Progress and Challenges of Enteric Vaccines

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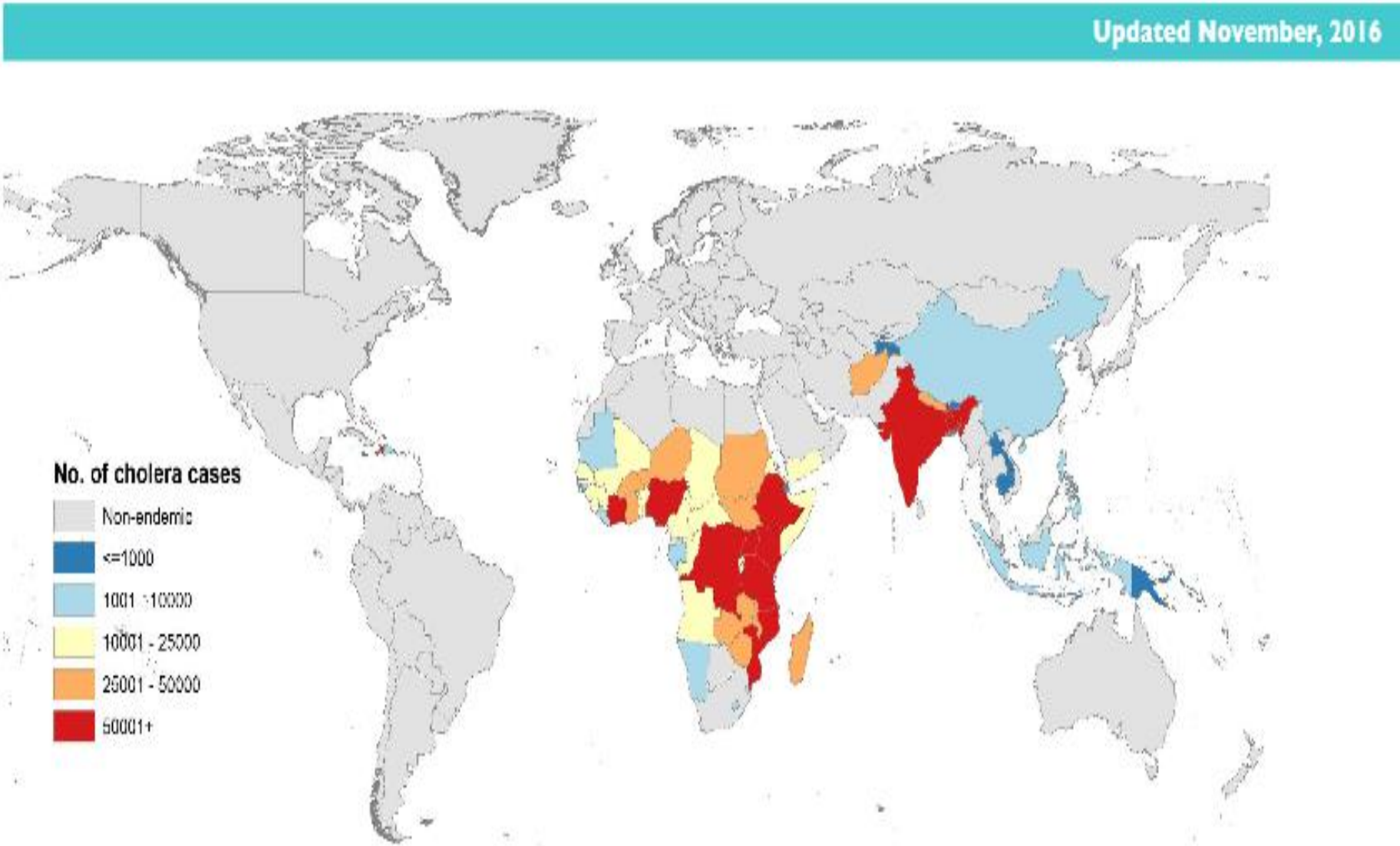
New enteric vaccines in use

- Cholera
- Rotavirus
- Typhoid

Cholera- History

- During the 19th century, cholera spread across the world from its original reservoir in the Ganges delta in India;
- Six subsequent pandemics killed millions of people across the world;
- The current 7th pandemic started in South Asia in 1961, and reached Africa in 1971 and the Americas in 1991;
- *V. cholerae* O139 – first identified in Bangladesh in 1992 – caused outbreaks in the past, but recently has only been identified in sporadic cases;
- Cholera is now endemic in many countries (69 endemic & 18 non-endemic)

Estimate of the Global Burden of Cholera in Endemic Countries

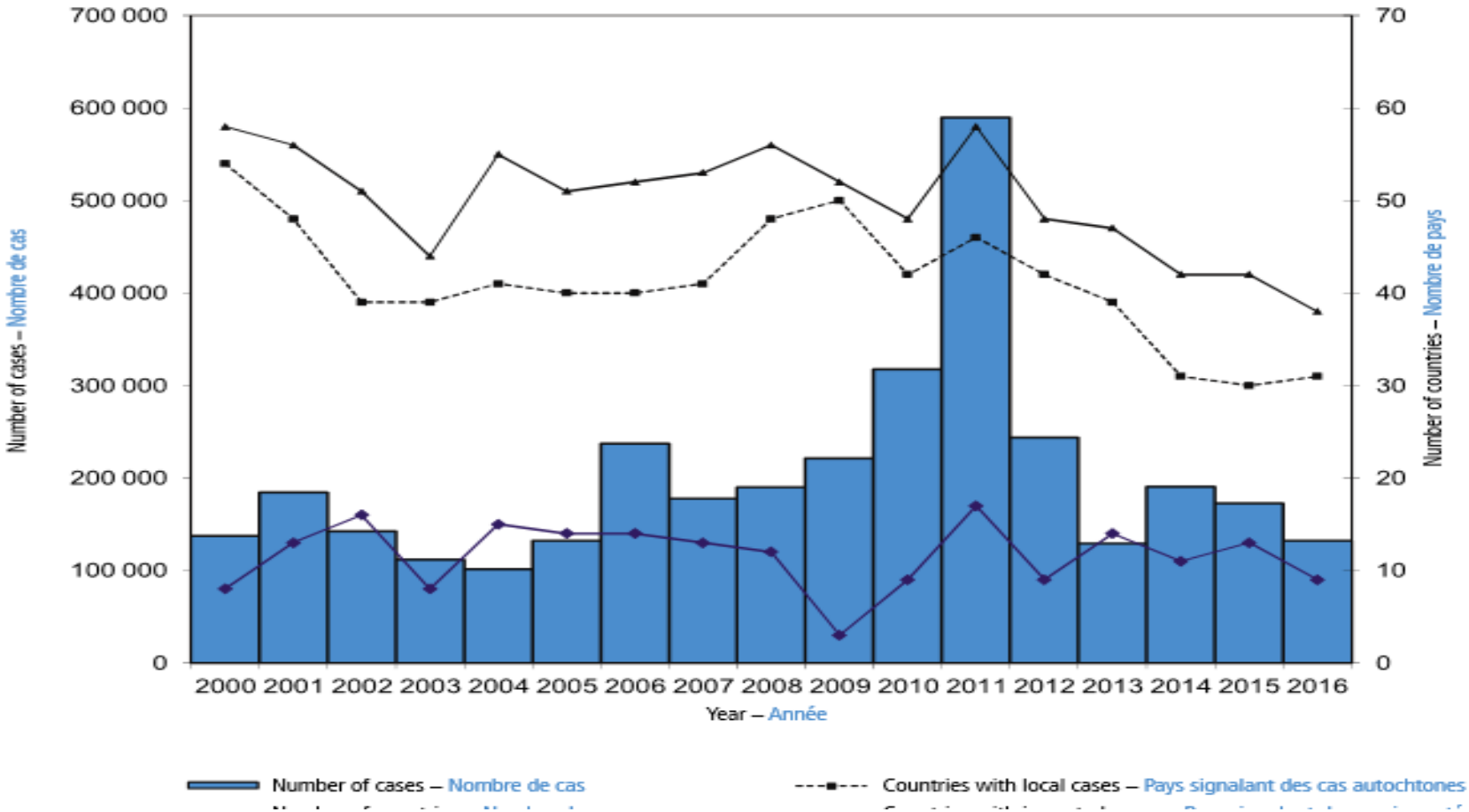


World Health Organization
Organisation mondiale de la Santé

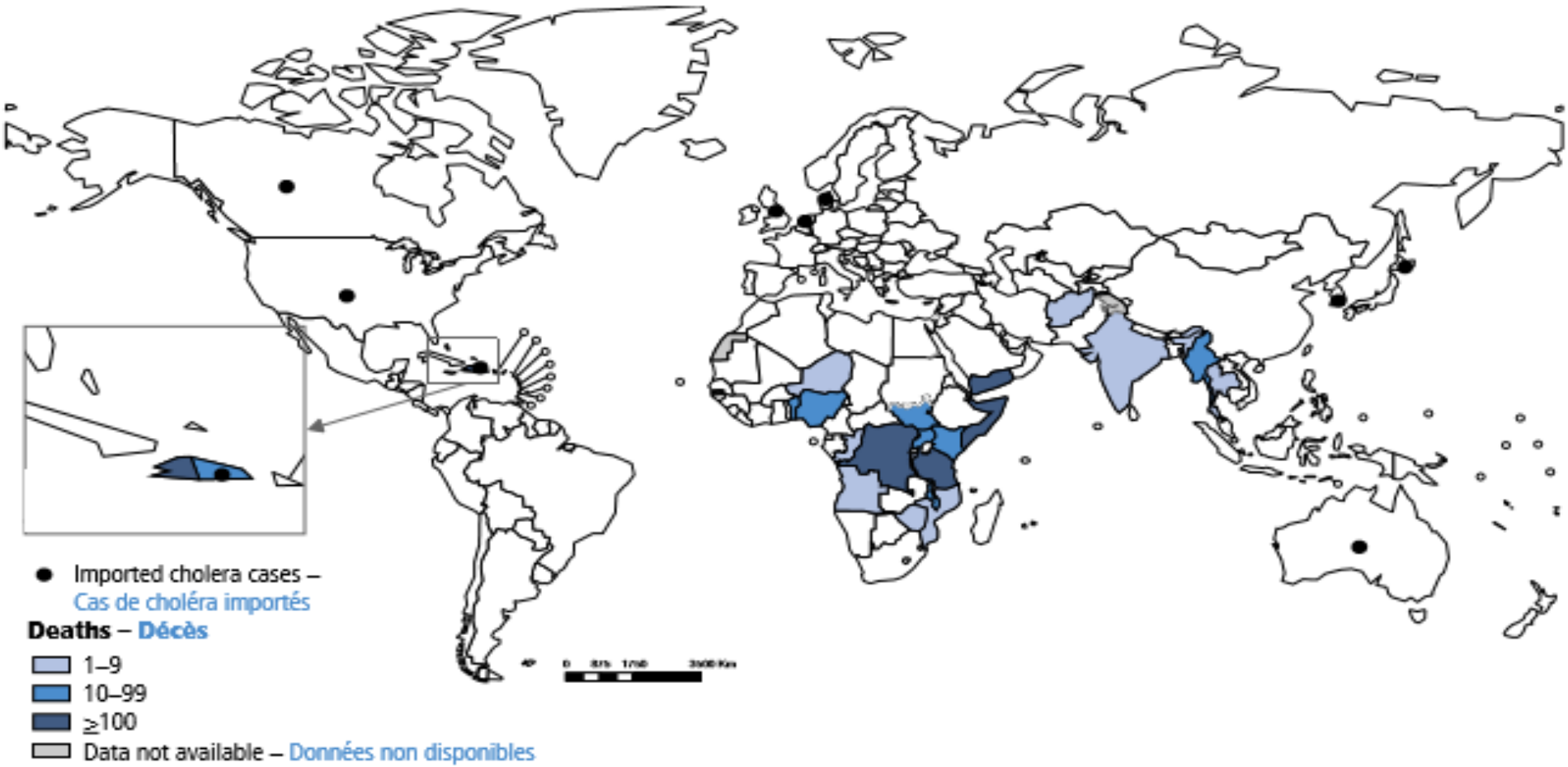
Weekly epidemiological record
Relevé épidémiologique hebdomadaire

8 SEPTEMBER 2017, 92th YEAR / 8 SEPTEMBRE 2017, 92e ANNÉE
No 36, 2017, 92, 521–536

Figure 1 **Countries/areas reporting cholera and cases reported by year, 2000–2016**
Figure 1 **Pays/territoires ayant déclarés des cas de choléra et nombre de cas déclarés par année, 2000-2016**



Map 1 **Countries reporting cholera deaths and imported cases in 2016**
Carte 1 **Pays ayant déclaré des décès dus au choléra et des cas importés en 2016**



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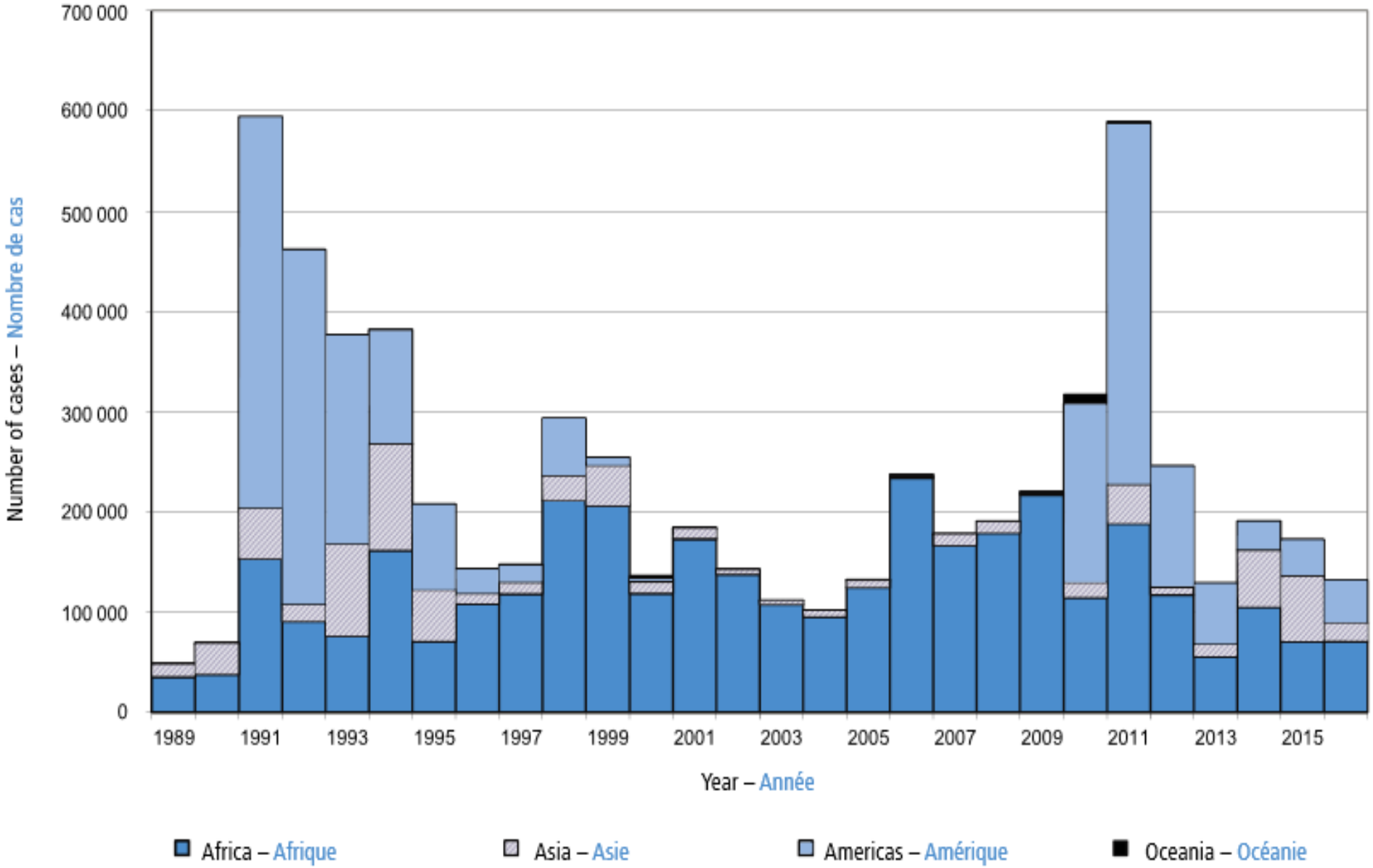
Source: World Health Organization/ Department of Control of Epidemic Diseases. – Source: Organisation mondiale de la santé / Département de lutte contre les maladies épidémiques.

Map production: World Health Organization/ Department of Information Evidence and Research. – Production de la carte: Organisation mondiale de la santé / Département Information, bases factuelles et recherche.

Figure 2 **Cholera cases reported to WHO by year and by continent, 1989–2016**

Figure 2 **Cas de choléra déclarés à l'OMS par année et par continent, 1989-2016**



The Global Burden of Cholera

- About 2.86 million cholera cases resulting in appox. 95,000 deaths in 69 endemic countries per year and 87,000 cases & 2500 deaths in 18 non endemic

- Countries with estimates of more than 100,000 cases per year are: •India •Ethiopia •Nigeria •Haiti •DRC •Tanzania •Kenya •Bangladesh

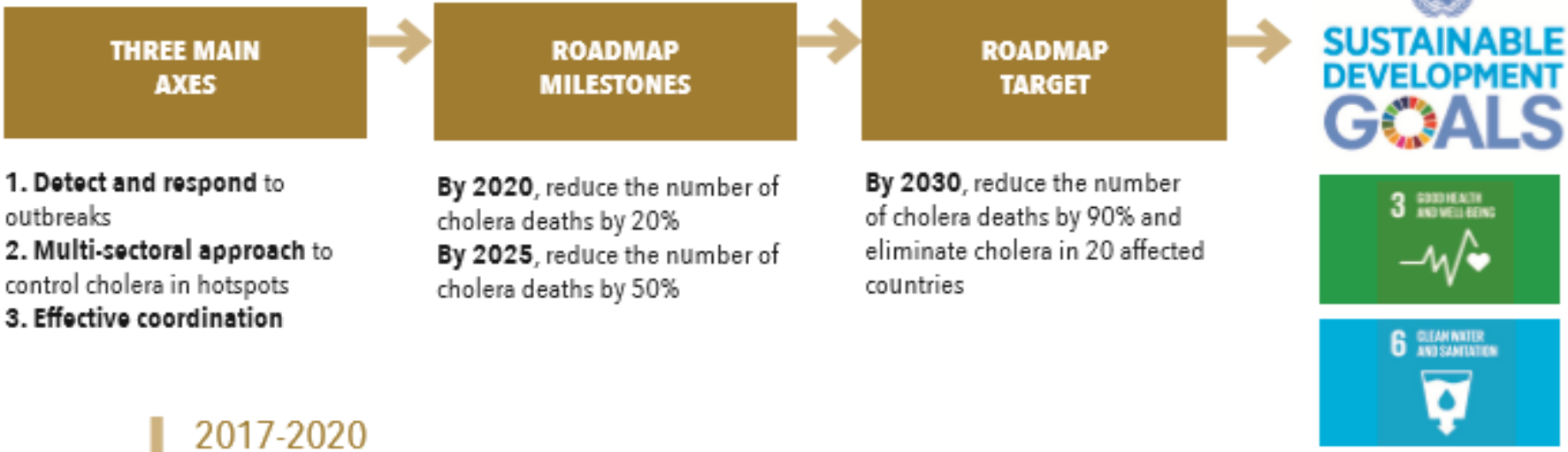
(Contd.)

- The number of cholera cases reported to WHO has continued to be high over the last few years
- During 2016, a total number of 132121 cases were notified from 38 countries, including 2420 deaths
- Yemen faced the worst cholera outbreak in the world, with over 250,000 suspected cases by July 2017
- The discrepancy between these figures and the estimated burden of the disease is due to the fact that many cases are not recorded due to limitations in surveillance systems and fear of impact on trade and tourism

Map 1. Areas reporting cholera outbreaks 2010–2014

Source: WHO

Ending Cholera: A Global Roadmap to 2030



2017-2020

Governments establish multi-sectoral institutional coordination mechanisms, supported by partners

OCV rollout integrated with WaSH interventions

Countries update/develop costed multi-sectoral cholera plans with national targets and milestones

june 2017

All partners endorsed the renewed strategy

may 2018

World Health Assembly resolution on cholera

2017 ..... INTERIM MILESTONES 2020

october 2017

4 October / High-level Meeting

WHO and the GTFCC launch the renewed cholera strategy and Roadmap to 2030

New financial and political commitments to end cholera are made

Planning for 2018 WHA cholera resolution

2018

Regional cholera platforms established

Presentation of the cholera roadmap at the SDG6 High-level Political Forum

2019

Cholera Global Roadmap resource mobilisation meeting: presentation of results to date and way forward

Cholera vaccine situation (OCV)

- Significant global burden
- Prequalifies WC, killed OCVs are available for use
- Vaccine safety: Currently available WC, killed OCVs are safe for use including for pregnant women
- Vaccine efficacy and effectiveness: Single dose is efficacious and effective for at least 6 months; two dose is effective for at least 3 years among adults

WHO Recommendations

- **Given the current availability of pre-qualified WC killed oral cholera vaccines (OCV) and data on their safety, efficacy, field effectiveness, feasibility, impact and acceptability in cholera-affected populations, these vaccines should be used in conjunction with other cholera prevention and control strategies:**
  - **in areas with endemic cholera,**
  - **in humanitarian crisis with high risk of cholera,**
  - **during cholera outbreaks.**

(contd.)

- **Vaccination should be done in synergy with other activities such as appropriate case management, WaSH interventions, surveillance and community mobilization, which remain cornerstones for cholera control.**

- **Mass vaccination campaigns are usually the most practical option for delivering OCV. Schools, religious institutions and other community settings can be appropriate venues for vaccination campaigns using fixed sites.**
  - **Campaigns should be accompanied by WaSH interventions.**

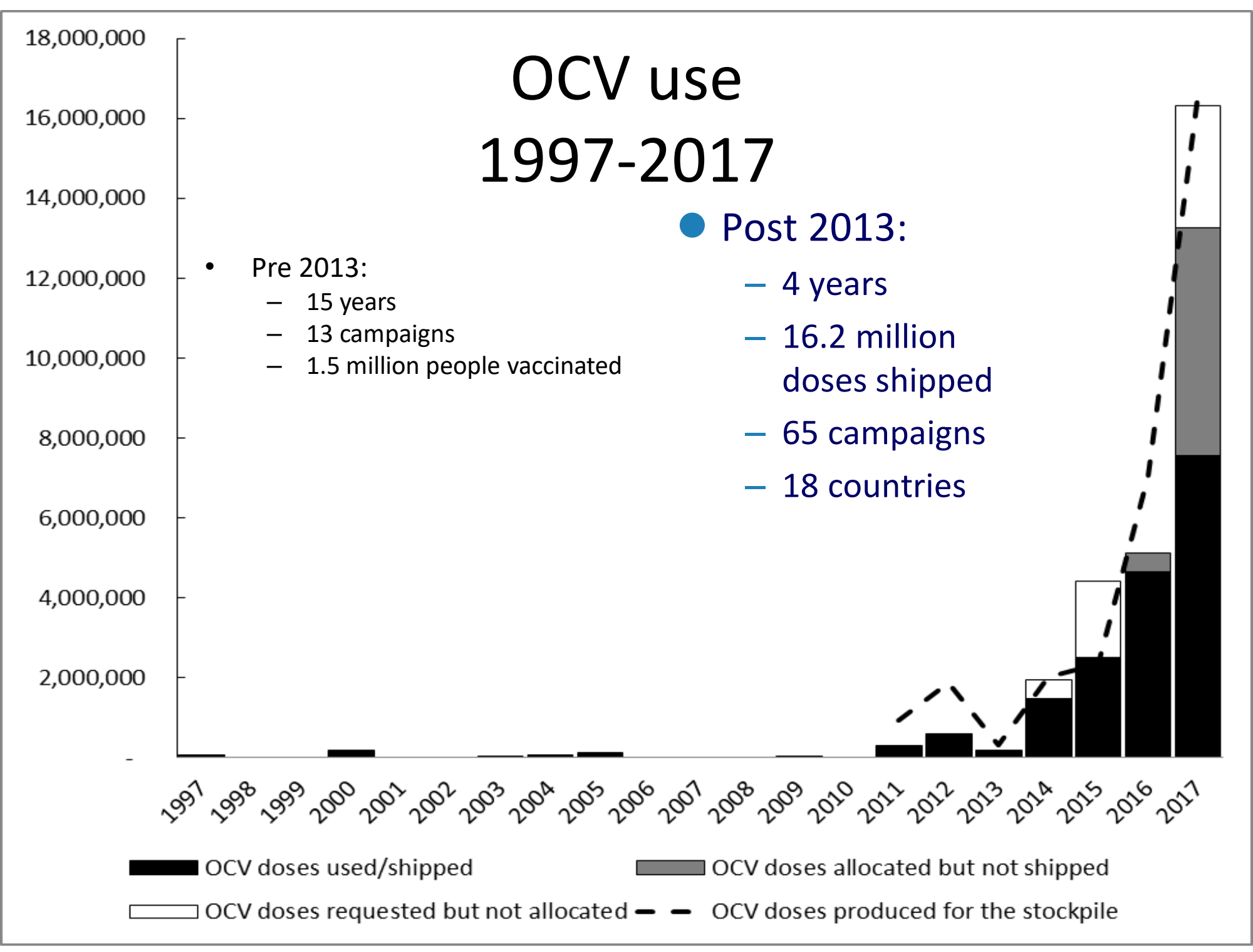
WHO position

- Epidemiological and laboratory surveillance is essential to estimate the burden of disease and understand the impact of vaccination and other interventions.
- A stockpile has been in operation since 2013 to ensure that underserved populations have equitable access to OCVs for use in both emergency response and endemic settings.
- Requests to access OCV in any setting should follow the established mechanisms for stockpile management.

OCV use 1997-2017

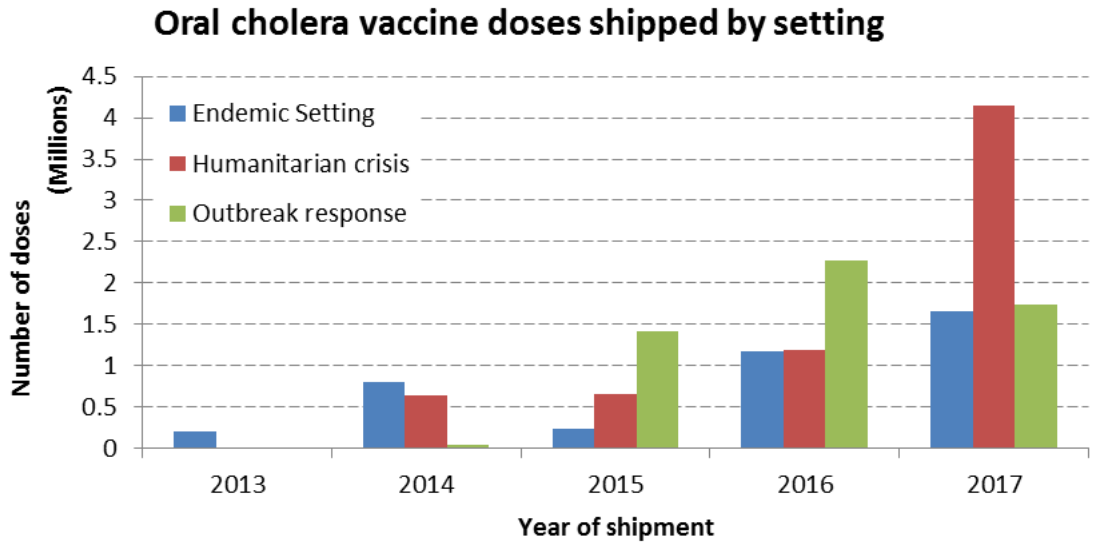
- Pre 2013:
  - 15 years
  - 13 campaigns
  - 1.5 million people vaccinated

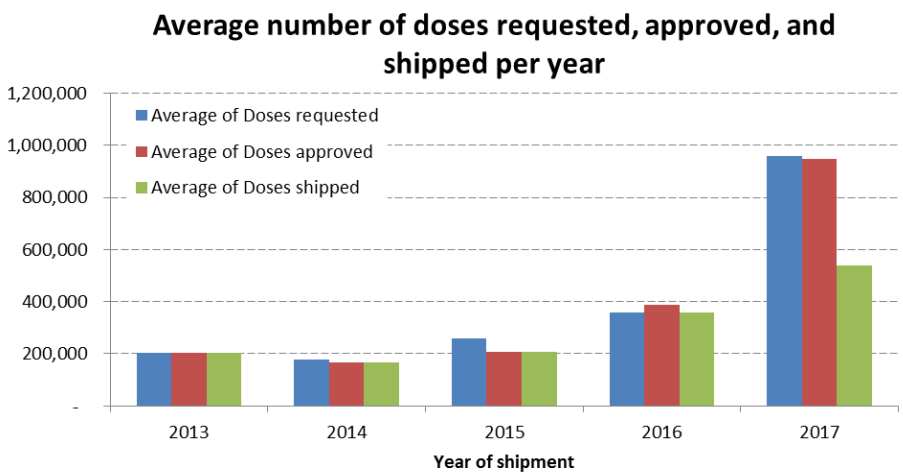
- Post 2013:
  - 4 years
  - 16.2 million doses shipped
  - 65 campaigns
  - 18 countries

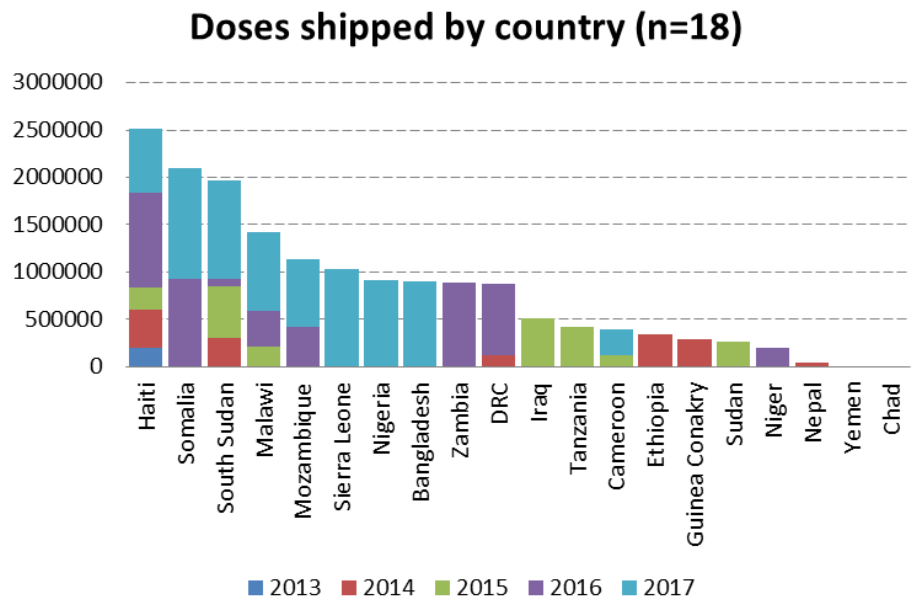


OCV deployments from the stockpile (as of 11 October 2017)

Year	No of doses	%
2013	204,500	1.26
2014	1,486,215	9.17
2015	2,302,775	14.21
2016	4,645,345	28.67
2017 (Oct)	7,562,215	46.68
TOTAL	16,201,050	100.0







GLOBAL CHOLERA STOCKPILE

UNICEF SD PROCUREMENT

EMERGENCY STOCK

Includes at least 1 million* doses locked AT ALL TIMES to respond to emergencies

Decisions from the International Coordinating Group (ICG) on vaccine provision for cholera control (IFRC/MSF/UNICEF/WHO)
http://www.who.int/cholera/vaccines/ocv_stockpile_2013/en/

Within 2 working days

NON EMERGENCY RESERVE

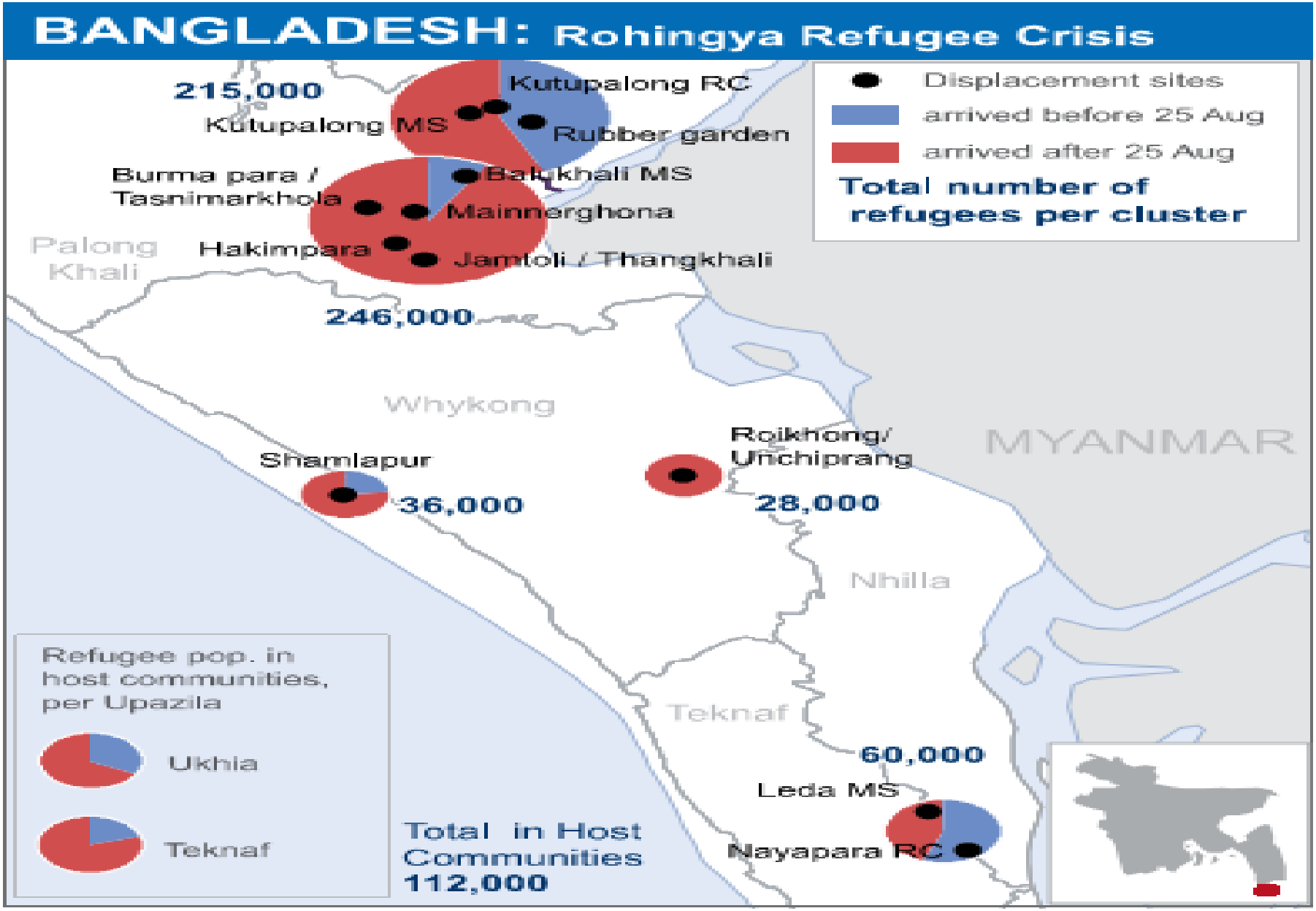
To control endemic cholera in "hotspots"

Decisions from the OCV Working Group of the Global Task Force on Cholera Control (GTFCC)
http://www.who.int/cholera/task_force/en/

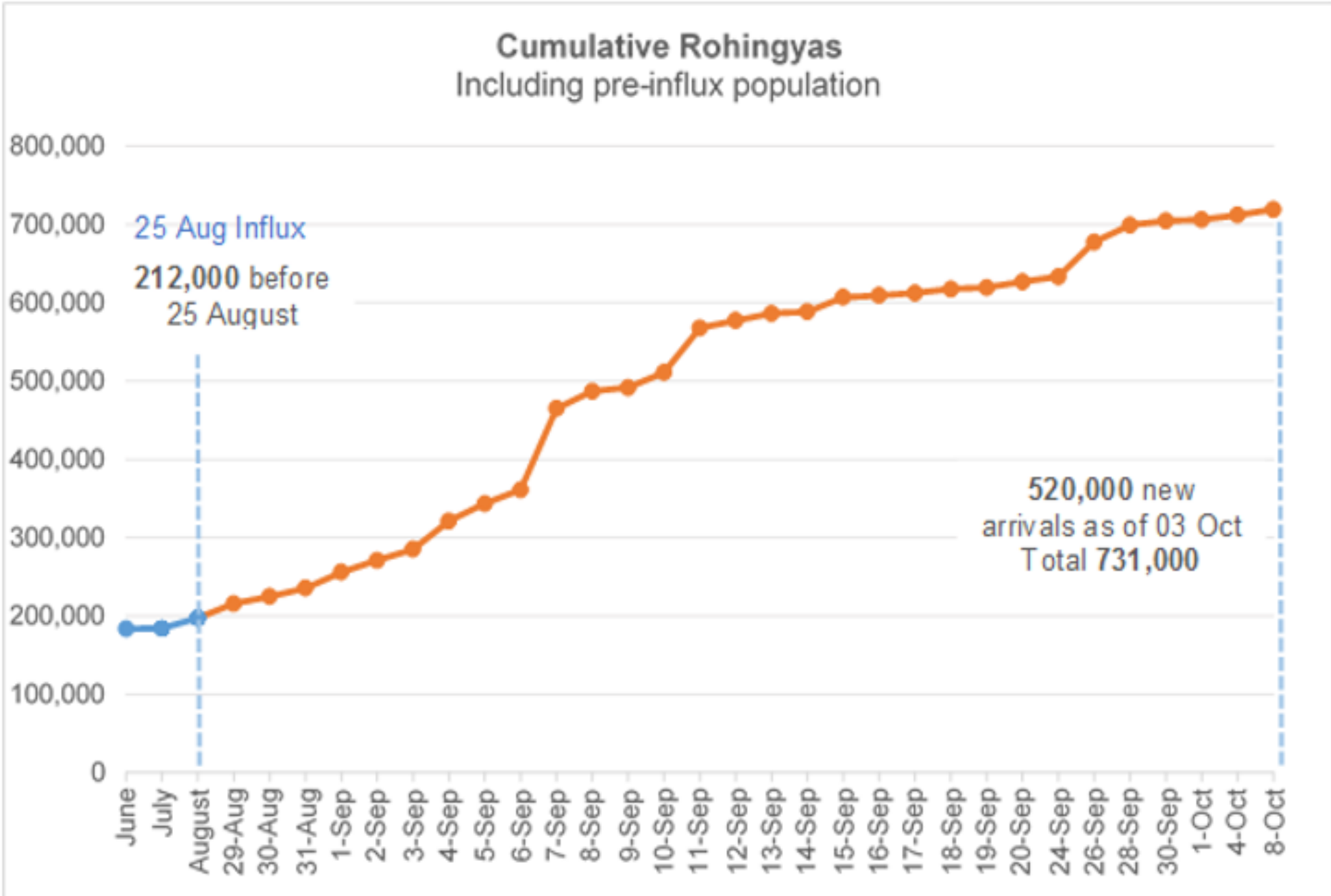
Within 2 weeks

* Flexibility around the remaining available doses for use as needed in emergency and/or non-emergency settings

Vaccine	Dukoral	ORC-Vax and mORC-Vax	Shanchol	Euvichol
Manufacturer	Valneva (Lyon, France)	Vabiotech (Vietnam)	Shantha Biotechnics (India) / Sanofi Pasteur	EuBiologics Co., Ltd (Korea)
Description	Monovalent inactivated vaccine	Bivalent (serotypes O1 & O139) inactivated vaccine	Bivalent (serotypes O1 & O139) inactivated vaccine	Bivalent (serotypes O1 & O139) inactivated vaccine
Components	Killed whole-cells of *V. cholerae* O1 (Classical and El Tor biotypes) and recombinant B-subunit of cholera toxin	Killed whole cells of *V. cholerae* O1 (Classical and El Tor biotypes) and *V.cholerae* O139	Killed whole cells of *V. cholerae* O1 (Classical and El Tor biotypes) and *V. cholerae* O139	Killed whole cells of *V. cholerae* O1 (Classical and El Tor biotypes) and *V. cholerae* O139
Recommended age	2 years and older	1 year and older	1 year and older	1 year and older
Delivery	Oral	Oral	Oral	Oral
Doses	2 given ≥1 week apart	2 given ≥2 weeks apart	2 given ≥2 weeks apart	2 given ≥2 weeks apart
Buffer solution	Buffer dissolved in 75 ml (2-6 years old) or 150 ml (>6 years old) water	Not required	Not required	Not required
Booster dose	Every 2 years (every 6 months for children 2-5 years)	Every 3 years	Every 3 years (more research needed)	Every 3 years (more research needed)
Licensure	International (1991)	Vietnam (1997/2009)	India (2009)	Korea (2015)
WHO pre-qualification	Yes (2001)	No	Yes (2001)	Yes (2015)
Public sector price (per dose, USD)	$5	$1.25	$1.85	$1.85
Storage temperature	2 to 8 ℃	2 to 8 ℃	2 to 8 ℃	2 to 8 ℃
Packaging	Single dose 3 ml/vial, 2 doses per package	Single dose 1.5 ml/vial and multiple dose vial (5 doses per vial)	Single dose 1.5 ml/vial	Single dose 1.5 ml/vial



Map Sources: UNCS, ISCG, -- UMN: Undocumented Myanmar National
The boundaries and names shown and the designations used on this map do not imply official endorsement or acceptance by the United Nations. Map created on 08 Oct, 2017


Cumulative Rohingyas
Including pre-influx population
800,000
700,000
600,000
500,000
400,000
300,000
200,000
100,000
0
25 Aug Influx
212,000 before 25 August
520,000 new arrivals as of 03 Oct
Total 731,000
June
July
August
29-Aug
30-Aug
31-Aug
1-Sep
2-Sep
3-Sep
4-Sep
5-Sep
6-Sep
7-Sep
8-Sep
9-Sep
10-Sep
11-Sep
12-Sep
13-Sep
14-Sep
15-Sep
16-Sep
17-Sep
18-Sep
19-Sep
20-Sep
24-Sep
26-Sep
28-Sep
30-Sep
1-Oct
4-Oct
8-Oct

OCV campaign in Cox's Bazar, Bangladesh

Second largest OCV campaign in the World!!

- Following violence in Myanmar, >520,000 refugees reached Cox's Bazar since 25 August, 2017
- Poor living conditions, overcrowding, lack of sanitation
- Joint assessment for the risk of a large cholera outbreak has been conducted among stakeholders including WHO, IOM, UNICEF and icddr,b
- The report concluded a high risk of a large outbreak
- Request made by DGHS to ICG for OCV was approved within 24 hrs following submission
- Vaccines arrived in country on 7th October
- Campaign started on 10th October
- **As 15th October, 555,619 already been vaccinated -84.39% (658,371)**

In 2018 the Gavi Alliance Board will decide on future funding for new vaccines and vaccination approaches

Potential candidate investments ('long list')

Incremental investments

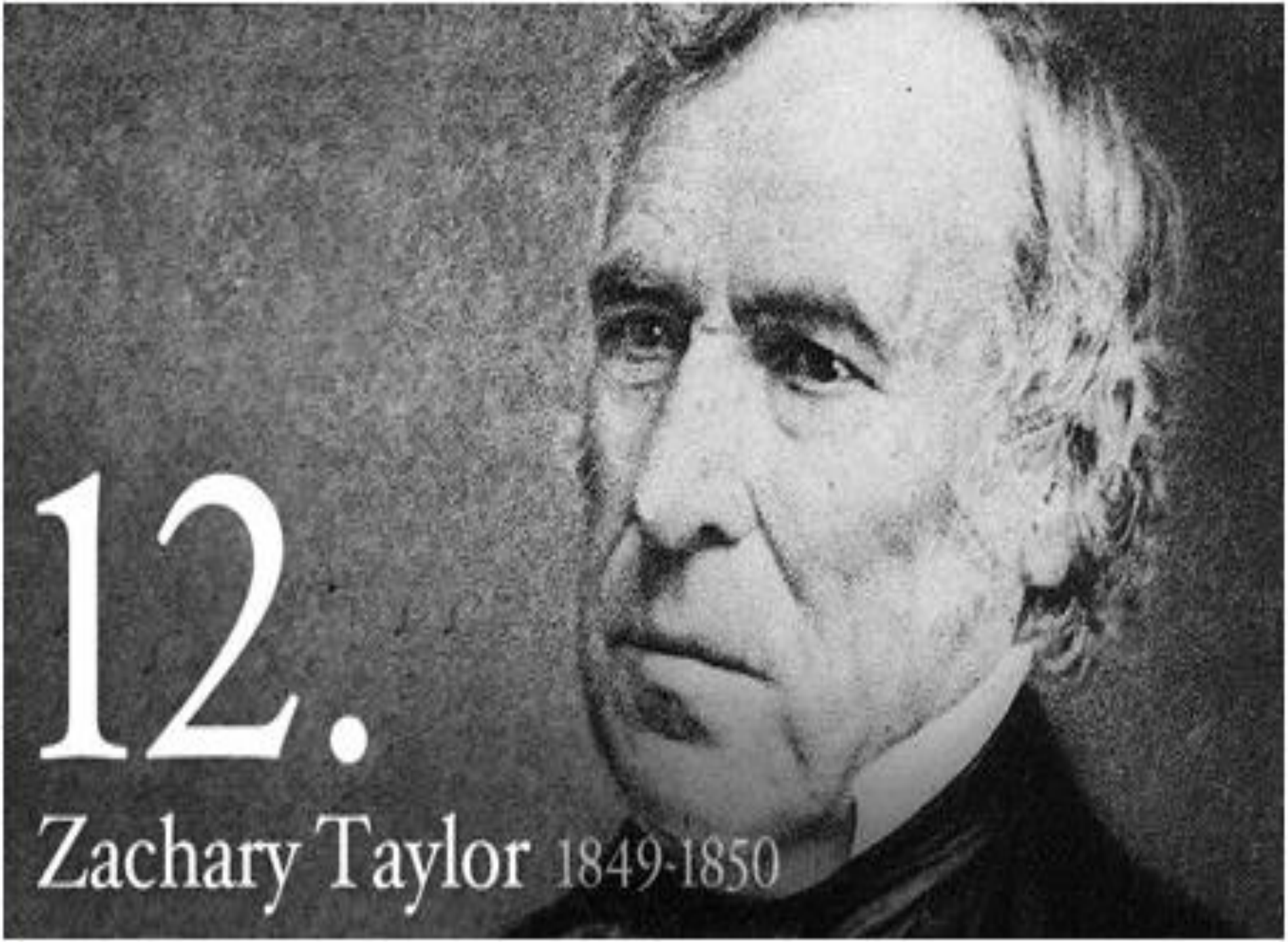
- OCV endemic*
- Mening B, C, W, X, Y, Z
- Hep B birth dose
- PCV catch-up
- Ebola*
- TT/TD*

Already licenced

- Dengue
- Influenza
- Rabies PEP
- Hepatitis E
- Malaria
- Acellular pertussis

Under development

- RSV
- Group B strep
- Norovirus
- ETEC
- Zika


12.
Zachary Taylor 1849-1850

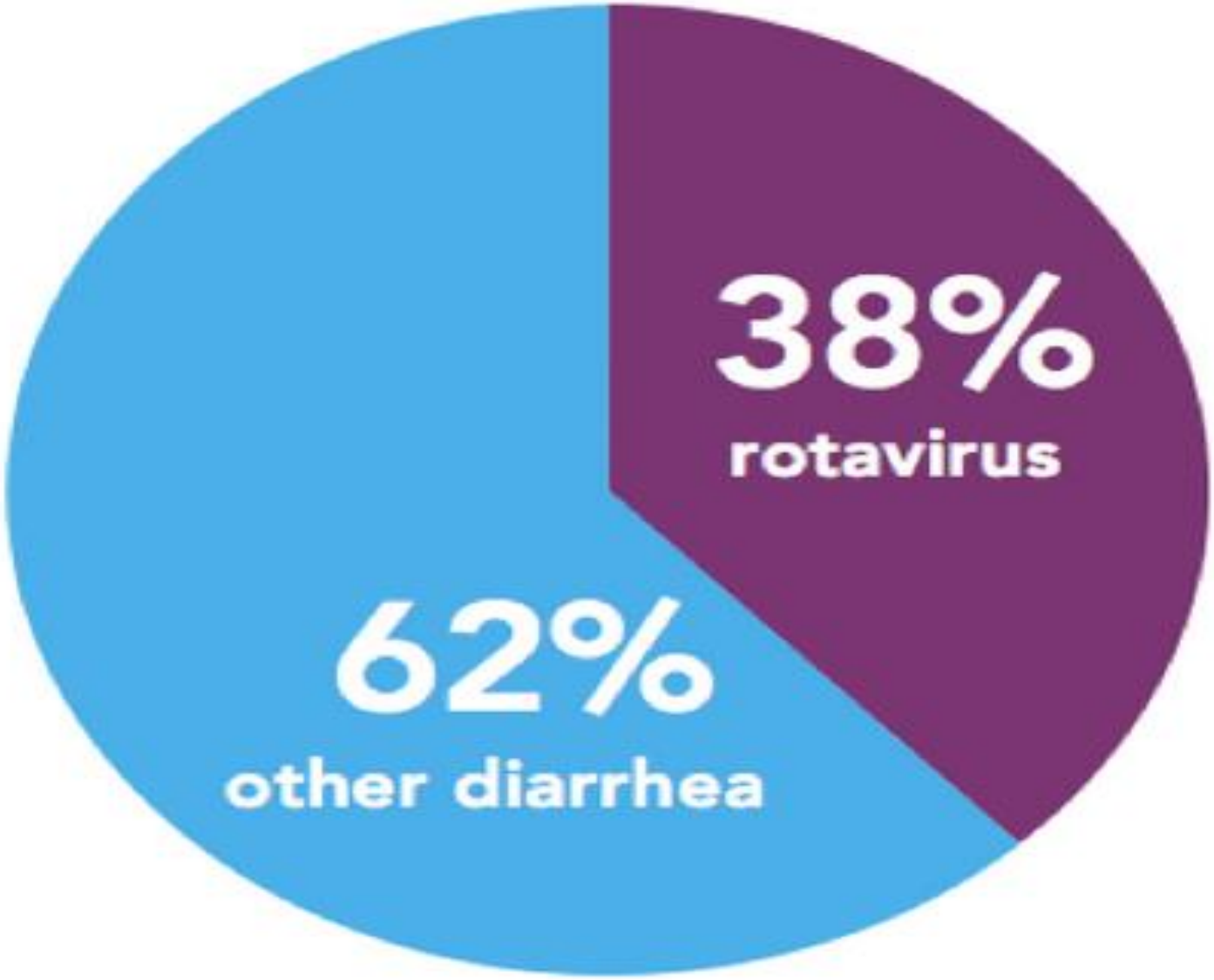
Rotavirus, key facts

- Diarrhea is one of the world's leading causes of child illness and death, and rotavirus is the most common cause of severe diarrhea.
- Each year, rotavirus kills about 200,000 children in countries around the world, and hospitalizes hundreds of thousands more.
- 2 out of every 5 diarrhea-related hospitalizations among children under age five are caused by rotavirus – it is NOT your typical "stomach bug" or "flu." Preventing illness in the first place is critical.
- The WHO recommends that all countries introduce rotavirus vaccines into their national immunization programs.
- There are two WHO-prequalified, orally administered rotavirus vaccines available today: Rotarix, manufactured by GlaxoSmithKline, and RotaTeq, manufactured by Merck & Co., Inc.
- Rotavirus vaccines are already saving lives and improving health in countries where they are in use, and are essential to a comprehensive approach to preventing and treating diarrhea.
- Rotavirus vaccines have been shown to provide broad protection, even against strains not included in the vaccine.
- Rotavirus vaccines are projected to be highly cost-effective, particularly in regions suffering from the highest levels of rotavirus mortality.
- Despite the WHO recommendation, 94 million infants still do not have access to this critical intervention.


In 2013, rotavirus killed 215,000
young children worldwide.

Global Hospitalization Rates

Figure: Global diarrhea hospitalizations for children under 5[3, 4]



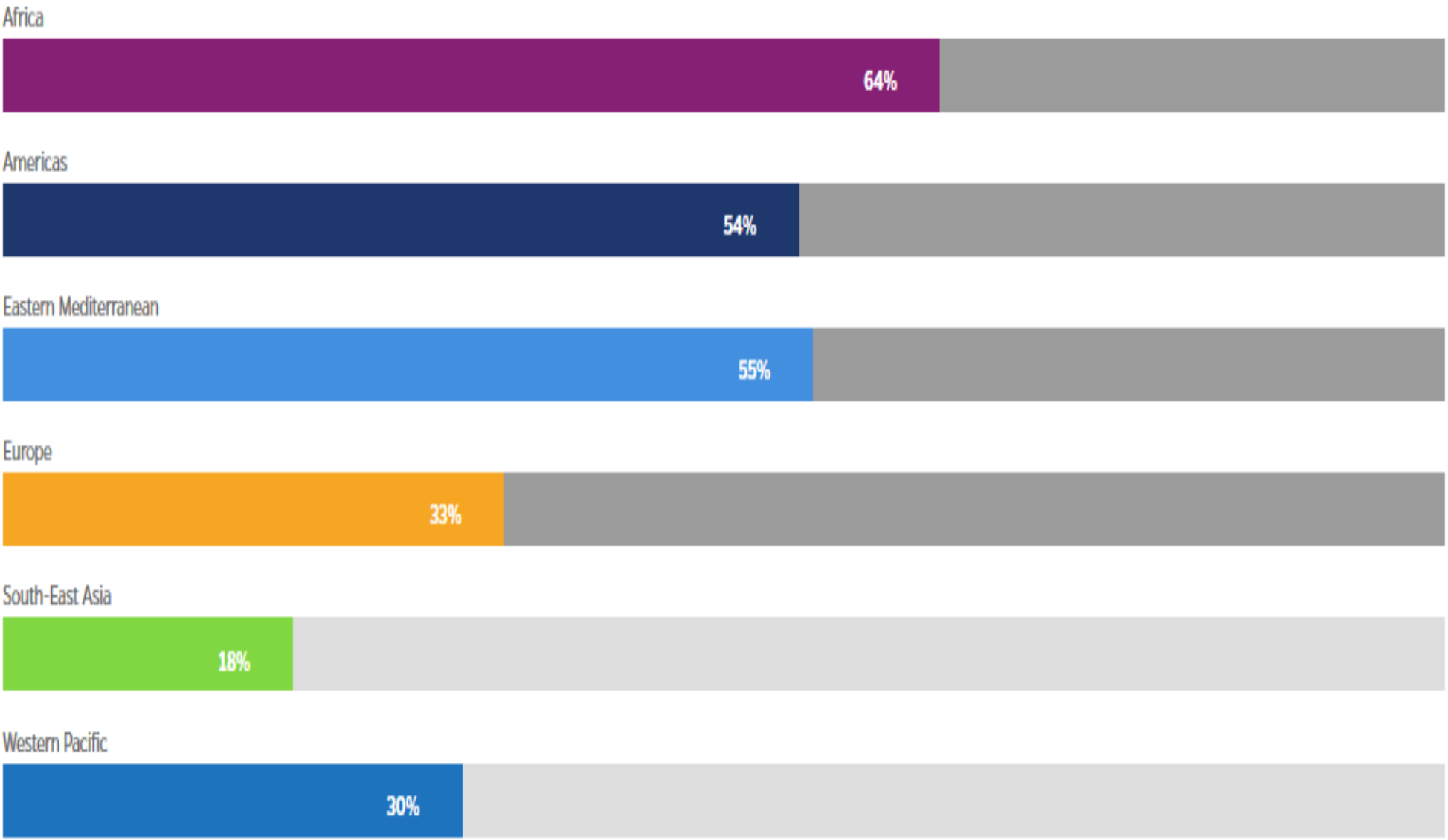
Current products: Two vaccines licensed for global use (cont.)

VACCINE	Rotarix™	RotaTeq®
DOSAGE	At least 10^6 of live attenuated human G1P[8] particles per dose	A minimum titer of approximately 2.0 to 2.8 x 10^6 infectious units per reassortant and not greater than 116 x 10^6 infectious units per aggregate dose
SCHEDULE	2-dose Given on same schedule as DPT1 and 2 vaccine doses	3-dose Given on same schedule as DPT1,2, and 3 vaccine doses
PRESENTATION	1. Liquid vaccine in oral, single-dose applicator 2. Liquid vaccine in squeezable, polyethylene single-dose tube 3. Lyophilized vaccine, reconstituted with $CaCO_3$ buffer, oral applicator	Liquid vaccine in oral squeezable tube
SHELF-LIFE	36 months	24 months

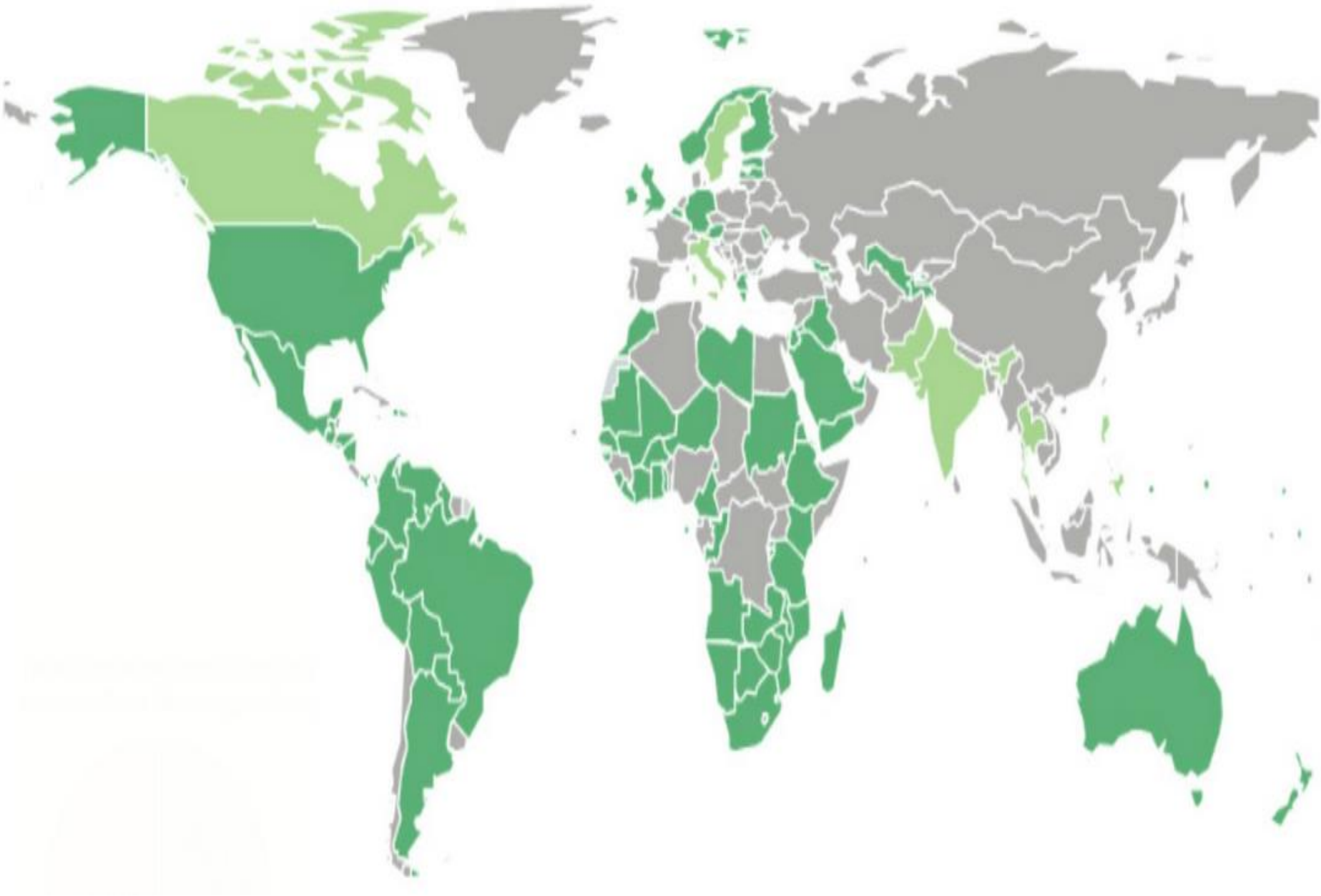
Nationally available vaccines and upcoming products

VACCINE	NAME	COMPANY	STATUS	STRAIN(S)
Indian neonatal (bovine-human reassortant)	ROTAVAC® 116E	Bharat Biotech (India) and Department of Biotechnology (GOI) in collaboration with US partners (PATH, NIH, CDC, Stanford)	Licensed in India. Began phased introduction in 2016 in 4 states: Odisha, Himachal Pradesh, Haryana, Andhra Pradesh. Awaiting WHO prequalification.	G9, P[11]
Australian neonatal	RV3	Biofarma (Indonesia) and MCRI (Australia)	Early clinical trials ongoing in New Zealand and Indonesia	G3, P[6]
NIH (bovine-human reassortant)	UK	Licensed to various manufacturers: Wuhan & Chengdu (China), SSI, Shantha, Biologicals E, Bharat (India), Butantan (Brazil)	Serum Institute and Shantha vaccines undergoing Phase 3 clinical trials	Bovine (G6P[7]) + G1, G2, G3, G4 reassortants
Vietnamese	Rotavin M1	POLYVAC	Licensed in Vietnam	G1P[8]
Lamb rotavirus (lamb-human reassortant)	LLR LLR+	Lanzhou Biologicals / Xinkexian Biological Technology (China)	Licensed in China	G10, P[12] + G1, G2, G3, G4

Proportion of Countries with Rotavirus Vaccine in each WHO Region



Current Rotavirus Vaccine Introduction Map



Typhoid

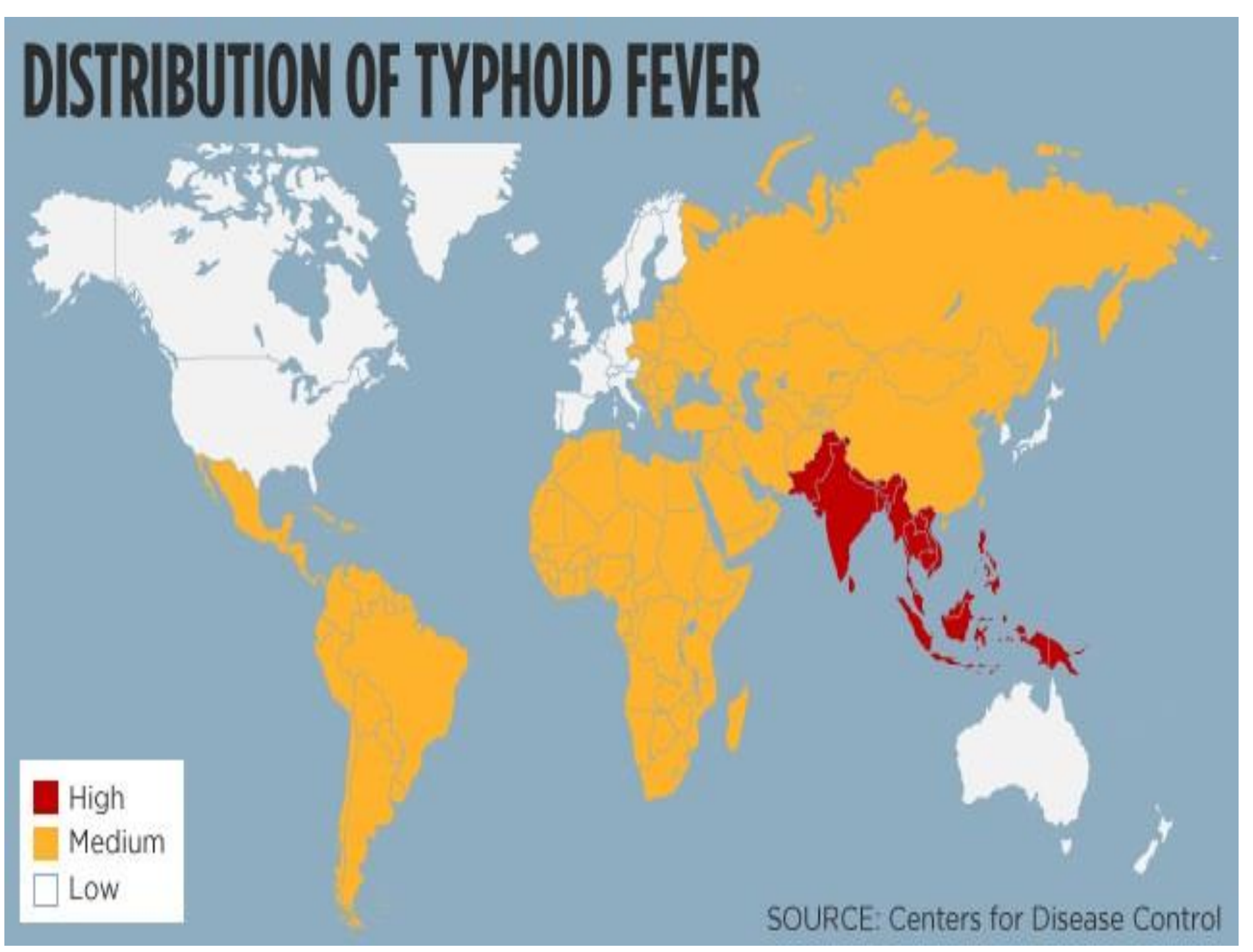
Global estimate of disease burden ranging between 11 and 12 million typhoid fever cases;

Approximately 145 000 to 161 000 deaths annually;

A large portion of disease occurring between 6 months and 2 years of age;

Increasing frequency of outbreaks of MDR strains of S. Typhi;

The UN SDGs provide a relevant framework within which control through integration of vaccination with other interventions


DISTRIBUTION OF TYPHOID FEVER
High
Medium
Low
SOURCE: Centers for Disease Control

Prevention of typhoid fever by Vaccines

Vaccination as a public health tool and as a short term preventive mechanism

Live attenuated oral Ty21a (Vivotif) enteric coated vaccine:

vaccine recommended for those >5 years

Vi capsular polysaccharide vaccine:

Vi polysaccharide given as a single IM dose & is contraindicated in children <2 years. A booster dose is required every two years

Conjugated Vi PS (TCV):

a) Typbar-TCV, BBIL b) PedaTyph-BMPL

Undergoing Licensure review By NRA

1. Vi conjugate vaccine: Vi-rEPA, a conjugate of the capsular polysaccharide of *Salmonella typhi,* Vi, bound to nontoxic recombinant *Pseudomonas aeruginosa* exotoxin A [rEPA]

2. Vi-DT conjugate vaccine: Diphtheria toxoid conjugated with Vi polysaccharide

Challenges

- Some countries are not reporting cholera cases to WHO even though it is categorized as endemic country fearing embargoes or similar restrictions on trade and travel
- Inadequate surveillance in certain countries ??
- Economic reasons
- Competing priorities
- Implementation strategies

Country's capacity to introduce new vaccines

- ✓ Extensive involvement of policy makers and technical experts
- ✓ Updating guidelines, National and district level advocacy meetings, trainings etc.
- ✓ Effective vaccine management
- ✓ Cold chain capacity
- ✓ Budget allocation for new vaccine introduction
- ✓ Gavi support and post Gavi era?

Thank you!!