify TCV vaccination status. If the OCV-TCV card was not available or other vaccines were reported, verbal report of vaccination was recorded.

Using standardized forms, nurses conducted chart abstraction for patient age, gender, vaccines received, date of vaccination(s), date of symptom onset, discharge diagnosis, and relevant medical history and clinical course information (e.g., findings of laboratory and imaging studies). Completed AESI forms underwent secondary review by a physician at the U.S. Centers for Disease Control and Prevention (CDC) to concur with Brighton determinations and inclusion in the analysis. Anaphylaxis cases were included if the reported onset of symptoms was within one day or 24 h of vaccination, consistent with

previous research [24]. Given the lack of Brighton Collaboration criteria for non-anaphylaxis hypersensitivity, completed Anaphylaxis forms were reviewed by the CDC physician to ensure that the signs and symptoms reported could be consistent with hypersensitivity based upon the clinical judgement of the primary care team and were not consistent with an alternative diagnosis. For example, the largest group of excluded hypersensitivity cases were diagnosed with “acute gastroenteritis” by hospital clinicians; if the reported signs and symptoms were consistent with “acute gastroenteritis” the case was reclassified as “acute gastroenteritis” and not included in the analysis of hypersensitivity. The three most common excluded conditions among reported hypersensitivity cases were acute gastroenteritis, upper respiratory tract infection, and pneumonia.

All nurse-completed paper-based AESI forms were submitted electronically using tablets loaded with SurveyCTO mobile forms [25]. Data were reviewed daily to identify missing or inconsistent data, and these were relayed to the hospital teams for follow up.

Vaccinated cases (TCV or other vaccine reported in the 42 days prior to symptom onset) were also reported through the passive national AEFI surveillance system for investigation and causality assessment by the national AEFI committee. Reports from the Pharmacovigilance and Clinical Trials Committee (National AEFI Committee) were reviewed to capture causality assessment findings for the cases reported by the two surveillance hospitals. This committee is responsible for review of available data to determine if there is sufficient evidence to determine that vaccine caused the reported event.

## 2.2. Passive national AEFI surveillance

The passive national AEFI surveillance system in Zimbabwe relies on healthcare worker identification, management, reporting, and investigation of AEFI. For minor AEFI, healthcare workers complete a standardized national AEFI reporting form with aggregation of AEFI reports at provincial and national levels. For serious AEFI, reporting is required within 24 h of identification, then district or provincial investigation teams conduct an investigation and complete a standardized national AEFI case investigation form. The Pharmacovigilance and Clinical Trials (PVCT) Committee—the National AEFI Committee comprised of pediatrician, physicians, epidemiologists, academics, pharmacists, and technical experts—conducts causality assessment and determines whether the event was related to the vaccine using the WHO AEFI Causality Assessment Manual 2019 and electronic algorithm tool 2019 [26].

To strengthen passive surveillance during the TCV campaign, training was conducted in November 2018 for over 150 vaccinating and supervising healthcare workers in Harare to ensure all AEFI were detected, investigated, and reported during and following the campaign per national AEFI guidelines [8]. WHO conducted a refresher training for the National AEFI Committee in January 2019 to strengthen causality assessment [8]; the committee members had been previously trained by WHO in 2015 and 2017.

Reported cases of AEFI following TCV administration were extracted from the national AEFI database maintained by the MOHCC. Information available in the database included

age, type of AEFI, vaccine received, and results of causality assessment for those reviewed by the National AEFI Committee.

### 2.3. Coverage survey AEFI module

A household survey to determine vaccination coverage of the TCV campaign was conducted in April 2019 and included a subset of open-ended questions about side effects following TCV receipt. The coverage survey methods will be described separately. Questions specific to AEFI included whether TCV vaccinees experienced an AEFI, the type of AEFI experienced, and if the vaccinee sought care for the AEFI.

The coverage survey was not powered to estimate the rate of AEFIs following the TCV administration but was conducted to provide additional descriptive information on AEFIs experienced among vaccinees that may not have been reported through the passive or active surveillance systems.

**2.4. Analysis**—Reports from the active and passive surveillance systems were compared to account for duplicate reporting. The number, frequency, and type of reported adverse events were described. Brighton Collaboration determinations, seriousness, and risk windows were described for all TCV-vaccinated AESI cases. Reporting rates per 100,000 doses were calculated for AESI conditions using the number of TCV doses administered as the denominator (number of AESI / total doses administered\*100,000).

Both hospitals utilize the Inpatient Morbidity and Mortality Information System (IMMIS) which codes hospital admissions using standardized ICD10 codes [27]. In July 2019, IMMIS databases were queried using ICD10 codes corresponding to the AESI conditions identified during the active surveillance period (February 25–April 15, 2019) in patients aged 1–45 years (age not available in months for children < 1 year), including seizure (ICD10 codes: R56.0 and R56.8), GBS (G61), thrombocytopenia (D69.9 and D69.5), and non-anaphylaxis hypersensitivity (T78.4 and T88.7), to assess the number of cases missed during active surveillance. Anaphylaxis cases corresponding to the ICD10 codes T78.4 and Y57.9 were considered missed if admitted during February 25–March 6, 2019 as anaphylaxis cases were of interest if onset was within one day of TCV administration. Aseptic meningitis cases were not reviewed in IMMIS, as CSF results were not available in the database to ascertain if cases were aseptic. Modified reporting rates were calculated inclusive of the additional cases identified and assuming all missed cases were vaccinated (i.e., vaccination status not reported in IMMIS).

Data from the passive AEFI surveillance system and campaign coverage AEFI survey module were analyzed descriptively. All analyses were conducted in R [28].

### 2.5. Ethical considerations

This assessment received a non-research determination from the Medical Research Council of Zimbabwe and the U.S. Centers for Disease Control and Prevention because it represented a routine surveillance and public health program activity. No names or addresses were collected during hospital chart abstractions or review of passive surveillance cases, and the data were stored on a password-protected server.

### 3. Results

A total of 318,698 people were vaccinated with TCV in Harare during February 25–March 4, 2019. By age group, 82,768 doses were administered to children 6 months–4 years, 202,457 doses to children 5–15 years, and 33,473 doses to persons 16–45 years.

#### 3.1. Active surveillance

A total of 130 potential AESI cases were reported (Fig. 1). Among the 78 cases that met inclusion criteria, 39 (50%) reported vaccination with TCV, and 21 (54%) of these patients with AESI cases were hospitalized. Thirty-eight (97%) of 39 AESI patients recovered, and one AESI patient with non-anaphylaxis hypersensitivity was referred to another facility (final outcome unknown). Vaccination status was verified using OCV-TCV campaign cards for 14 (36%) of 39 TCV-vaccinated cases.

Of the 78 included cases, 42% of patients were female and the median age was 3 years (interquartile range: 2–10 years) (Table 1). The conditions reported among the 78 cases were seizure (45 cases), hypersensitivity (21), thrombocytopenia (4), anaphylaxis (2), aseptic meningitis and thrombocytopenia (2), GBS (2), aseptic meningitis (1), and seizure and thrombocytopenia (1). Among 41 conditions in 39 TCV-vaccinated AESI cases, 18 of the 25 (72%) Brighton determinations for the conditions excluding hypersensitivity were Level 1 or Level 2, indicating a high degree of certainty in the diagnosis (Table 2). Risk windows (time from vaccination to onset) varied by condition (Table 2).

Among the 20 TCV-vaccinated seizure cases, 16 (80%) were febrile seizures, with onsets from 0 to 40 days after vaccination (Fig. 2). Of the seizure cases, 8 (40%) had a documented seizure history in the clinical notes. All were pediatric (under 18 years of age) and 95% of cases were in children under 5 years of age. Six also reported receiving OCV during a March 2019 campaign. Eight seizure cases from these hospitals were referred to the National AEFI Committee for causality assessment determination; all 8 were classified as indeterminate causal association (B1, temporal relationship is consistent, but there is insufficient definitive evidence for vaccine causing the event).

Reporting rates per 100,000 TCV campaign doses administered were highest for seizures (6.27 overall; 5.02 for febrile and 1.25 for afebrile seizures), hypersensitivity (5.02), and thrombocytopenia (0.94) (Table 3). Review for missed cases in IMMIS identified 30 additional seizure cases, and 1 additional hypersensitivity case. Conservatively assuming that all additional patients were vaccinated with TCV, the modified reporting rates were 15.68 and 5.33 for seizures and hypersensitivity, respectively.

#### 3.2. Passive surveillance

A total of 51 minor AEFI reports indicating TCV vaccination were reported to the passive AEFI surveillance system during February 25–April 15, 2019, of which 45 were reported by the two tertiary referral hospitals participating in active surveillance for AESI. Among the remaining 6 AEFI reports, patients were aged 7–13 years. Most patients (5, 83%) reported more than one symptom. Symptoms reported included headache (3 cases), rash (2 cases),

and abdominal pain, dizziness, fever, malaise, sore throat, and vomiting (1 case, each). All reported cases were classified as minor AEFI and all these patients recovered.

### 3.3. Coverage survey

A total of 1,817 respondents reported being vaccinated. Of these, 177 (10%) reported one or more AEFI, with 34 reports (2%) from respondents aged 6 months–4 years, 132 (7%) from respondents aged 5–15 years, and 11 (1%) from respondents aged 16–45 years (Table 4). The most commonly reported AEFIs (number of cases, %) included pain at injection site (51, 3%), fever (43, 2%), nausea and vomiting (23, 1%), weakness and fatigue (21, 1%), and headache (16, 1%). Twenty-five (14%) sought care for their AEFI.

## 4. Discussion

Following the first outbreak response vaccination campaign with TCV in Africa and the second campaign globally for outbreak control, monitoring for adverse events following TCV vaccination suggest TCV is safe, consistent with prior experience elsewhere [5,7,15]. All AEFI documented during passive surveillance and the majority reported during the coverage survey did not result in seeking healthcare. Though just over half of AESI cases were hospitalized (i.e., classified as serious AEFI), all patients with known outcomes recovered without sequelae (one hypersensitivity non-anaphylaxis case was referred to another facility and the outcome is unknown). Active surveillance for AESI was rapidly organized and demonstrated that hospital surveillance nurses can be utilized to detect and report adverse events during emergency campaigns.

In this evaluation, data collected through active surveillance and a campaign coverage survey complemented the passive national AEFI surveillance system. Only 6 passive AEFI reports were received from healthcare facilities other than the two active surveillance hospitals. While few vaccinees (10%) reported experiencing an AEFI during the coverage survey, only 14% sought care at a facility.

Thirty-nine AESI were identified through active surveillance, and seizures were the most commonly reported AESI, with an observed reporting rate of 6.27 seizures per 100,000 TCV doses administered and a modified rate of 15.68. Baseline rates of adverse events among the general population in LMICs are poorly understood [29]. While difficult to directly compare, experience from other vaccination campaigns in the African region demonstrated higher rates of seizures following immunization than what we observed in our evaluation. One study of the Meningitis A vaccination campaign in Burkina Faso reported a seizure rate of 29.76 per 100,000 [30]. In a study of children aged 0–13 years in Kenya the hospital incident admission rate for seizures was 466 per 100,000 population per year [31].

We observed a number of hypersensitivity cases through active surveillance, which was not documented in a previous TCV evaluation in Navi Mumbai, India [15]. However, standardizing the identification and classification of hypersensitivity non-anaphylactic reactions was challenging because of the lack of Brighton Collaboration criteria for hypersensitivity. In the study of a Meningitis A vaccination campaign in Burkina Faso, active surveillance found hypersensitivity reactions at much higher rates per 100,000 doses

than we observed (16.74 (urticaria) and 13.02 (bronchospasm) compared with 5.02 for hypersensitivity reactions in the present evaluation) [30]. Future attempts to document hypersensitivity following vaccination should consider clearer criteria for the diagnosis of hypersensitivity to reduce the possibility of misclassification. In this evaluation, after careful review of the signs, symptoms, final diagnoses, and other available clinical information, many hypersensitivity cases were re-classified as acute gastroenteritis, upper respiratory tract infection, and pneumonia.

Active surveillance for adverse events may be a valuable tool for monitoring safety during new vaccine introductions [32]. Despite training on AEFI surveillance for healthcare workers before the TCV campaign [8], the passive surveillance system received only a small number of reports in addition to those identified through active surveillance at two hospitals. Despite global recommendations, AEFI surveillance systems in LMICs struggle to meet minimum global reporting requirements [33], and a recent study identified barriers to passive AEFI surveillance, including healthcare worker fear of punishment for causing an AEFI [34]. However, active surveillance may put additional burdens on safety systems with already limited resources. Increased AEFI reporting in Zimbabwe has been observed since 1997 and may peak during immunization campaigns [12]; thus, the increased AEFI reporting of the TCV 2019 campaign and active surveillance generated more cases than was typical for a six-week period. As a result, AEFI case investigations in Harare were delayed by the added active surveillance cases, resulting in delays in causality assessment. Thus, a key lesson learned is to increase support for AEFI investigations by public health authorities when implementing active surveillance to accommodate for the increased number of cases requiring investigation.

#### 4.1. Limitations

There are a number of limitations of this evaluation. First, surveillance in pediatric wards was likely better than the surveillance in adult wards, as the pediatric staff were experienced with active surveillance from previous projects [35]. Adults were only vaccinated in one of nine suburbs in Harare and unlike children, who utilize health services accompanied by their parents with child health record books, adults are vaccinated less frequently and do not usually carry documentation of vaccinations, further limiting the ability to identify AEFI in adult populations. It is also possible that AEFI cases were missed by surveillance nurses, although in this evaluation hospital-based IMMIS databases were reviewed to identify additional cases and modify reporting rates; however, IMMIS databases do not include age in months, so only additional cases in patients aged 1–45 years were identified and we do not know vaccination status for any of these additional cases. Furthermore, it is possible that vaccine recipients sought care for AESI conditions at other healthcare centers in Harare or did not seek medical care for their adverse event. To account for possible underreporting, active surveillance was complemented by data from the passive national AEFI surveillance system and data collected during the campaign coverage survey. However, underreporting is still likely given challenges identified with the passive system.

Finally, causality assessment results from the National AEFI Committee were shared for 8 of the seizure cases, all of which were classified as indeterminate causal association with

vaccination. Challenges were identified in the process for causality assessment, including the timeliness of reporting serious cases from the hospitals through the passive surveillance system for investigation and referral to the National AEFI Committee for causality assessment, and the hospital-based investigation team limited collection of personal identifying information that would have facilitated better matching between the causality assessment findings in the passive surveillance system records which was maintained separately from the active hospital-based surveillance data, which limited our ability to share causality results for all identified cases. However, among those who received TCV, most reported AEFI were minor and among reported serious cases all but one recovered (one referred; outcome unknown).

## 4.2. Conclusion

In line with previous evaluations of TCV [5–7,15], enhanced surveillance for adverse events in Zimbabwe supports the safety profile of TCV vaccine. Future studies should evaluate the occurrence of hypersensitivity reactions using standardized definitions and document the safety of TCV in older populations (>15 years). In Zimbabwe, effort is needed to improve the passive national AEFI surveillance system, including the timeliness of causality assessment when additional cases are generated during campaigns, and to address the challenges identified in this evaluation and earlier work [13]. Finally, background rates for AEFI conditions in LMICs are incompletely known, making it difficult to frame our results within “expected” rates of AEFI. More work to establish background rates in LMICs is greatly needed, especially since conditions such as seizure, are likely much higher in LMIC settings due to a higher burden of febrile illnesses [29].

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## References

- [1]. Polonsky JA, Martinez-Pino I, Nackers F, Chonzi P, Manangazira P, Van Herp M, et al. Descriptive epidemiology of typhoid fever during an epidemic in Harare, Zimbabwe, 2012. *PLoS ONE* 2014;9(12). e114702. [PubMed: 25486292]
- [2]. Davis WW, Chonzi P, Masunda KP, Shields LM, Mukeredzi I, Manangazira P, et al. Notes from the Field: Typhoid Fever Outbreak - Harare, Zimbabwe, October 2016-March 2017. *MMWR Morb Mortal Wkly Rep* 2018;67 (11):342–3. [PubMed: 29565843]
- [3]. Mashe T, Gudza-Mugabe M, Tarupiwa A, Munemo E, Mtapuri-Zinyowera S, Smouse SL, et al. Laboratory characterisation of *Salmonella enterica* serotype Typhi isolates from Zimbabwe, 2009–2017. *BMC Infect Dis* 2019;19(1):487. [PubMed: 31151421]

- [4]. World Health Organization. Typhoid vaccine prequalified. Available at: <http://www.who.int/medicines/news/2017/WHOprequalifies-breakthrough-typhoid-vaccine/en/>. Accessed October 10, 2018.
- [5]. 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 (Tybbar-TCV) in healthy infants, children, and adults in typhoid endemic areas: a multicenter, 2-cohort, open-label, double-blind, randomized controlled phase 3 study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2015;61(3):393–402. [PubMed: 25870324]
- [6]. 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 (London, England)* 2017;390 (10111):2472–80. [PubMed: 28965718]
- [7]. Global Advisory Committee on Vaccine Safety. 30 November - 1 December 2016. *Wkly Epidem Record* 2017;92(2):13–20.
- [8]. Poncin M, Marembo J, Sreenivasan N, Makwara I, Machekeyanga Z, Nyabyenda W, et al. Implementation of an Outbreak Response Vaccination Campaign with Typhoid Conjugate Vaccine—Harare, Zimbabwe, 2019. SSRN preprint 2022.
- [9]. Qamar FN, Yousafzai MT, Khaliq A, Karim S, Junejo A, Baig I, et al. Adverse events following immunization with typhoid conjugate vaccine in an outbreak setting in Hyderabad. *Pakistan Vaccine* 2020;38(19):3518–23. [PubMed: 32201138]
- [10]. Council for International Organizations of Medical Sciences. Definition and application of terms for vaccine pharmacovigilance. Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance. 2012.
- [11]. Ministry of Health and Child Care Z. Adverse Events Following Immunization (AEFI) Surveillance Guidelines. 3rd ed, 2016.
- [12]. Masuka JT, Khoza S. Adverse events following immunisation (AEFI) reports from the Zimbabwe expanded programme on immunisation (ZEPI): an analysis of spontaneous reports in Vigibase® 2019;19(1):1–11. from 1997 to 2017.
- [13]. Zvanaka S, Tsitsi J, Chonzi P, Shambira G, Gombe NT, Tshimanga M. Evaluation of the adverse events following immunizations surveillance system in Harare City, Zimbabwe, 2016: a descriptive cross sectional study. *The Pan African medical journal* 2017;28:308. [PubMed: 29721138]
- [14]. Chikadaya H, Madziyire MG, Munjanja SP. Incidence of maternal near miss in the public health sector of Harare, Zimbabwe: a prospective descriptive study. *BMC pregnancy childbirth* 2018;18(1):458. [PubMed: 30477449]
- [15]. Longley AT, Date K, Luby SP, Bhatnagar P, Bentsi-Enchill AD, Goyal V, et al. Evaluation of vaccine safety after the first public sector introduction of typhoid conjugate vaccine—Navi Mumbai, India, 2018. *Clin Infect Dis* 2021;73(4): e927–33. [PubMed: 33502453]
- [16]. Kohl KS, Bonhoeffer J, Braun MM, Chen RT, Duclos P, Heijbel H, et al. The Brighton Collaboration: Creating a Global Standard for Case Definitions (and Guidelines) for Adverse Events Following Immunization. In: Henriksen K, Battles JB, Marks ES, Lewin DI. *Advances in Patient Safety: From Research to Implementation (Volume 2: Concepts and Methodology)*. Rockville (MD): Agency for Healthcare Research and Quality (US), 2005.
- [17]. Ruggeberg JU, Gold MS, Bayas JM, Blum MD, Bonhoeffer J, Friedlander S, et al. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine* 2007;25(31):5675–84. [PubMed: 17448577]
- [18]. Wise RP, Bonhoeffer J, Beeler J, Donato H, Downie P. Thrombocytopenia: case definition and guidelines for collection, analysis, and presentation of immunization safety data. *Vaccine* 2007;25(31):5717–24. [PubMed: 17493712]
- [19]. Bonhoeffer J, Menkes J, Gold MS, de Souza-Brito G, Fisher MC, Halsey N, et al. Generalized convulsive seizure as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. *Vaccine* 2004;22(5–6):557–62. [PubMed: 14741144]

- [20]. Tapiainen T, Prevots R, Izurieta HS, Abramson J, Bilynsky R, Bonhoeffer J, et al. Aseptic meningitis: case definition and guidelines for collection, analysis and presentation of immunization safety data. *Vaccine* 2007;25(31):5793–802. [PubMed: 17574313]
- [21]. Sejvar JJ, Kohl KS, Gidudu J, Amato A, Bakshi N, Baxter R, et al. Guillain-Barre syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. *Vaccine* 2011;29(3):599–612. [PubMed: 20600491]
- [22]. Sejvar JJ, Kohl KS, Bilynsky R, Blumberg D, Cvetkovich T, Galama J, et al. Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM): case definitions and guidelines for collection, analysis, and presentation of immunization safety data. *Vaccine* 2007;25(31):5771–92. [PubMed: 17570566]
- [23]. Jorch G, Tapiainen T, Bonhoeffer J, Fischer TK, Heininger U, Hoet B, et al. Unexplained sudden death, including sudden infant death syndrome (SIDS), in the first and second years of life: case definition and guidelines for collection, analysis, and presentation of immunization safety data. *Vaccine* 2007;25(31):5707–16. [PubMed: 17408816]
- [24]. Su JR, Moro PL, Ng CS, Lewis PW, Said MA, Cano MV. Anaphylaxis after vaccination reported to the Vaccine Adverse Event Reporting System, 1990–2016. *J Allergy Clin Immunol* 2019;143(4):1465–73. [PubMed: 30654049]
- [25]. Dobility I SurveyCTO. Cambridge, Massachusetts.
- [26]. Causality assessment of an adverse event following immunization (AEFI): user manual for the revised WHO classification second edition, 2019 update. Geneva: World Health Organization, 2019.
- [27]. World Health Organization. ICD-10: International statistical classification of diseases and related health problems: Tenth revision. 2nd ed. World Health Organization; 2004.
- [28]. R Core Team. R. A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2018.
- [29]. Kariuki SM, Abubakar A, Stein A, Marsh K, Newton C. Prevalence, causes, and behavioral and emotional comorbidities of acute symptomatic seizures in Africa: A critical review. *Epilepsia open* 2017;2(1):8–19. [PubMed: 29750209]
- [30]. Ouandaogo CR, Yameogo TM, Diomande FV, Sawadogo C, Ouédraogo B, Ouédraogo-Traoré R, et al. Adverse events following immunization during mass vaccination campaigns at first introduction of a meningococcal A conjugate vaccine in Burkina Faso, 2010. *Vaccine* 2012;30(Suppl 2):B46–51. [PubMed: 22230584]
- [31]. Idro R, Gwer S, Kahindi M, Gatakaa H, Kazungu T, Ndiritu M, et al. The incidence, aetiology and outcome of acute seizures in children admitted to a rural Kenyan district hospital. *BMC Pediatrics* 2008;8(1):5. [PubMed: 18261215]
- [32]. CIOMS Guide to active vaccine safety surveillance: report of CIOMS Working Group on Vaccine Safety. Geneva, Switzerland: Council for International Organizations of Medical Sciences (CIOMS), 2017.
- [33]. Lei J, Balakrishnan MR, Gidudu JF, Zuber PLF. Use of a new global indicator for vaccine safety surveillance and trends in adverse events following immunization reporting 2000–2015. *Vaccine* 2018;36(12):1577–82. [PubMed: 29454518]
- [34]. Gidudu JF, Shaum AM, Dodoo AN, Bosomprah S, Bonsu G, Amponsa-Achiano K, et al. Barriers to adverse events following immunization (AEFI) reporting among healthcare workers in four regions of Ghana. *Vaccine* 2020 Jan 29;38(5):1009–14. [PubMed: 31787409]
- [35]. Tate JE, Mwenda JM, Armah G, Jani B, Omoro R, Ademe A, et al. Evaluation of Intussusception after Monovalent Rotavirus Vaccination in Africa. *New England J Medicine* 2018;378(16):1521–8.

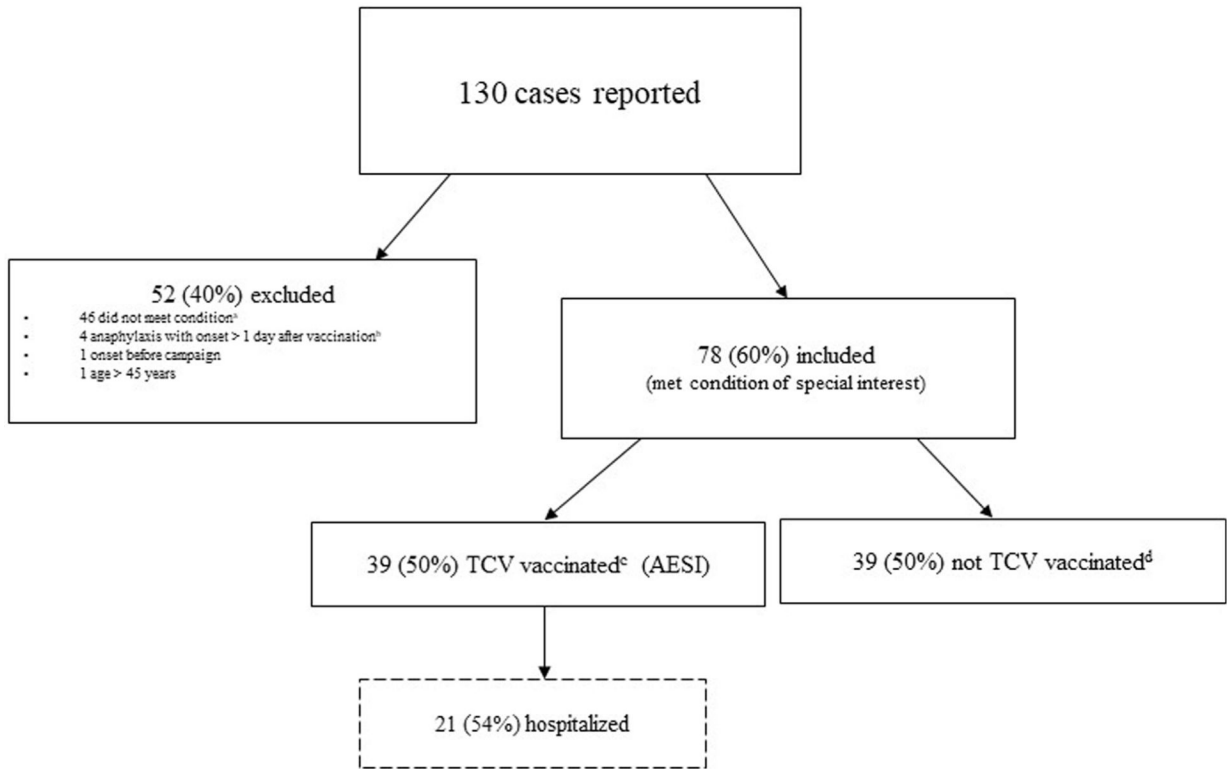
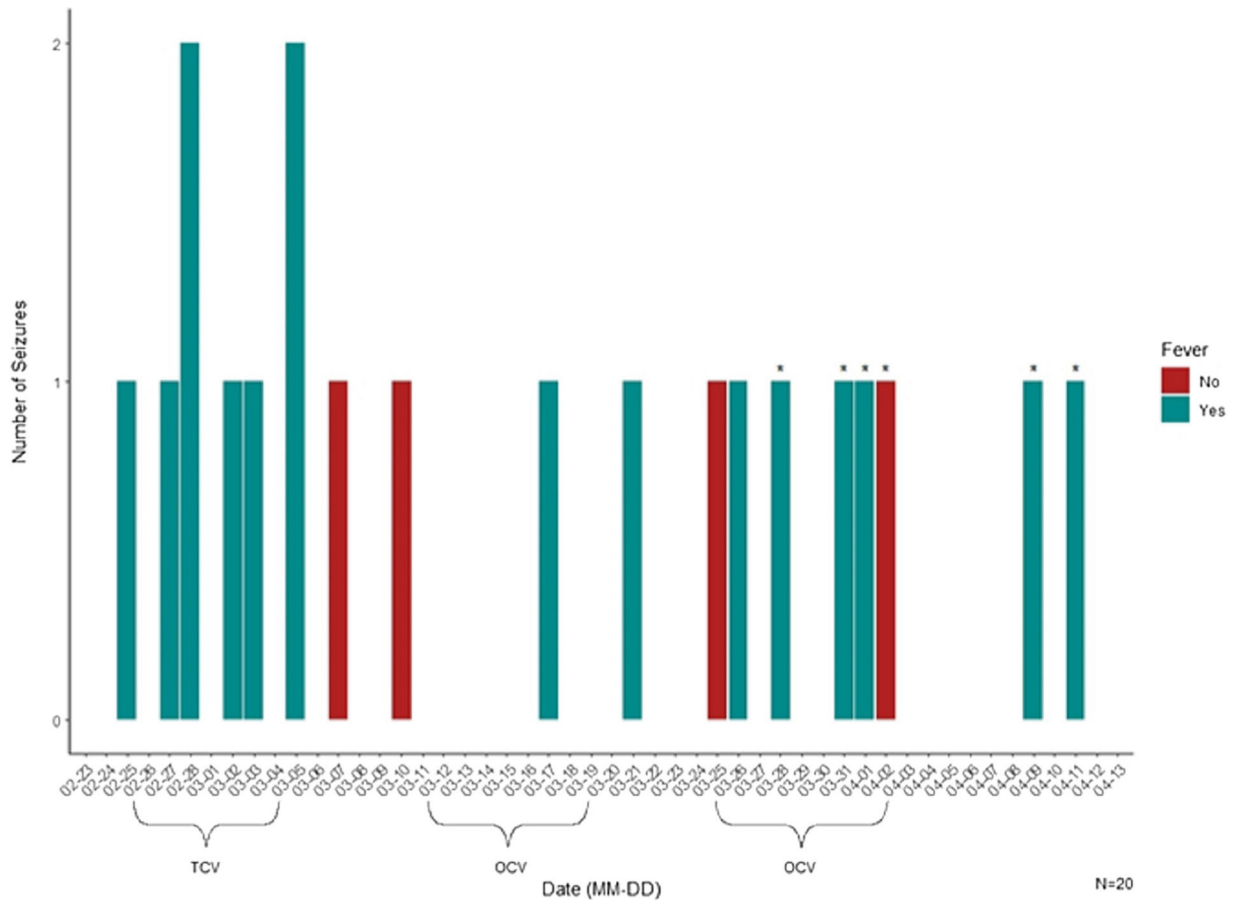
**Fig. 1.**

Diagram of 130 cases reported through active surveillance at two tertiary referral hospitals, following a vaccination campaign with typhoid conjugate vaccine (TCV), Harare, Zimbabwe, February 25–April 15, 2019. Abbreviations: AESI = Adverse event of special interest, TCV = Typhoid Conjugate Vaccine.

<sup>a</sup> Discharge diagnoses for excluded cases were gastroenteritis (14), upper respiratory tract infection (11), pneumonia (6), multiple diagnoses (4), bronchiolitis (3), meningitis (2), asthma (1), burn (1), hepatitis (1), Kawasaki's Disease (1), local injection site reaction (1), and pancreatitis (1). 44/46 received TCV vaccine. <sup>b</sup> Time from vaccination to onset for these 4 cases ranged from 7 to 35 days. <sup>c</sup> 7 TCV-vaccinated cases also received other vaccines in the previous 42 days: Oral Cholera Vaccine (OCV) (5 cases), Measles Rubella Vaccine (MR) (1), and multiple vaccines including OCV, MR, Oral Polio Vaccine and Diphtheria, Tetanus Pertussis Vaccine (1). <sup>d</sup> Two TCV-non-vaccinated cases received OCV.



**Fig. 2.** Onset dates of febrile and afebrile seizures among 20 cases following vaccination with typhoid conjugate vaccine (TCV)<sup>a</sup>, and in some cases oral cholera vaccine (OCV), Harare, Zimbabwe, February 25–April 15, 2019. Dates of the TCV and subsequent OCV campaigns are represented on the X-axis. Abbreviations: TCV = Typhoid Conjugate Vaccine, OCV = Oral Cholera Vaccine.  
 a One seizure case was also diagnosed with thrombocytopenia. \* Indicates the case also received OCV.

**Table 1**

Characteristics of 78 cases meeting one of 10 conditions of special interest reported through active surveillance in two tertiary referral hospitals Harare, Zimbabwe, February 25–April 15, 2019

	TCV Vaccination Status		Total (N = 78) n (%)
	Yes(N = 39) <sup>a</sup> n	No(N = 39) <sup>b</sup> n	
<b>Age, in years<sup>c</sup>, median (IQR)</b>	3 (2, 9)	4 (2, 23)	3 (2, 10)
6 months–4 years	22	22	44 (56)
5–15 years	15	6	21 (27)
16–45 years	2	11	13 (17)
<b>Gender</b>			
Female	15	18	33 (42)
Male	24	21	45 (58)
<b>Hospitalized</b>			
Yes	21	27	48 (61)
No	18	12	30 (39)
<b>Reported Conditions</b>			
Seizure	19	26	45 (57)
Hypersensitivity, non-anaphylaxis	16	5	21 (27)
Thrombocytopenia	1	3	4 (5)
GBS	0	2	2 (3)
Anaphylaxis	1	1	2 (3)
Aseptic meningitis and Thrombocytopenia	1	1	2 (3)
Aseptic meningitis	0	1	1 (1)
Seizure and Thrombocytopenia	1	0	1 (1)
Encephalitis	0	0	0 (0)
ADEM	0	0	0 (0)
Myelitis	0	0	0 (0)
Sudden death in child < 2 years	0	0	0 (0)

Abbreviations: TCV = Typhoid Conjugate Vaccine, GBS = Guillain-Barré Syndrome, ADEM = Acute Disseminated Encephalomyelitis.

<sup>a</sup>5 TCV-vaccinated cases also reported vaccination with Oral Cholera Vaccine (OCV); 1 reported Measles Rubella Vaccine (MR); 1 reported OCV, MR, Oral Polio Vaccine, and Diphtheria, Tetanus Pertussis Vaccine.

<sup>b</sup>2 TCV-non-vaccinated cases reported OCV.

<sup>c</sup>82,768 doses were administered those 6 months–4 years, 202,457 doses to those 5–15 years, and 33,473 doses those 16–45 years (Mbare only).

**Table 2**

Brighton Collaboration determination of level of diagnostic certainty and risk windows of the 41 adverse events of special interest (AESI)<sup>a</sup> reported among 39 cases vaccinated with typhoid conjugate vaccine (TCV), Harare, Zimbabwe, February 25–April 15, 2019.

Condition	Total No. of conditions	Brighton Collaboration Levels of Diagnostic Certainty				Risk window (days)
		Level 1 <sup>b</sup>	Level 2	Level 3	Category 4	
Seizure (total)	20	9	4	0	7	0–40
Febrile	16	8	4	0	5	0–40
Afebrile	4	1	0	0	2	9–33
Hypersensitivity <sup>c</sup>	16	-	-	-	-	0–8
Thrombocytopenia	3	3	0	0	0	1–11
Anaphylaxis <sup>d</sup>	1	0	1	0	0	1
Aseptic meningitis	1	1	0	0	0	11
<b>Total</b>	<b>41</b>	<b>13</b>	<b>5</b>	<b>0</b>	<b>7</b>	<b>0–40</b>

Abbreviations: No. = Number.

<sup>a</sup>Two of the 39 cases had two conditions, making the total number of conditions 41. The two cases with two conditions were a Level 1 thrombocytopenia and Category 4 seizure and a Level 1 thrombocytopenia and Level 1 aseptic meningitis.

<sup>b</sup>Level 1 indicates the highest level of diagnostic certainty as determined by case definitions provided by the Brighton Collaboration, while Category 4 indicates the lowest level of diagnostic certainty [16–24].

<sup>c</sup>Hypersensitivity was determined by hospital physicians; no Brighton Collaboration case definition exists. Most cases (n = 9 or 56%) were rash or urticaria.

<sup>d</sup>Anaphylaxis cases were only included if time from onset to vaccination was <24 h or 1 day.

Reporting rates per 100,000 TCv doses administered for adverse events of special interest (AESI) identified in two tertiary referral hospitals during active surveillance, Harare, Zimbabwe, February 25–April 15, 2019.

**Table 3**

Reporting Rates (N = 318,698 doses administered) <sup>a</sup>					
Reporting rate of AESIs identified during active surveillance			Modified rates including additional cases identified in hospital IMMIS databases, assuming all cases were vaccinated		
Condition	n	Rate(per 100,000 doses administered)	Additional cases found	Total cases <sup>c</sup> n	Rate(per 100,000 doses administered)
Seizure <sup>b</sup>	20	6.27	30	50	15.68
Hypersensitivity	16	5.02	1	17	5.33
Thrombocytopenia	3	0.94	0	3	0.94
Anaphylaxis	1	0.31	0	1	0.31
Aseptic meningitis	1	0.31	-	1	0.31
Total	41 <sup>d</sup>	12.95	31	72	22.59

Abbreviations: AESI = adverse event of special interest, IMMIS = Inpatient Morbidity and Mortality Information System.

<sup>a</sup>Number of doses administered was obtained from campaign administrative data.

<sup>b</sup>16 (80%) of the 20 vaccinated seizure cases were febrile. Reporting rates for febrile and afebrile seizures were 5.02 and 1.25, respectively.

<sup>c</sup>Total cases equals the number of cases identified during active surveillance and additional cases found in hospital records.

<sup>d</sup>Rates were calculated separately (for each condition) for the two cases with two conditions.

Adverse events following typhoid conjugate vaccine (TCV) receipt among 1,817 vaccinees during the post-campaign coverage survey, Harare, Zimbabwe, April 2019.

**Table 4**

AEFI Type	Age categories among vaccinated respondents					Total (N = 1,817) n (%)	
	6 months-4 years (N = 394)		5-15 years (N = 1,231)		16-45 years (N = 192) <sup>a</sup>		
	n	n (%)	n	n (%)	n		n (%)
No. of vaccinees reporting 1 AEFI <sup>b</sup>	34	132	11	177	10	177 (10)	
No. of vaccinees reporting no AEFI	360	1,099	181	1,640	90	1,640 (90)	
Pain at injection site	13	36	2	51	2.8	51 (2.8)	
Fever	16	27	0	43	2.4	43 (2.4)	
Nausea or vomiting	4	19	0	23	1.3	23 (1.3)	
Weakness or fatigue	1	16	4	21	1.2	21 (1.2)	
Headache	0	14	2	16	0.9	16 (0.9)	
Diarrhea	4	10	1	15	0.8	15 (0.8)	
Abdominal pain	4	8	2	14	0.8	14 (0.8)	
Fainting or dizziness	1	10	2	13	0.7	13 (0.7)	
Rash	1	10	0	11	0.6	11 (0.6)	
Swelling at injection site	3	7	1	11	0.6	11 (0.6)	
Other <sup>c</sup>	1	9	1	11	0.6	11 (0.6)	
Total No. of AEFI reported	48	166	15	229		229	

Abbreviations: AEFI = Adverse events following immunization, No. = Number.

<sup>a</sup>Vaccination only occurred in one suburb, Mbare.

<sup>b</sup>Some respondents reported more than one AEFI.

<sup>c</sup>Other AEFI types included chest pains (N = 2), dysuria and tonsillitis (N = 1), epistaxis (N = 1), feeling of heaviness (N = 1), flu and cough (N = 1), minimal bleeding on injection site (N = 1), painful and swollen eyes (N = 1), sleepy (N = 1), sore throat (N = 1), and tonsillitis (N = 1).