Evaluation of Vaccine Safety during the First Public Sector Introduction of Typhoid Conjugate Vaccine (TCV), Navi Mumbai, India

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Navi Mumbai Municipal Corporation
City of the 21st Century

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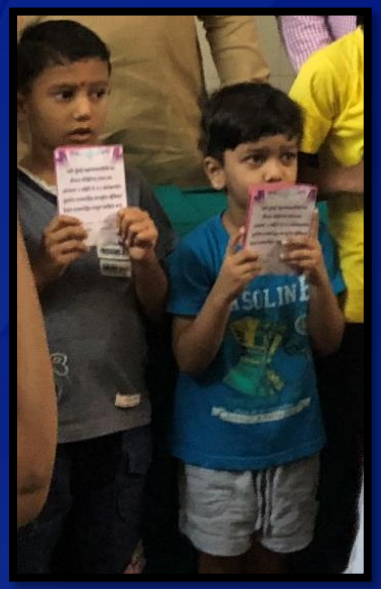
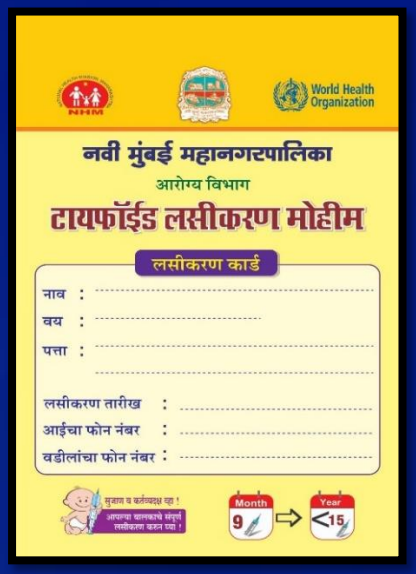
Outline

- Background
- Objective
- Methods
- Results
- Conclusions

Typhoid Conjugate Vaccine Campaign

- **Vaccine: Typbar- TCV**
- **Mass vaccination campaign: July 14 – August 25, 2018**
  - **Aged 9 months to < 15 years**
- **113,420 doses administered**





Rationale for Safety Evaluation

- Global Advisory Committee on Vaccine Safety (GACVS) review of Typbar-TCV safety data
  - Safety profile similar to comparator vaccine
  - No new safety signals
  - Limitations
- Recommendations
  - Robust safety evaluations with TCV introductions
  - Active monitoring of serious adverse events of interest
  - Use of Brighton Collaboration case definitions

2017, 92, 13-20 No 2

World Health Organization

Organisation mondiale de la Santé

Weekly epidemiological record

Relevé épidémiologique hebdomadaire

13 JANUARY 2017, 92th YEAR / 13 JANVIER 2017, 92e ANNÉE

No 2, 2017, 92, 13–20

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Contents

13 Global Advisory Committee on Vaccine Safety, 30 November – 1 December 2016

Sommaire

13 Comité consultatif mondial pour la sécurité des vaccins, 30 novembre - 1er décembre 2016

Global Advisory Committee on Vaccine Safety, 30 November – 1 December 2016

The Global Advisory Committee on Vaccine Safety (GACVS), an independent expert clinical and scientific advisory body, provides WHO with scientifically rigorous advice on vaccine safety issues of potential global importance.[1] GACVS held its 35th meeting in Geneva, Switzerland, on 30 November and 1 December 2016.[2]

Comité consultatif mondial pour la sécurité des vaccins, 30 novembre - 1er décembre 2016

Le Comité consultatif mondial pour la sécurité des vaccins (GACVS) est un organe consultatif indépendant composé d'experts cliniques et scientifiques qui fournissent à l'OMS des conseils d'une grande rigueur scientifique sur des problèmes de sécurité des vaccins susceptibles d'avoir une portée mondiale.[1] Le GACVS a tenu sa 35e réunion à Genève (Suisse) les

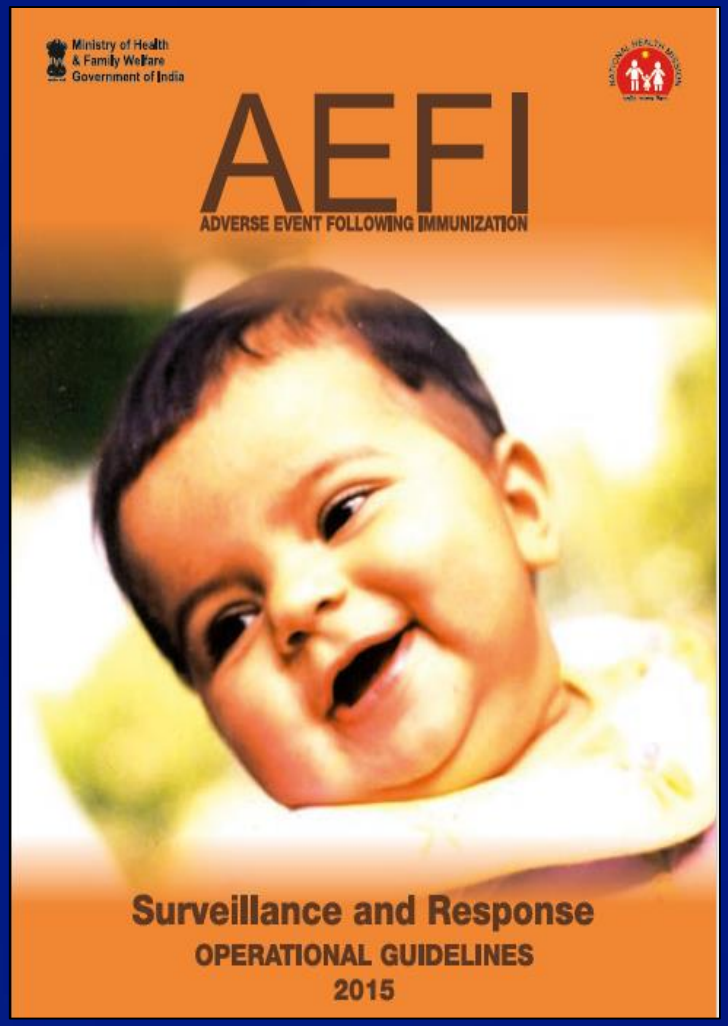
Objective

- **Describe the safety profile of Typbar-TCV using passive and active approaches**
  1. **Existing adverse event following immunization (AEFI) surveillance by the Navi Mumbai Municipal Corporation**
  2. **Active phone interviews for common adverse events**
  3. **Hospital-based surveillance for adverse events of special interest using Brighton Collaboration definitions**

METHODS

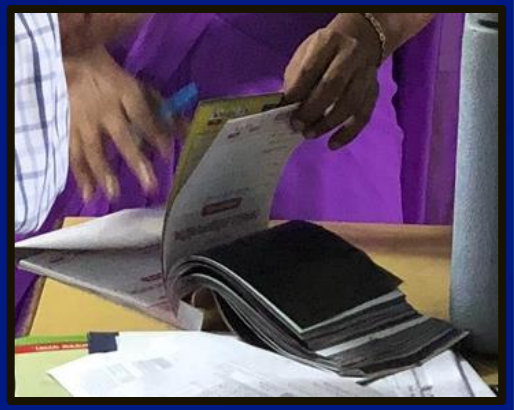
Routine AEFI Surveillance

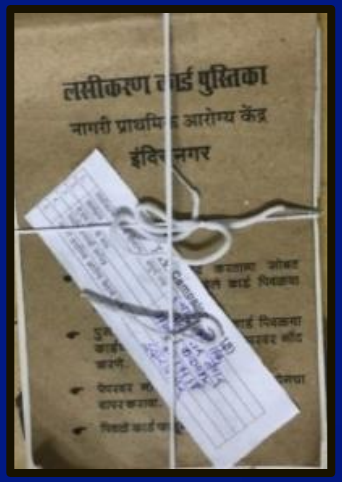
- National AEFI guidelines, 2015
  - Non-serious and serious AEFIs within 30 days of vaccination
- Data shared by the Navi Mumbai Municipal Corporation



Active Phone Follow-up for Common Adverse Events

- Conducted phone interviews among a representative subset (5%) of vaccine recipients
  - Vaccination cards printed in duplicate (vaccine recipient and session site)
  - Systematically sampled from the duplicate copy of the vaccination cards from each session site
- 2 contact points following vaccination
  - 48 hours
  - 7 days





Active Phone Follow-up for Common Adverse Events

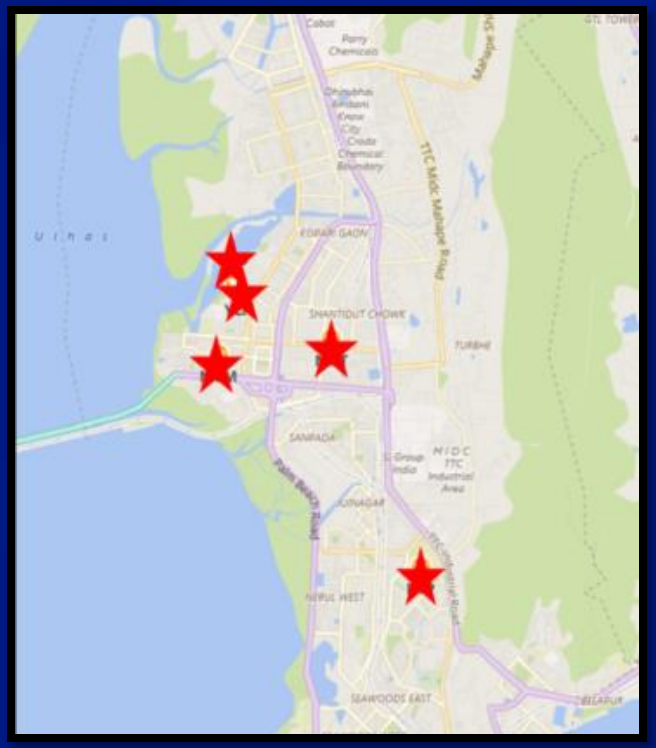
- Standard questionnaire translated into local languages for commonly reported mild events, plus additional adverse events reported by caregiver
  - Localized reactions (pain, swelling, redness)
  - Generalized reactions (fever, malaise)
  - Gastrointestinal reactions (vomiting, diarrhea)
  - Others

Hospital-based Surveillance for Adverse Events of Special Interest

- Conditions of special interest
  - Anaphylaxis
  - Aseptic Meningitis
  - Seizures
  - Encephalitis
  - Myelitis
  - Guillain-Barré syndrome (GBS)
  - Acute disseminated encephalomyelitis (ADEM)
  - Thrombocytopenia
  - Sudden/unexplained death
  - Hypersensitivity, non-anaphylaxis
- 5 surveillance hospitals – inpatient, emergency departments, and intensive care units

Hospital-based Surveillance for Adverse Events of Special Interest

- Children 9 months to < 15 years old with at least one adverse event of special interest
- Chart abstraction
- Used Brighton Collaboration Criteria for diagnostic certainty followed by ascertainment of vaccination status
- Surveillance from 1 week prior to the campaign through 42 days following the campaign



Definitions

- **Brighton Collaboration case definitions and guidelines to standardize assessment of AEFI data for comparability**
- **Classified according to level of diagnostic certainty**
  - **Level 1: Highest level of specificity, least sensitive**
  - **Level 2: Intermediate level of specificity, lower sensitivity**
  - **Level 3: Lower level of specificity, highly sensitive for respective AEFI**
  - ***Category 4: Insufficient Information***
  - ***Category 5: Not a case***

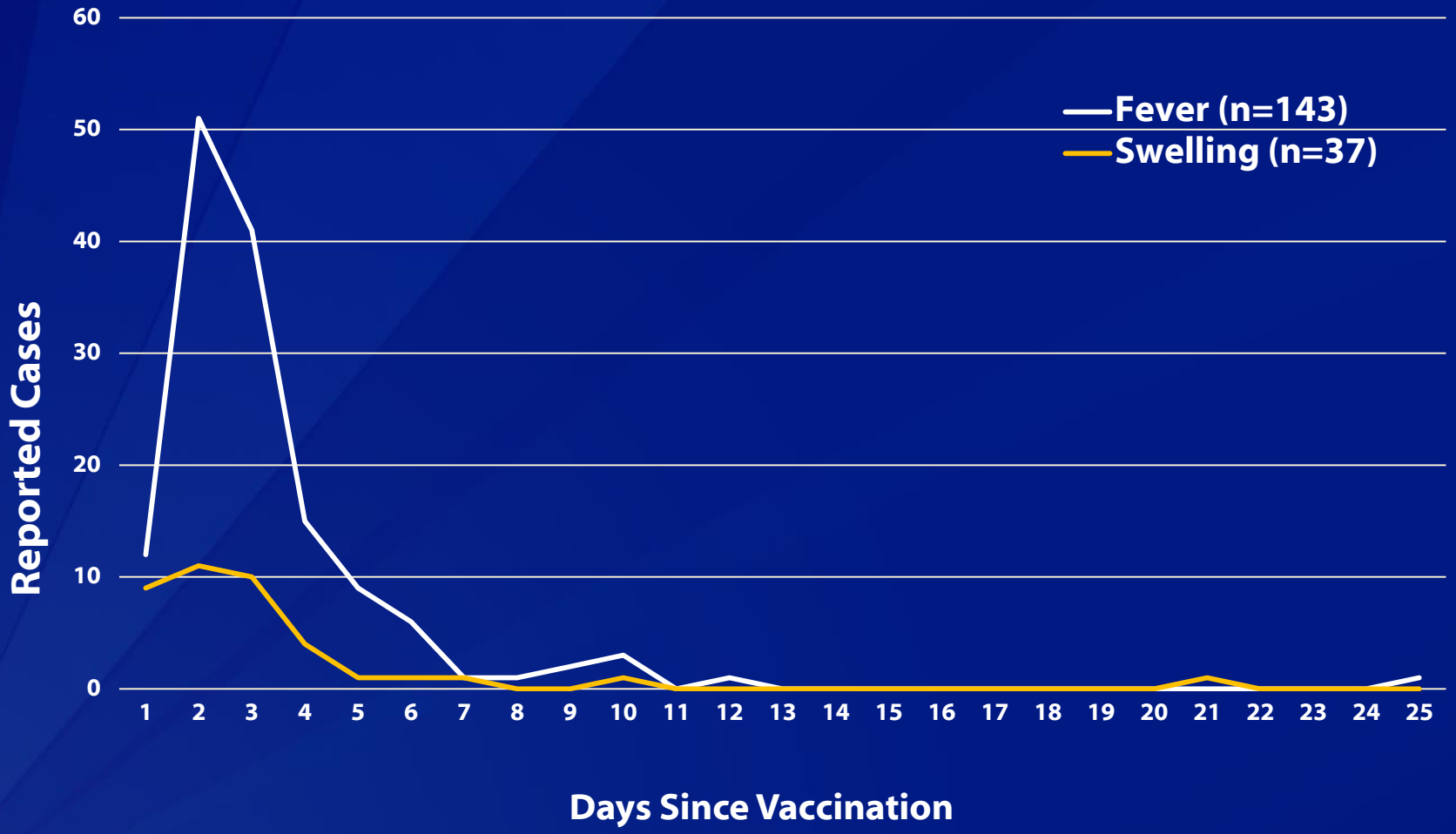
RESULTS

Reported AEFIs, Routine AEFI Surveillance System

AEFI	n
Total Reporting 1 or more AEFI	222
Mild	211
Fever	143
Swelling	37
Pain	23
Rash	15
Vomiting	11
Giddiness	6
Body aches	3
Itching	3
Headache	2
Cough/cold	2
Severe	2
Abscess	1
Inability to walk	1
Serious	9
Hospitalized*	9

*hospitalized with fever, giddiness, itching, swelling

Fever and Swelling by Days Since Vaccination



Adverse Events Reported by Time Point, Active Phone Follow-up

		48-hour (n=5,605)	7-day (n=4,728)
Total reporting 1 or more events		1,852 (33%)	343 (7%)
Conditions		n (%)	n (%)
Local reactions	Pain	1,452 (26)	52 (1)
	Swelling	419 (8)	21 (<1)
	Redness	117 (2)	11 (<1)
	Induration	56 (1)	4 (<1)
	Pustule with discharge	18 (<1)	7 (<1)
Systemic reactions	Fever	416 (7)	200 (4)
	Malaise	14 (<1)	5 (<1)
	Headache	61 (1)	42 (1)
	Persistent Crying	26 (<1)	5 (<1)
	Myalgia	26 (<1)	14 (<1)
Gastrointestinal reactions	Vomiting	54 (1)	38 (1)
	Nausea	14 (<1)	12 (<1)
	Diarrhea	43 (1)	26 (1)
Other		20 (<1)	35 (1)
Total adverse events		2,736	508

Adverse Events of Special Interest by TCV Vaccination Status

Event of Special Interest	Unvaccinated*	Vaccinated
Total with 1 or more AESI	n= 465	n=60
Thrombocytopenia	322	43
Seizure	142	18
Encephalitis	8	0
Acute Disseminated Encephalomyelitis (ADEM)	7	0
Aseptic Meningitis	3	0
Anaphylaxis	3	0
Myelitis	2	0
Hypersensitivity, non-anaphylaxis	4	0
Guillain-Barré syndrome (GBS)	1	1
Sudden unexplained death	1	0
Total AESI	493	62

*includes unknown vaccination status (n=33)

Brighton Collaboration Level of Diagnostic Certainty among Vaccinated Patients

AESI	Level 1	Level 2	Level 3	Category 4	Category 5
Thrombocytopenia	37	6	N/A	0	0
Seizure	1	1	1	2	13
GBS	0	0	0	0	1

Level 1- Highest complexity of needed information for case validation (most confidence in diagnosis)
Level 2 - Intermediate complexity of needed information for case validation
Level 3- Lowest complexity of needed information for case validation
Category 4- Insufficient information
Category 5- Not a case

Final Diagnoses among Vaccinated Children with Adverse Events of Special Interest

Thrombocytopenia (n=43)	
Final Diagnosis	n(%)
Dengue fever	23 (54)
Acute febrile illness	8 (19)
Other viral fever	5 (12)
Malaria	4 (9)
Other	3 (7)
Seizures (n=18)	
Final Diagnosis	n(%)
Febrile seizures	10 (56)
Seizure disorders	3 (17)
Other	5 (28)

Limitations

- Underreporting of AEFI (general limitation for passive surveillance)
- Potential over-reporting of events due to reporting biases of Navi Mumbai Municipal Corporation healthcare workers and caregivers via phone
  - E.g. hospitalizations for mild events as a precautionary measure
- Adverse events of special interest not generalizable to the vaccinated population
  - Proportion presenting to surveillance sites currently unknown

CONCLUSIONS

Conclusions

- Majority of events reported through routine AEFI surveillance and active phone follow-ups were mild, within 5 days of vaccination
- Occurrence of adverse events of special interest in the unvaccinated population was higher than in vaccinated population
- Further evidence of excellent safety profile of Typbar-TCV when administered to children 9 months to < 15 years of age

Acknowledgements

- Navi Mumbai Municipal Corporation leadership and staff
- Government of India Ministry of Health and Family Welfare – Expanded Program on Immunization
- State of Maharashtra, Department of Public Health and Family Welfare
- Indian Academy of Pediatrics - Navi Mumbai Chapter
- Bharat Biotech International Limited
- WHO-India National Polio Surveillance Program (NPSP)
- Indian Council of Medical Research (ICMR)
- Stanford University
- Hospital and laboratory sites: Navi Mumbai Municipal Corporation hospital, Mathadi Trust Hospital, DY Patil Medical College and Hospital, MGM Vashi Hospital, Yewale Hospital, Joshi microbiology laboratory)
- WHO-SEARO and WHO-HQ
- International Vaccine Institute
- Grant Government Medical College
- Scientific Advisory Panel
- Bill and Melinda Gates Foundation
- CDC-Atlanta staff

Thank you

The findings and conclusions in this presentation are those of the author and do not necessarily represent the views of the Centers for Disease Control and Prevention

GBS: Case Summary

- 2 year old female presented to the pediatric IPD with decreased tone in both lower limbs
- Provisional diagnosis was GBS
- She was vaccinated in the campaign and the onset of symptoms was reportedly the same day as vaccination
- She presented to the hospital 23 days following TCV
- Physicians ruled out GBS but the patient was still under investigation for acute flaccid paralysis (AFP) following vaccination
- She was referred to tertiary hospital in Mumbai and was advised several investigations that were ultimately not conducted
- Patient fully recovered and was discharged within ~2 weeks of referral

Thrombocytopenia

Brighton Levels of Diagnostic Certainty

Thrombocytopenia

Level 1 of diagnostic certainty	**Level 2 of diagnostic certainty**
Platelet count less than 150 x 10^9 L^1 AND	Platelet count[2] less than 150 x 10^9 L^1
Confirmed by blood smear examination OR	
The presence of clinical signs and symptoms of spontaneous bleeding	

Footnotes

[1] Measured by an automated hematology analyzer or assessed by hand count of platelets on a cell count slide

[2] Presentations of spontaneous (i.e. non-traumatic) bleeding include purpura (i.e. petechiae, purpura sensu stricto, ecchymosis), hemorrhage oozing of skin lesions including rashes, hematoma, bruising, hematemesis, hematochezia, occult bleeding per rectum, epistaxis, hemoptysis, hematuria, conjunctival bleeding, intracranial bleeding.

After review of findings, please check Level of diagnostic certainty below

Level 1 [ ]

Level 2 [ ]

Category 4: Insufficient evidence [ ]

Category 5: Not a case of thrombocytopenia [ ]

Seizure

Brighton Levels of Diagnostic Certainty

Seizures

Level 1 of diagnostic certainty	Level 2 of diagnostic certainty	Level 3 of diagnostic certainty
Witnessed sudden loss of consciousness AND	History of unconsciousness AND	History of unconsciousness AND
Any of the following motor manifestations: • Generalized • Tonic • Clonic • Tonic-clonic • Atonic	Any of the following motor manifestations: • Generalized • Tonic • Clonic • Tonic-clonic • Atonic	Other generalized motor manifestations described

Active Phone Follow-up: Most Common Adverse Event by Age Group

	48 hour phone call			7 day phone call		
	Pain	Swelling	Fever	Fever	Pain	Headache
Age Groups	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
9 months - 5 years	330 (17)	99 (5)	177 (9)	90 (5)	11 (1)	14 (1)
6 - 10 years	579 (30)	150 (8)	134 (7)	58 (4)	25 (2)	15 (1)
10 -15 years	543 (33)	170 (10)	105 (6)	52 (4)	16 (1)	13 (1)
Total	1,452	419	416	200	52	42