Diphtheria treatment center. @Ehab Zawati

Virtual Training 15, "Focus on the Agents of Diphtheria",

Diphtheria : vaccines, antitoxin, treatments Recent experiences in Bangladesh and in West Africa

Julien Potet, MSF-Access, March 2025

Intended Learning Objectives

Specific objectives of this session:

1. Learn about diphtheria outbreak control responses
2. Learn about challenges to access tools against diphtheria in resource-limited access settings

Outline

1. A couple of questions on vaccination coverage and DAT
2. Overview of the diphtheria outbreaks in Bangladesh and West Africa
3. Outbreak response gaps:
    1. Diagnostic capacity
    2. Access to parenteral macrolides
    3. Hospital bed capacity
    4. Access to DAT
    5. Delayed vaccination campaign

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What was the estimated DPT3 vaccination coverage rate in Nigeria before the outbreak emerged at the end of 2022 (i.e. DPT3 coverage = percentage of children aged 12-59 months who have received at least 3 doses of DPT-containing vaccine)?

ⓘ Start presenting to display the poll results on this slide.

slido

Please download and install the Slido app on all computers you use

What is the active ingredient of Diphtheria Anti Toxin (DAT) ?

ⓘ Start presenting to display the poll results on this slide.

2. Overview of the diphtheria outbreaks in Bangladesh and West Africa


NIGER
NIGERIA
BENIN
CHAD
CAMEROON
ATLANTIC OCEAN
BIOKO (EQUATORIAL GUINEA)
Niamey
Kano
Lagos
Abuja
Kaduna
Jos
Ibadan
Port Harcourt
Douala
Yaoundé
Malabo
Cotonou
Maiduguri
N'Djamena
Kumo
Gombe
Bauchi
Sokoto
Katsina
Zaria
Kafanchan
Lafia
Makurdi
Calabar
Onitsha
Enugu
Awka
Asaba
Benin City
Ibadan
Ilorin
Oshogbo
Ife
Ondo
Owo
Ikere-Ekiti
Ado-Ekiti
Ijebu-Ode
Sapele
Warri
Umuahia
Aba
Uyo
Ikot Ekpene
Abakaliki
Ugep
Gboko
Wukari
Ibi
Lokoja
Kabba
Bida
Minna
Keffi
Lafiagi
Jimeta
Yola
Mubi
Biu
Gambe-Ya
Dukku
Miya
Azare
Potiskum
Jajere
Dikwa
Ngurtuwa
Gashua
Nguru
Hadejia
Gumel
Kaura Namoda
Gusau
Jega
Birnin Kebbi
Argungu
Funtua
Mada
Sabon Birni
Gidan Kaya
Kontagora
Deba Habe
Pindiga
Asari
Chimola
Wurno
Shaki
Igboho
Kishi
Igbetti
Iseyin
Oyo
Iwo
Abeokuta
Porto-Novo
Mushin
Epe
Ikorodu
Sapele
Forcados
Yenagoa
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Opobo Town
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4°
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NEPAL
INDIA
INDIA
BANGLADESH
MYANMAR
Saidpur
Rangpur
Dinājpur
Sylhet
Bogra
Jamālpur
Mymensingh
Nawābganj
Naogaon
Rājshāhi
Sirajganj
Kishorganj
Ishurdi
Tangail
Bhairab Bāzār
Kushtia
Pābna
Narsinghdi
Brāhmanbāria
Dhaka
Chuadānga
Faridpur
Nārāyanganj
Comilla
Jessore
Chāndpur
Mādāripur
Chaumuhāni
Khulna
Bāgerhāt
Noākhāli
Sātkhira
Barisāl
Rāngāmāti
Chālna Port
Patuākhāli
Chittagong
Cox's Bāzār
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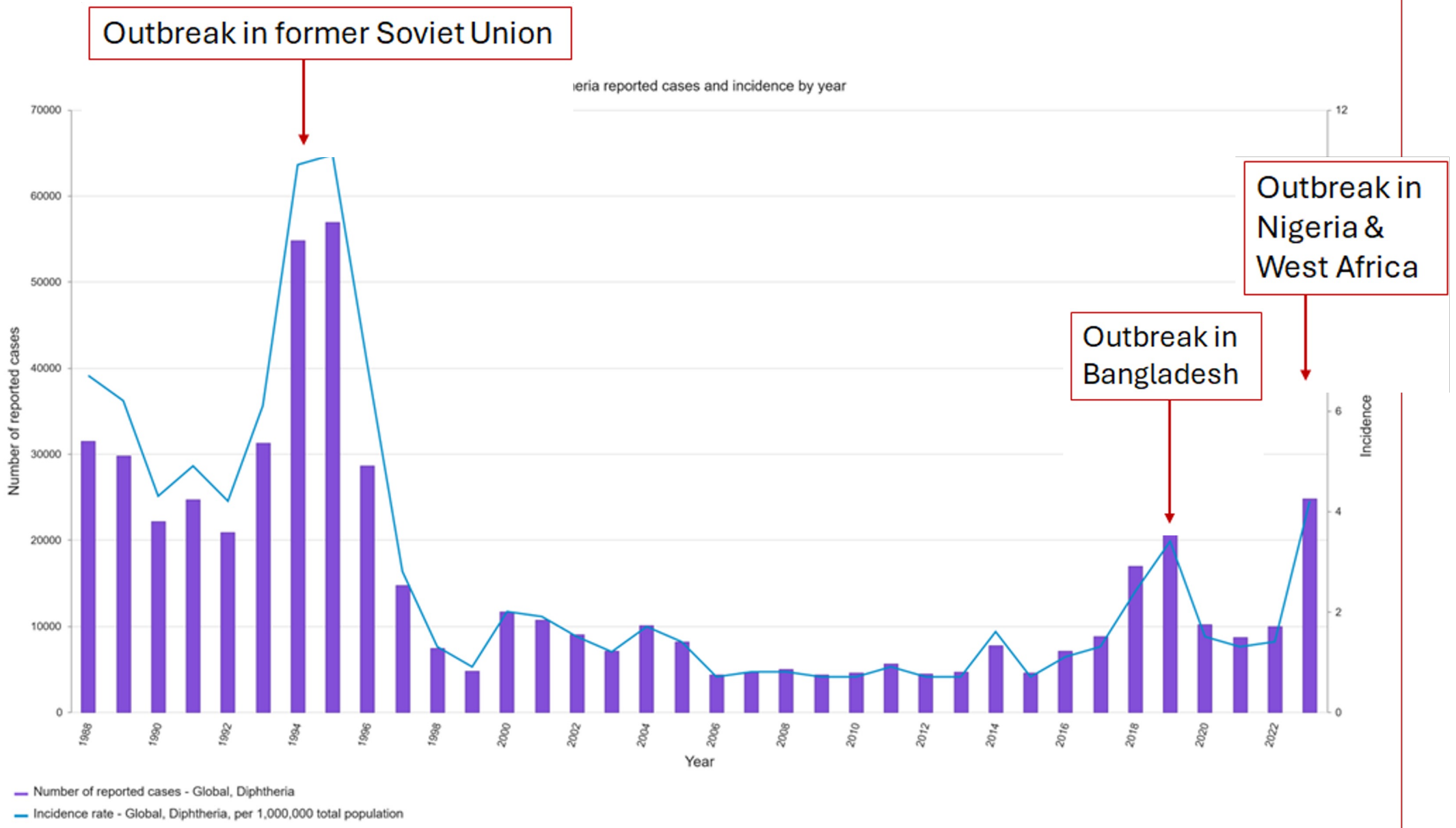
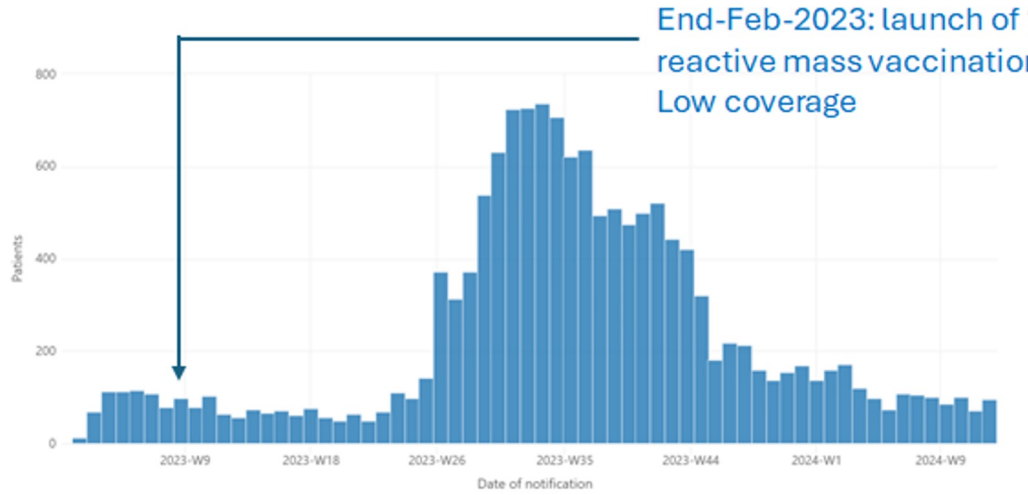


Pre-outbreak situation / Kano vs Cox Bazar

- Very low pre-outbreak vaccination coverage (DTP3):
  - Bangladesh : 90% (2017)
  - Rohyinga refugee camp in Cox Bazar: 20% of 5y-14y were estimated to be immune
    Finger, BMC Med, 2019
  - Nigeria: 57% (2022)
  - Kano State: 52% of <4y were estimated to be immune
    Tohme, Vaccines, 2023

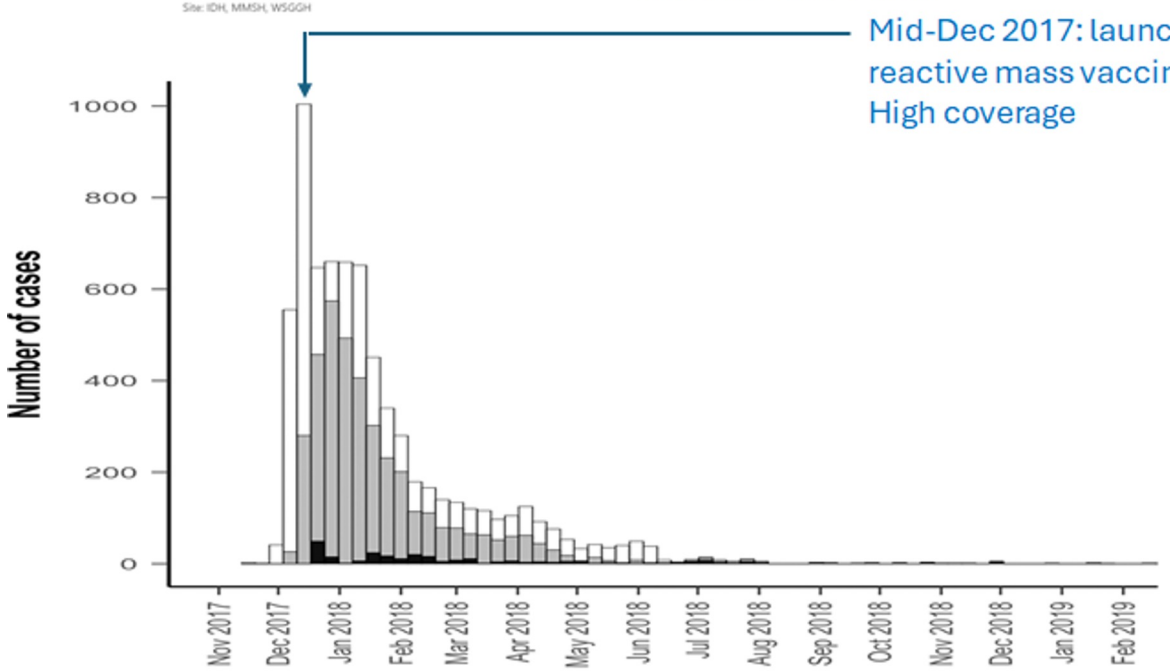
- Td boosters not offered

- Densely populated areas
  - Refugee camp in Cox Bazar : population 1M; up to 60,000 persons per km2
  - Kano metropolitan area: population 4,9M; up to 30,000 persons per km2



Source: Epicentre Dashboard

Outbreak in Kano, Nigeria (2023-2024)
Low number of cases during the first 6 months
Then gradual increase
High number of cases during 4 months
Then a long tail during >5 months



Source: https://doi.org/10.1371/journal.pmed.1003587.g001

Outbreak in Cox Bazar, Bangladesh (2017-2018)
Low number of cases for a very short period of time (1 month)
Then sudden increase
High number of cases during 2 months
Then a long tail during 4 months

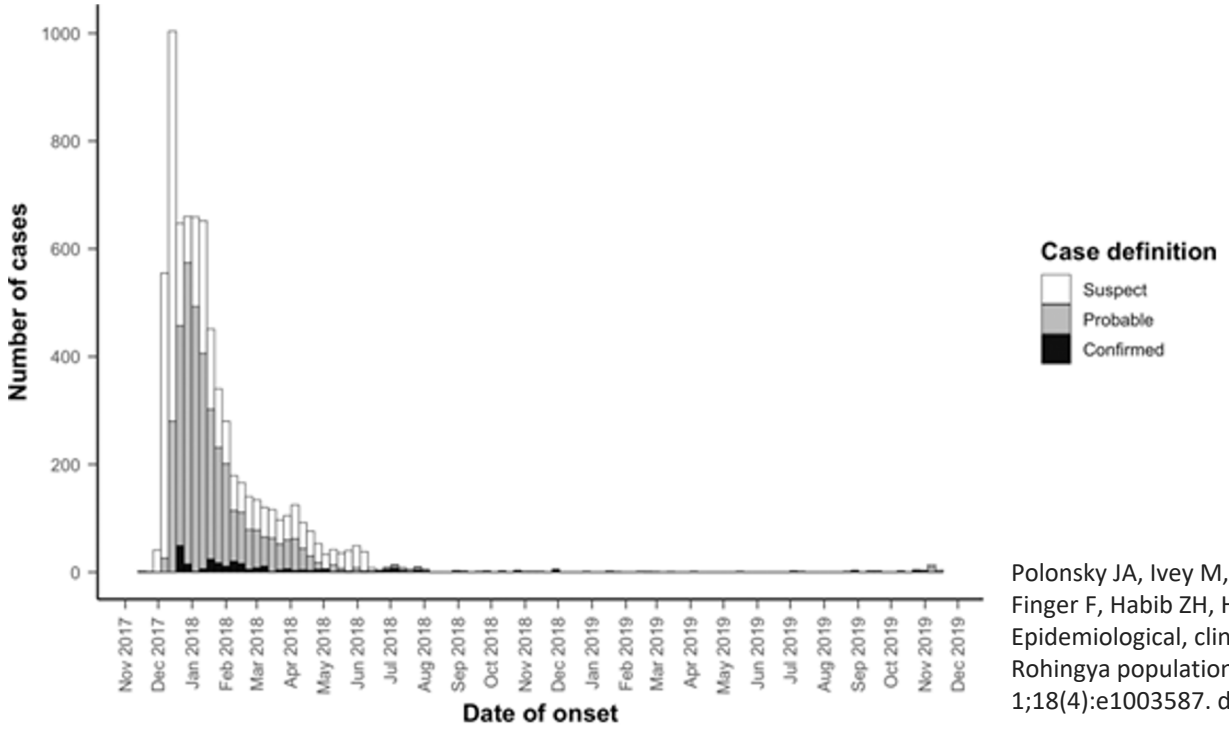
MSF and diphtheria outbreak response

- Prevention
  - Contact tracing, early case detection and isolation
  - Antibiotics for cases and contacts
  - Vaccination for contacts
  - « Catch up » mass vaccination campaigns

- Case management
  - Hospitalisation, home based care
  - Access to diphtheria anti toxin
  - Post-discharge follow up (i.e. delayed complications)

3. Outbreak response gaps

Gap#1: limited diagnostic capacity



Cox Bazar, Bangladesh

<1% of cases were lab-confirmed

Polonsky JA, Ivey M, Mazhar MKA, Rahman Z, le Polain de Waroux O, Karo B, Jalava K, Vong S, Baidjoe A, Diaz J, Finger F, Habib ZH, Halder CE, Haskew C, Kaiser L, Khan AS, Sangal L, Shirin T, Zaki QA, Salam MA, White K. Epidemiological, clinical, and public health response characteristics of a large outbreak of diphtheria among the Rohingya population in Cox's Bazar, Bangladesh, 2017 to 2019: A retrospective study. PLoS Med. 2021 Apr 1;18(4):e1003587. doi: 10.1371/journal.pmed.1003587. PMID: 33793554; PMCID: PMC8059831.

Nigeria (not just Kano)

<1% of cases were lab-confirmed

Need for a rapid diagnostic test for diphtheria

- Access to lab for bacterial culture + Elek is very limited
- Target product profile for diphtheria RDT under discussion (not published)
  - accuracy (Se/Sp),
  - type of sample,
  - number of steps,
  - time to results,
  - level of care & use case scenarios.
- Several mAbs with good affinity for diphtheria toxin are available to develop prototype antigen-detecting lateral flow assays.
- Challenges:
  - what's the business model for a rapid test for diphtheria?
  - collection of pharyngeal swab is challenging (risk of bleeding).

Gap#2: limited access to parenteral macrolides

- WHO recommends macrolides over penicillin for treatment of diphtheria
- About 20% of suspected cases in Kano couldn't swallow oral drugs.
- However, due to customs restrictions, MSF couldn't easily import injectable macrolides. Doses from the local market were scarce.

Gap#3: limited hospital bed capacity

- In Kano, 152 beds (in two hospitals supported by MSF), including 10 intensive care beds, were allocated to diphtheria patients.

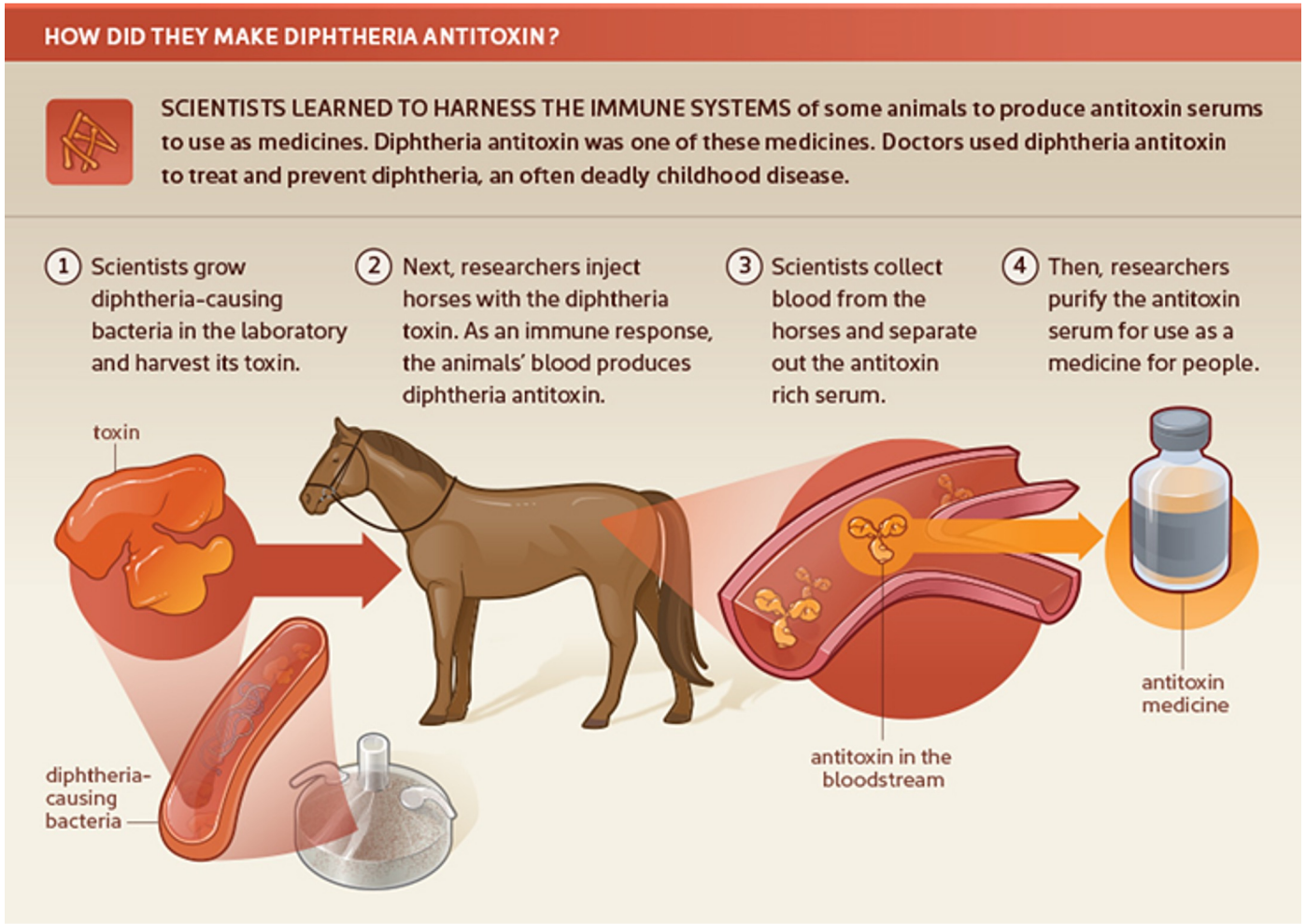
- But that wasn't enough. During the peak (July 2023-December 2023), most patients couldn't be admitted -> Home care was introduced for milder cases, but triage was difficult.

Gap#4: global shortage of eDAT

- During the West African outbreak, global demand for eDAT surged, but global supply couldn't keep pace.
- In Kano, 25% of patients in need received eDAT; often a suboptimal dose.
- eDAT was prioritized for : <5 days post-symptom onset, signs of severity (e.g. bull's neck), <5y

Few eDAT suppliers, limited manufacturing capacity

- WHO survey of eDAT suppliers (to be published soon): only 6 active suppliers (1 Brazil, 4 India, 1 Bulgaria) with varying production capacities, prices and quality standards
- Long lead time for manufacturing, relatively short shelf life
- Global manufacturing capacity per year: 100K-130K vials of 10,000IU; equivalent to 12,500-16,250 TCs of 80,000IU
- No international emergency stockpile during inter-epidemic periods
- In practice, in 2023-2024, supply relied on just two Indian companies -> inability to obtain sufficient quantities of eDAT to respond to outbreak.

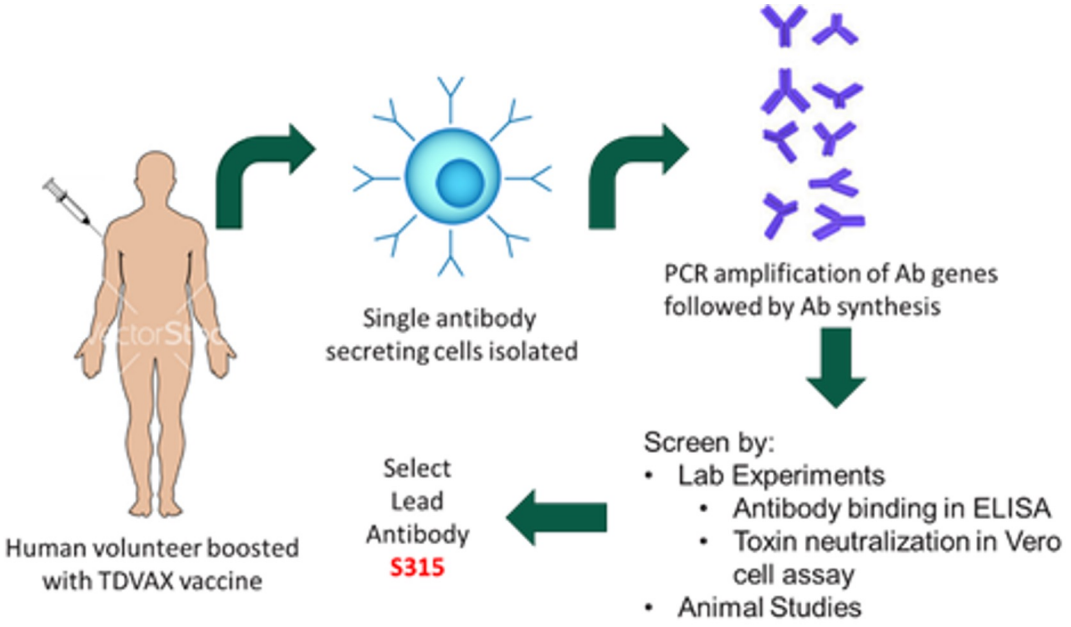


eDAT manufacturers will only purchase more horses if long-term contracts are secured.

Need to shape the market for eDAT and build international stockpiles during inter-epidemic periods

Need to accelerate development of mDAT

- mDAT: fully human diphtheria anti toxin mAb
- Target product profile mDAT:
  - safer than eDAT (less hypersensitivity reactions & serum sickness), at least as effective as eDAT,
  - more easily scalable,
  - not much more expensive than eDAT.
- S315:
  - developed by not-for-profit organization
  - ready for Phase II/III, but challenges to mobilise $2-3M to produce clinical grade S315 for RCT



Gap#5: Delay in launching mass vaccination campaign

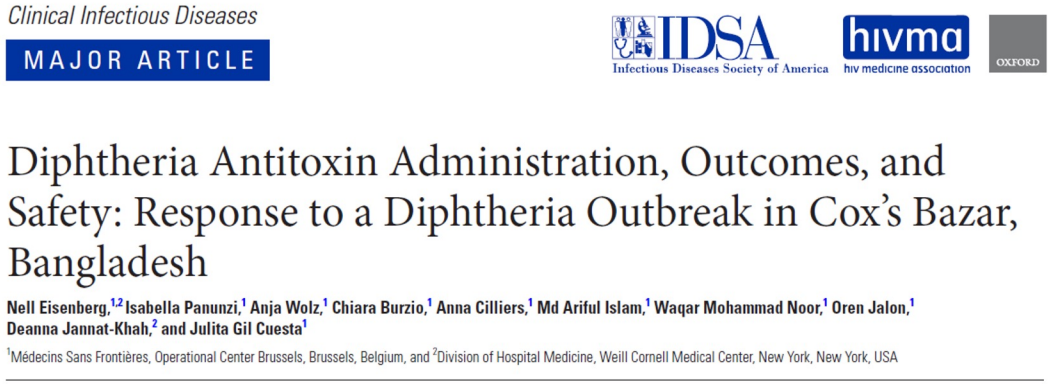
- Catch-up vaccination : Penta (DTwP+Hib+HBV) for <5y ; Td for >5y
- Delay in decision to vaccinate/how to vaccinate
  - Small clusters in highly dense populated areas
  - Schedule not suitable for 'reactive' vaccination = 3 doses/rounds
  - All age groups are at risk/eligible for vaccines
  - Area with few cases can be very wide
- July 2023: Nigeria requested 10M doses of Penta / Td for mass vaccination campaign, but
  - funding was not readily available
  - available doses of Penta and Td in Nigeria were reserved for routine immunization
  - lead time (new orders): 5 months for Penta & 2.5 months for Td
- Need to establish an international stockpile of Penta + Td for outbreak response (ICG model)

In summary

List of learning points from this session:

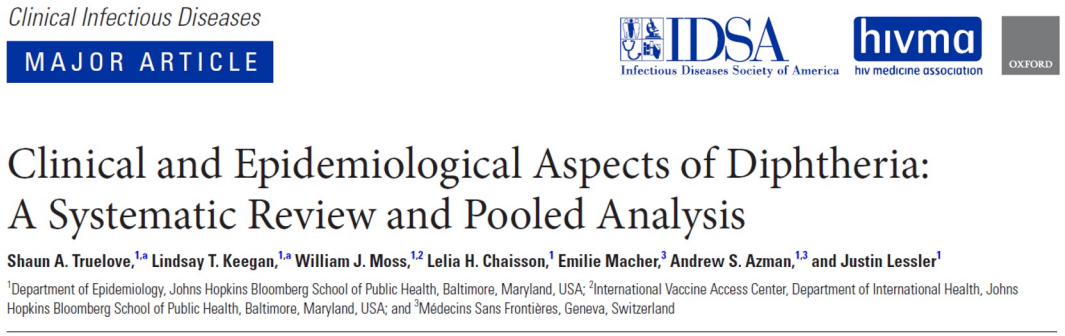
- There can be wide variation in coverage of diphtheria-containing vaccines between national and local levels.
- Outbreaks in Bangladesh and Kano had different dynamics, but both had a long tail
- Stockpiling of diphtheria tools is needed between epidemic periods.
- mDAT is a low-hanging fruit and needs further support to accelerate development.

Further reading

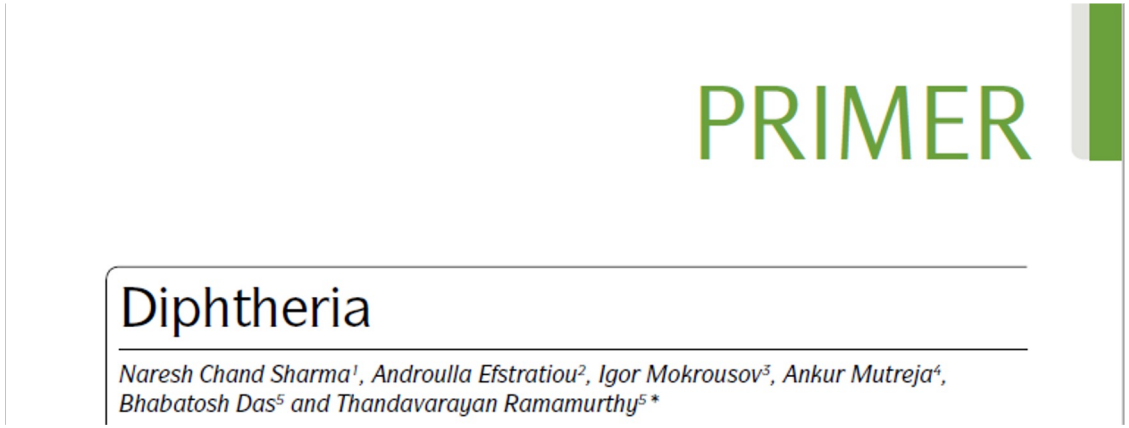


Eisenberg, Clinical Infectious Diseases, 2021

White, The Journal of Infectious Diseases, 2024



Truelove, Clinical Infectious Diseases, 2020



Sharma, Nature Disease Reviewers Primers, 2019

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Thank you !