Surveillance of rotavirus gastroenteritis (2015-2017); vital information for pre-and post-rotavirus vaccination in Myanmar

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[1]Department of Medical Research

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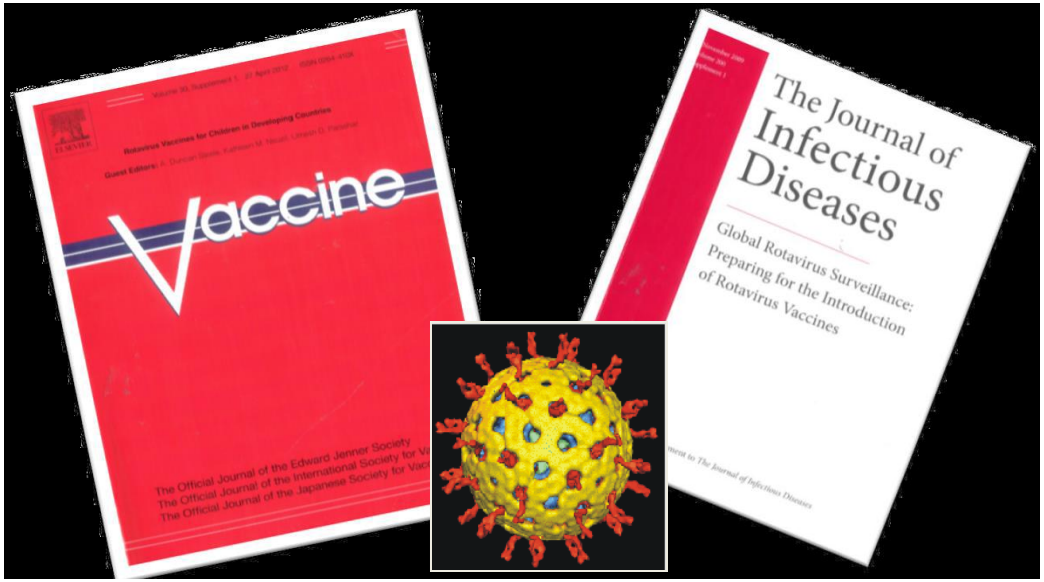
BACKGROUND INFORMATION

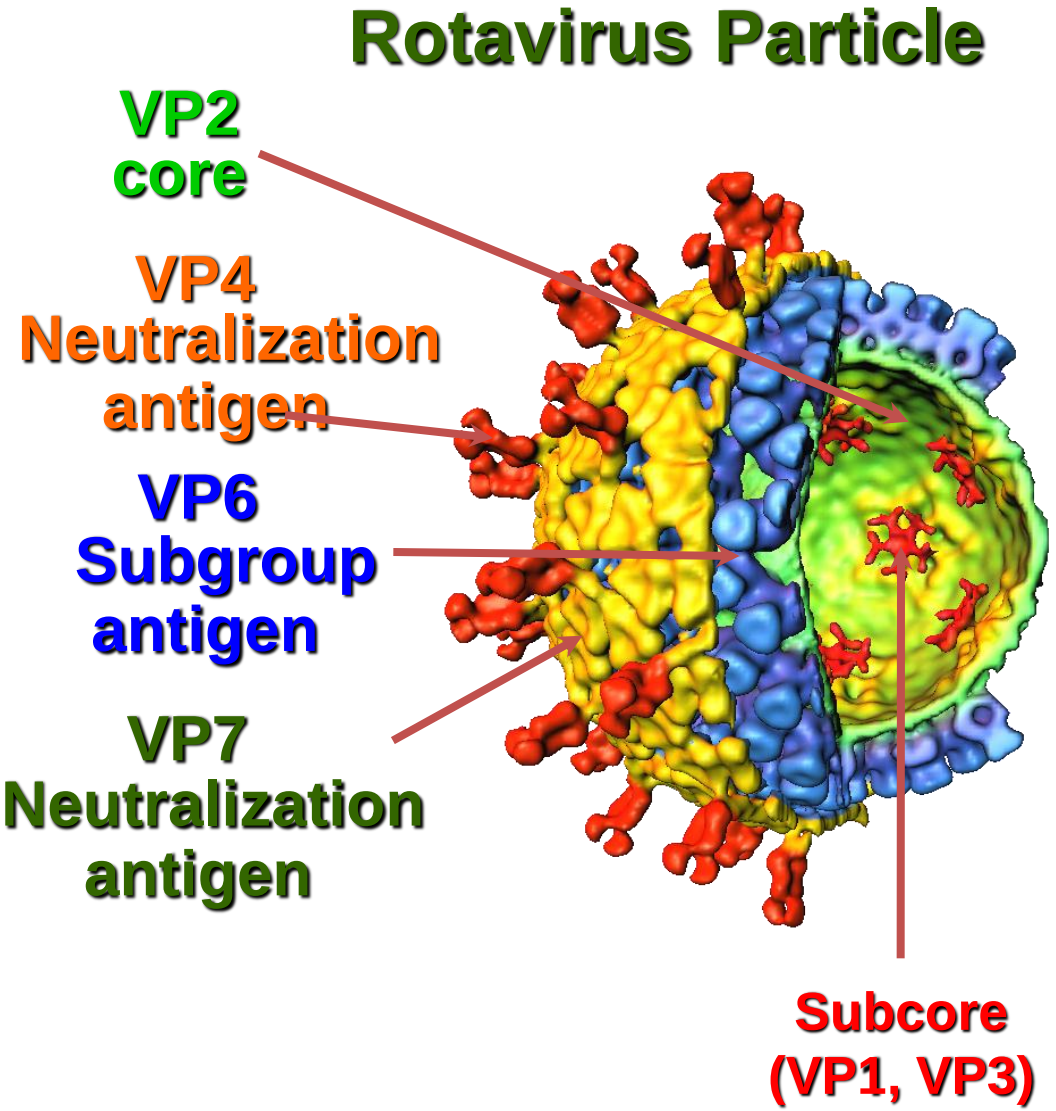
AND

JUSTIFICATION



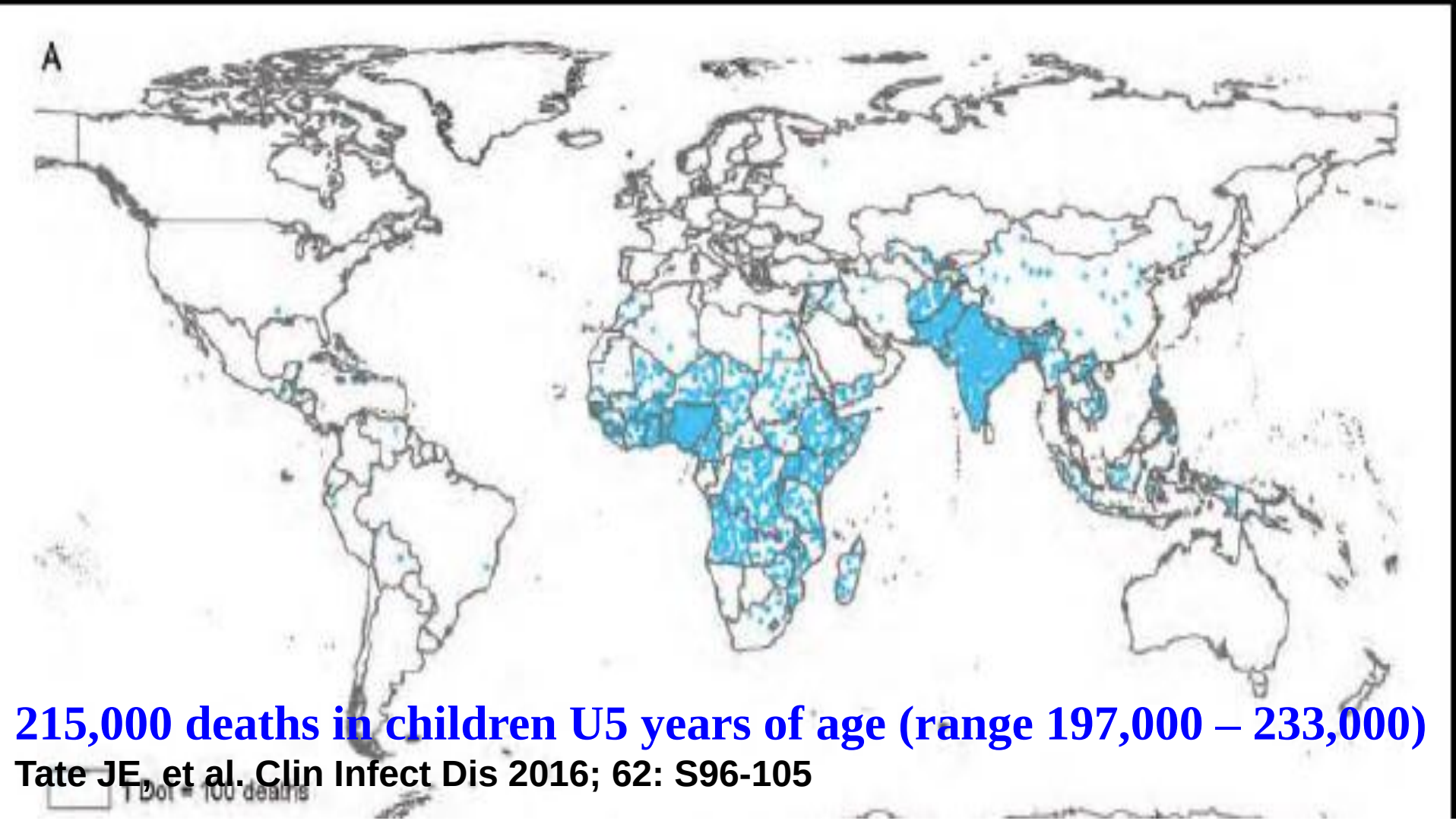
Rotavirus - leading cause of severe diarrhea

- **more than 125 million under five years old children develop RVGE**



Reconstruction courtesy of B. V. V. Prasad, Baylor College of Medicine, Houston, TX. Prasad BVV, et al. Nature. 1996;382:471–473.

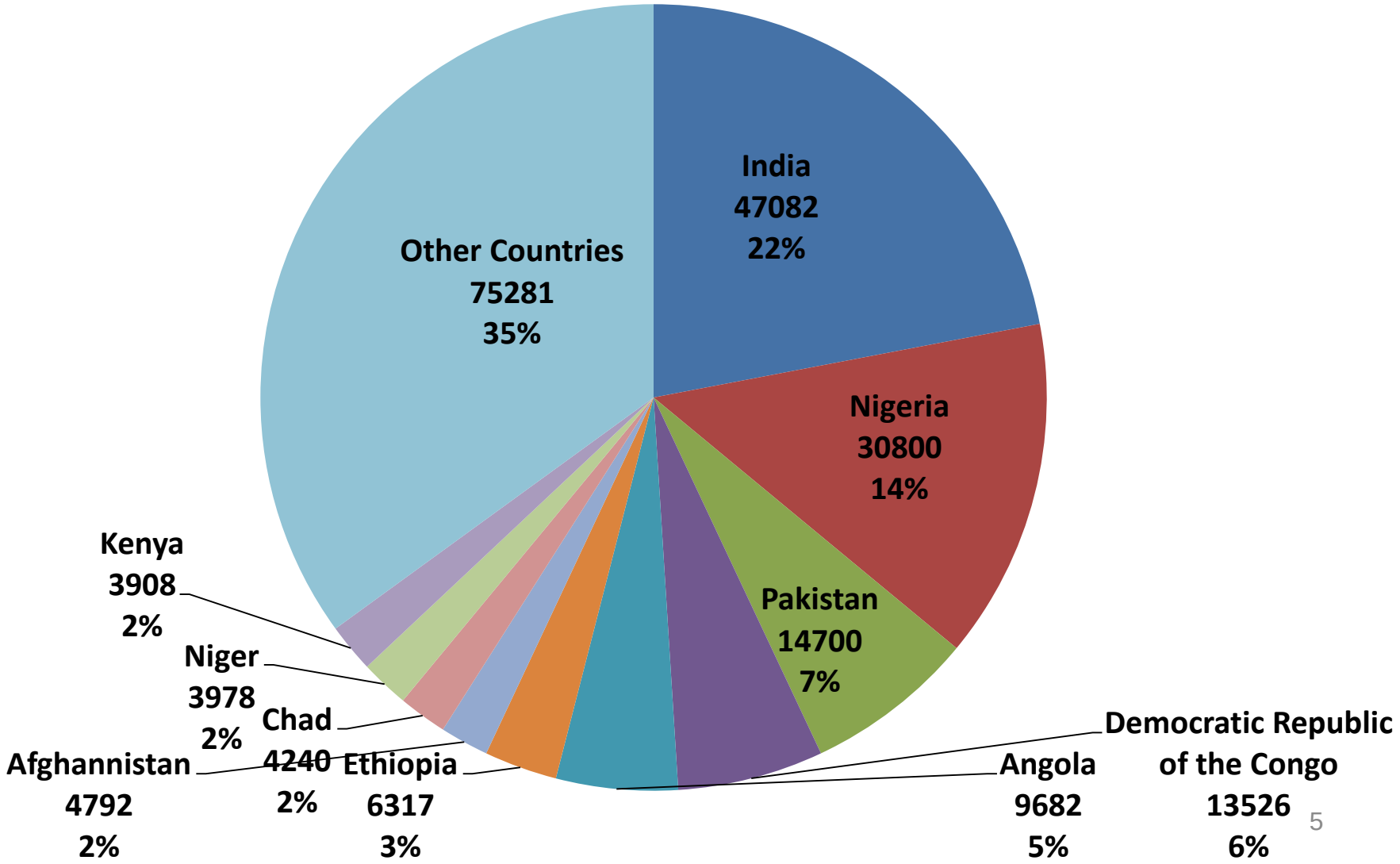
GLOBAL ESTIMATE OF ROTAVIRUS MORTALITY IN YOUNG CHILDREN <5 YEARS OF AGE (2000-2013)



215,000 deaths in children U5 years of age (range 197,000 – 233,000)

Tate JE, et al. Clin Infect Dis 2016; 62: S96-105

Countries with the highest number of rotavirus deaths in young children under-5, 2013



The most effective strategy to reduce burden and mortality of RVGE

↓

Prevention by Vaccination

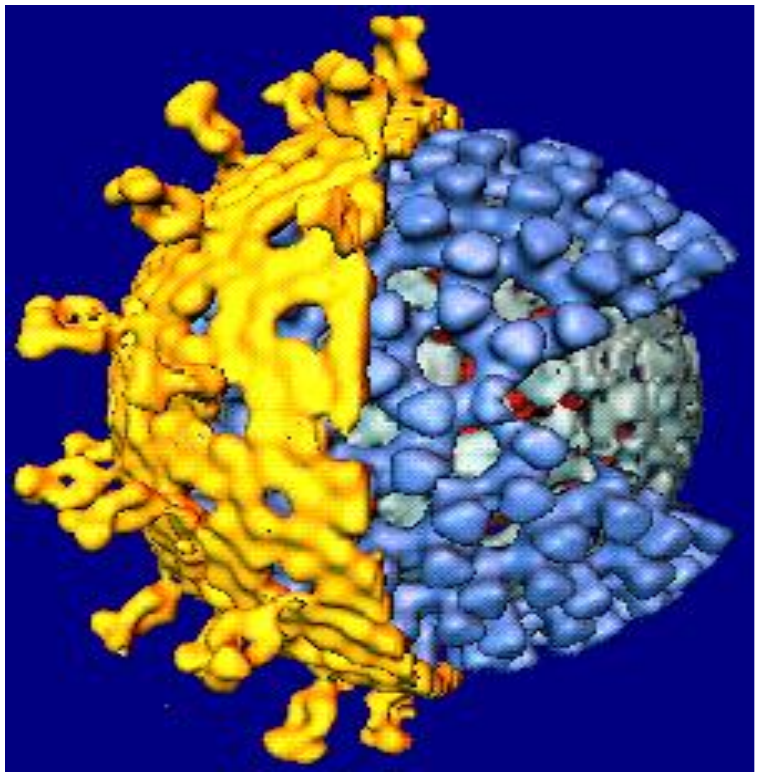
- **Two currently available rotavirus vaccines (RV) with demonstrated efficacy against severe RVGE**

- **Live, attenuated, orally administered vaccines**

- **In use globally**

Rotarix (GSK Bio)

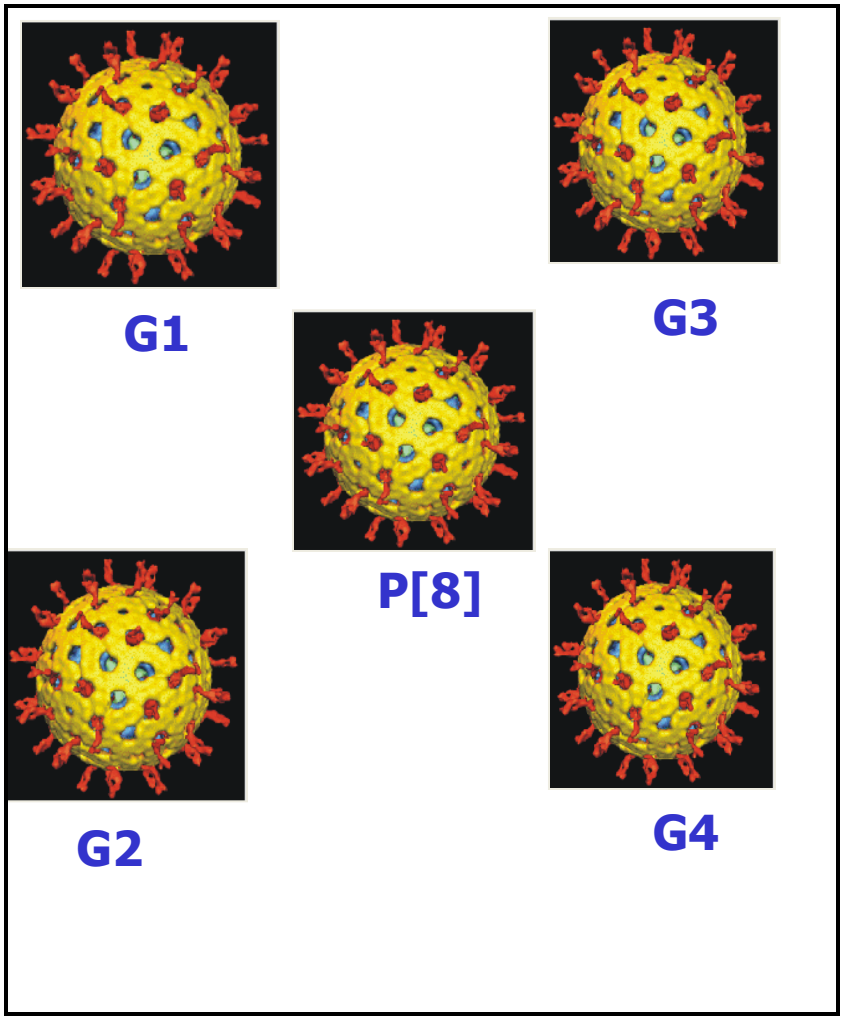
Human rotavirus (Monovalent Vaccine)



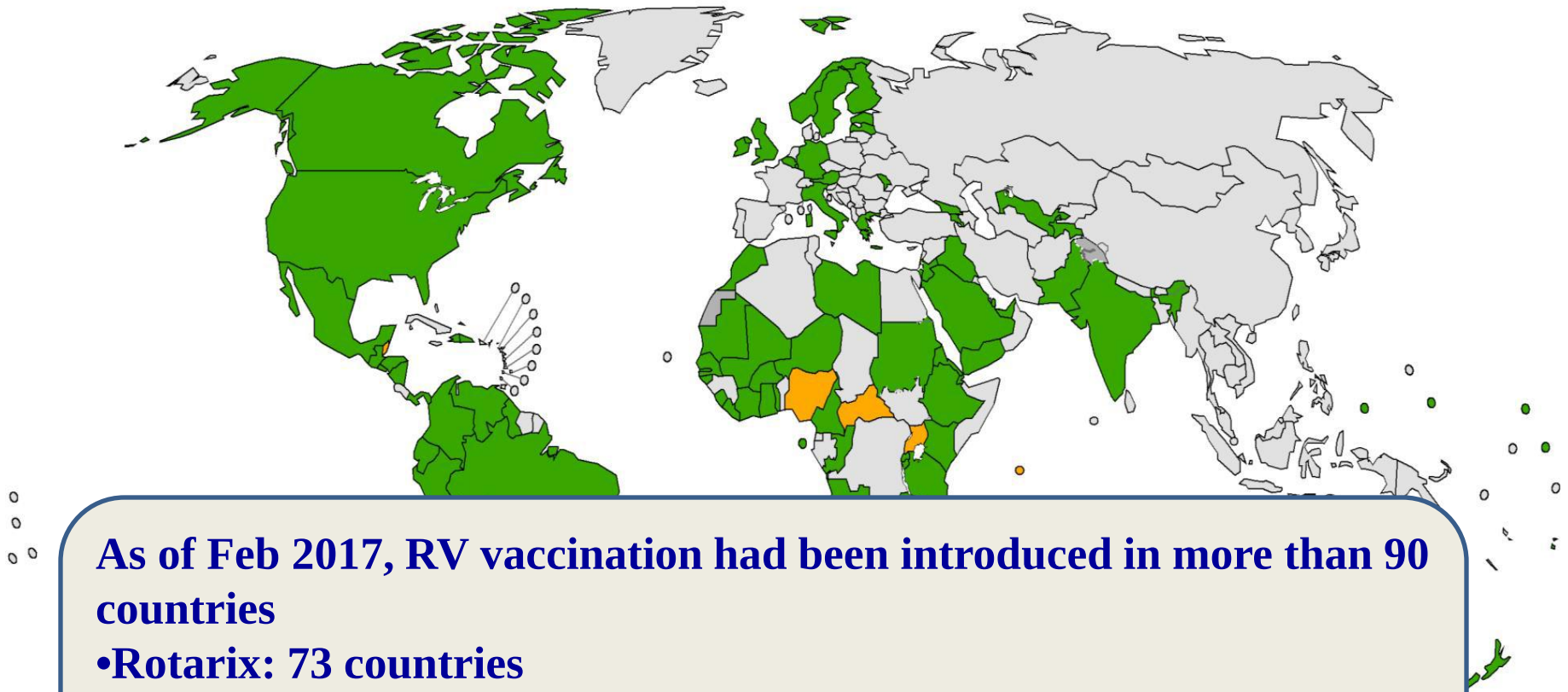
G1P[8]

RotaTeq (Merck)

Bovine rotavirus with single human rotavirus gene substitution (Pentavalent Vaccine)



Countries with rotavirus vaccine in the NIP; and planned introductions in 2017



As of Feb 2017, RV vaccination had been introduced in more than 90 countries

- **Rotarix: 73 countries**
- **RV5 : 17 countries**
- **Both : 6 countries**
- **Rotavac: 1 partially India**

Data source: WHO/IVB Database, as of 09 August 2017 Map production Immunization Vaccines and Biologicals (IVB), World Health Organization

- **Myanmar - diarrhea is among the priority childhood diseases according to the National Health Plan (2011-2016)**

- **proportion of RVGE among hospitalized <5 year old children with diarrhea at YCH ranged from 42% to 56% during 2009-2014**

Rotavirus Surveillance System

Monitoring of affecting genotypes

- Evaluation of effectiveness of the vaccine

Post-vaccination

Epidemiological Information

- Prevalence
- Age and gender distribution
- Seasonal variation
- Severity of disease
- Circulating genotypes

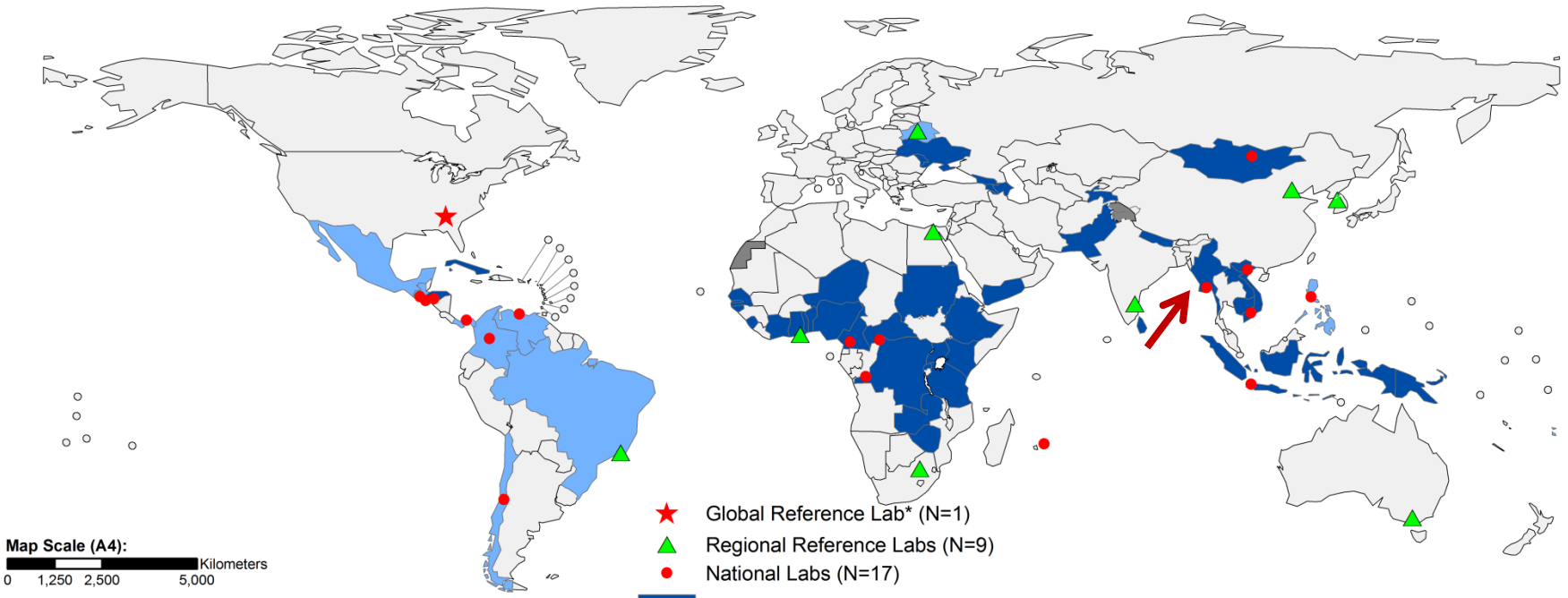
Pre-vaccination

- **“Global Rotavirus Surveillance Network” - coordinated by WHO with partners since 2008**

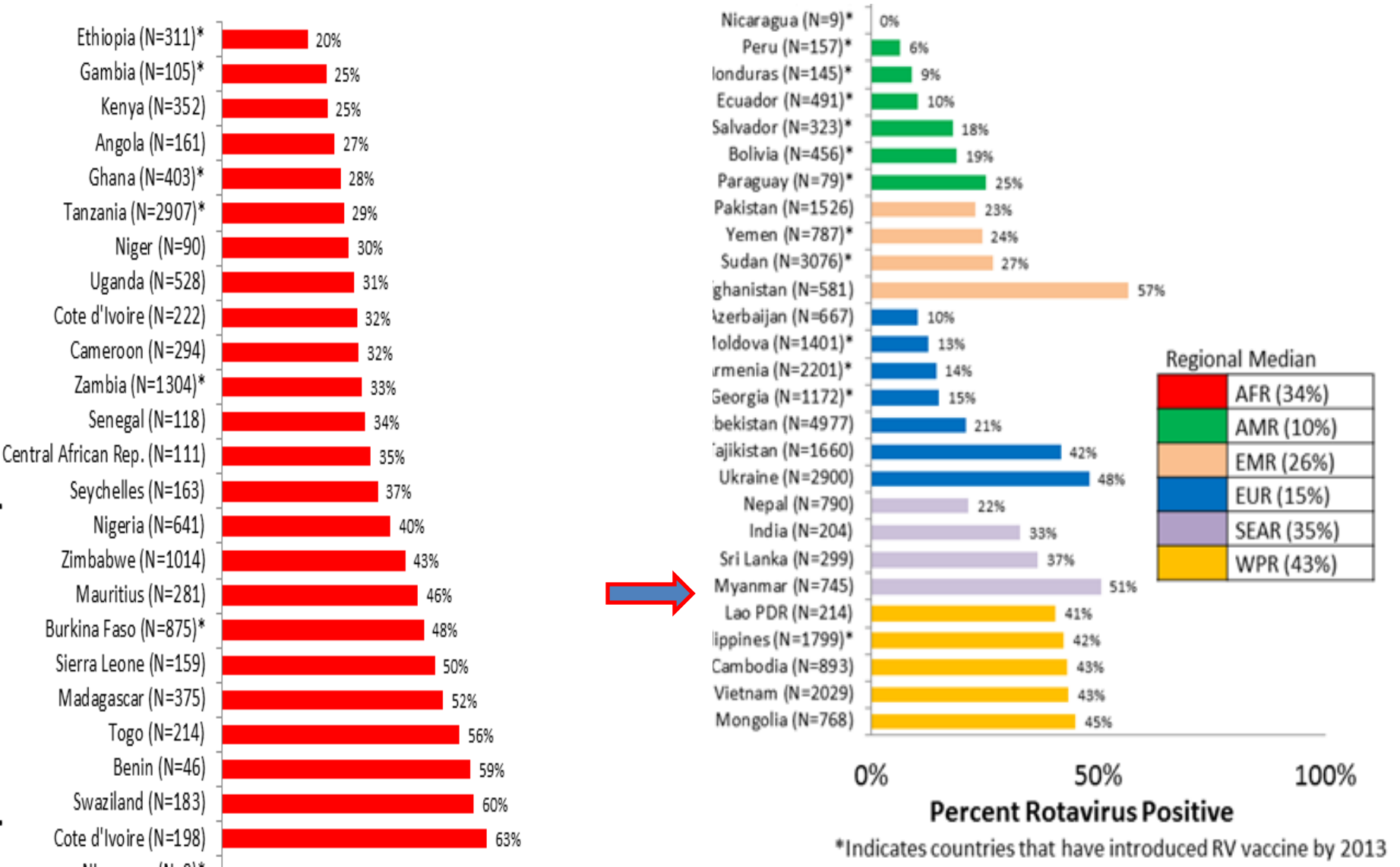
- **Myanmar - member in 2009**

- **Reported data to local WHO office and SEA WHO Regional office quarterly every year**

Global Rotavirus Laboratory Network and countries reporting genotype data



Rotavirus positivity among countries reporting data to GRSN



OBJECTIVES

During the pre-vaccine introduction period

- To describe the disease epidemiology and provide data for estimating disease burden
- To identify circulating genotypes

In the post-vaccine introduction period

- To assess disease trends over time
- To monitor vaccination program impact, vaccine effectiveness and safety evaluation
- To monitor changes in circulating genotypes

MATERIALS

AND

METHODS

- ***Study Design***

  Cross-sectional Descriptive Study

- ***Study Period***

  January 2015 to September 2017

Study population

Inclusion criteria:

1. Age: 0-59 months
2. Sex: Both males and females
3. Presenting with acute diarrhoea of any severity of dehydration

   (AGE: passage of 3 or more loose or liquid stool per day or more frequently than is normal)

   (WHO,2013)

Exclusion criteria:

1. Diarrhoea of more than 14 days before admission and develop 2 days after admission
2. Presence of blood and mucous in the stool

Study Site

Sample Collection - Yangon Children Hospital

(1300 bedded Hospital)

Laboratory Analysis – Virology Research Division

(Department of Medical Research)

Investigational Plan

Assessed for eligibility (Inclusion and Exclusion Criteria)

Obtained informed consent and enrolled in the study

Complete the pro-forma

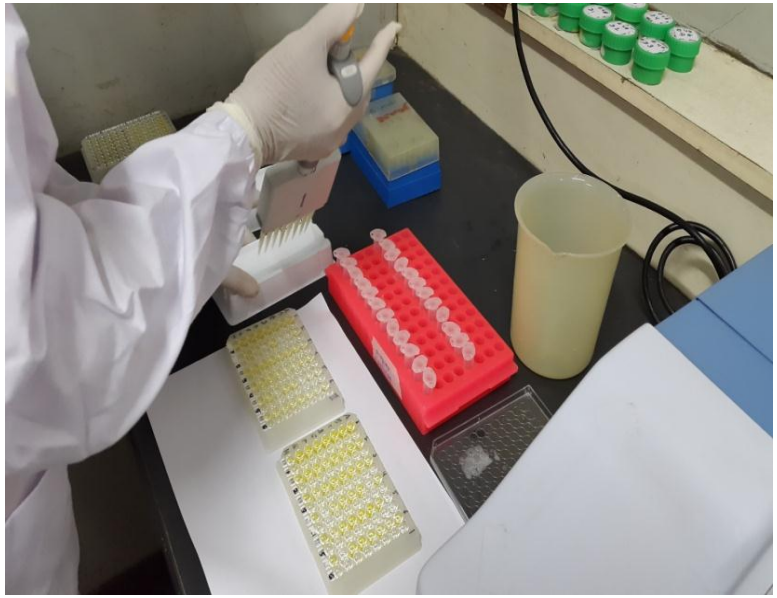
Stool sample collection (~3 ml, wide-mouth screw capped bottle)

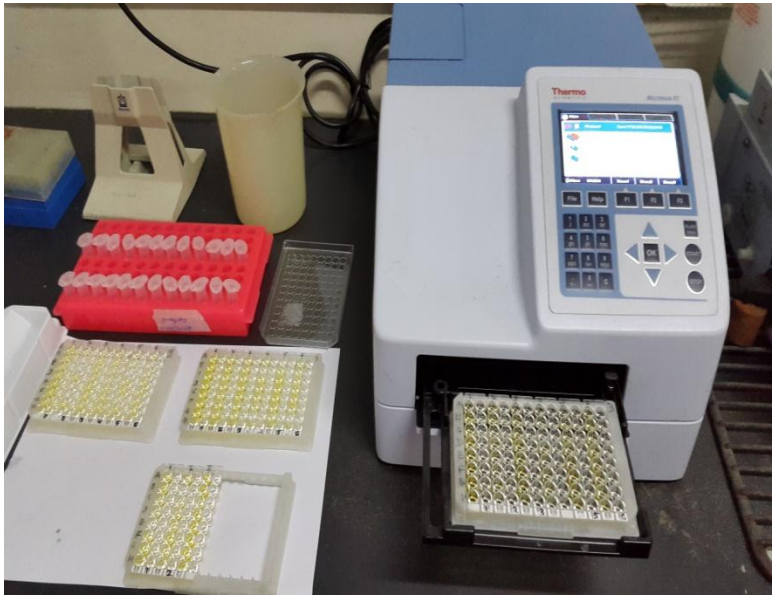
Transport in cold boxes to VRD, DMR

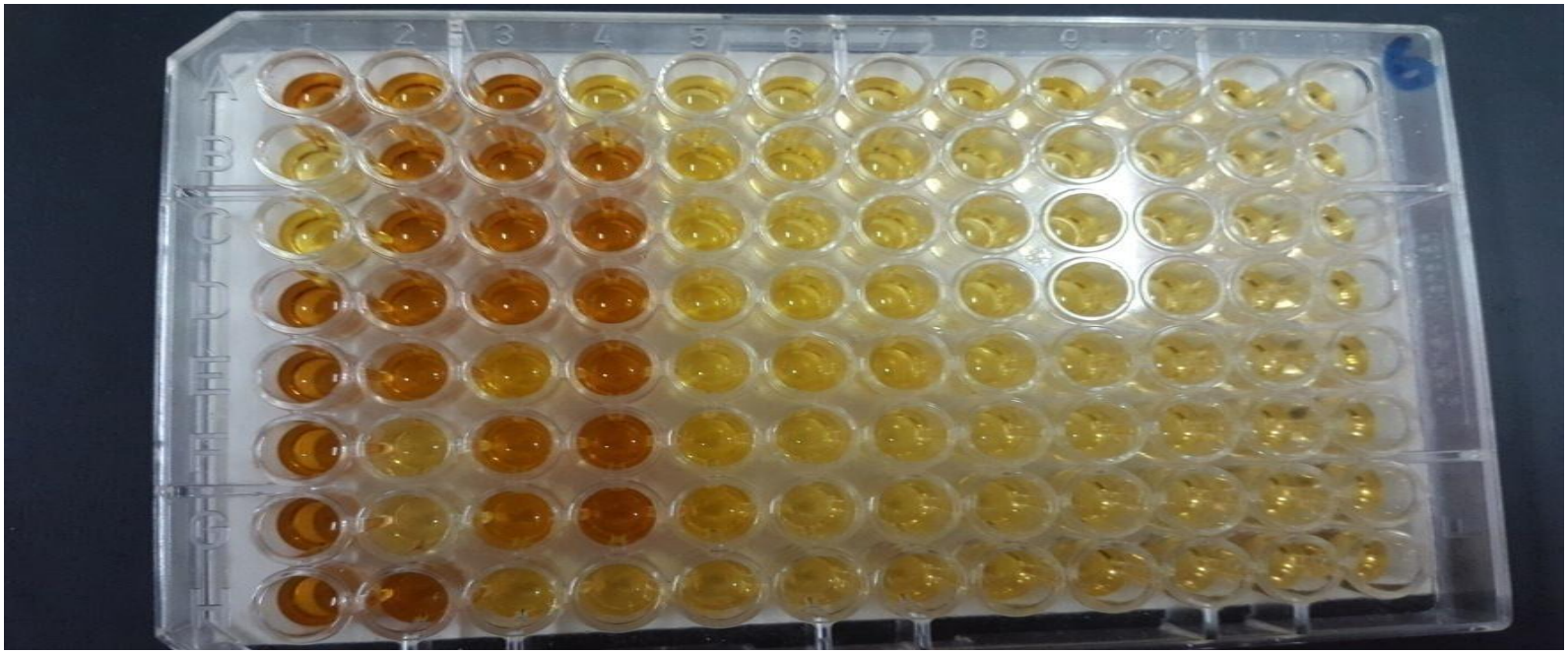
Screening of Rotvirus by ELISA (ProSpecT ™ Rotavirus, Oxoid Ltd, UK)

G and P Genotyping by RT-PCR (1/3 of Rotavirus positive samples with high OD value)

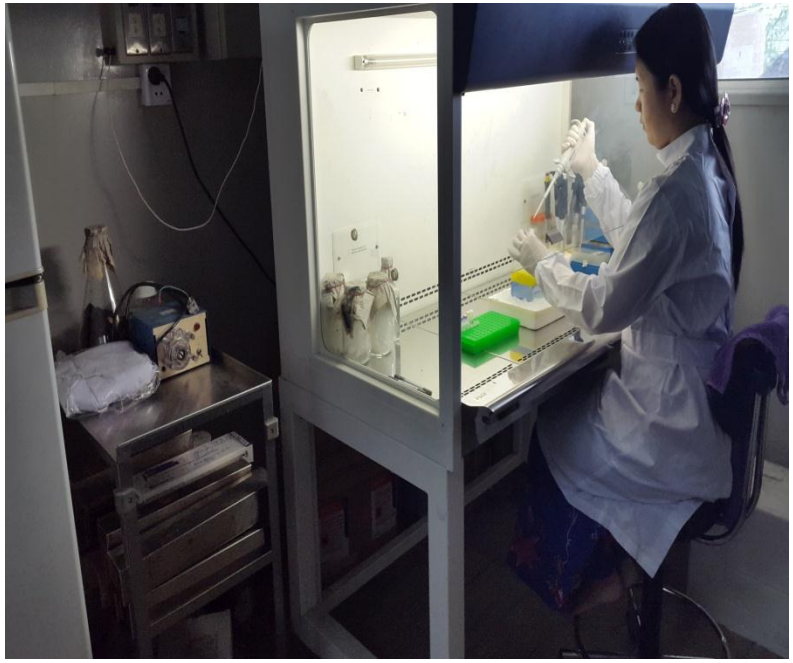
ELISA test (ProSpecT ™ , Oxoid)

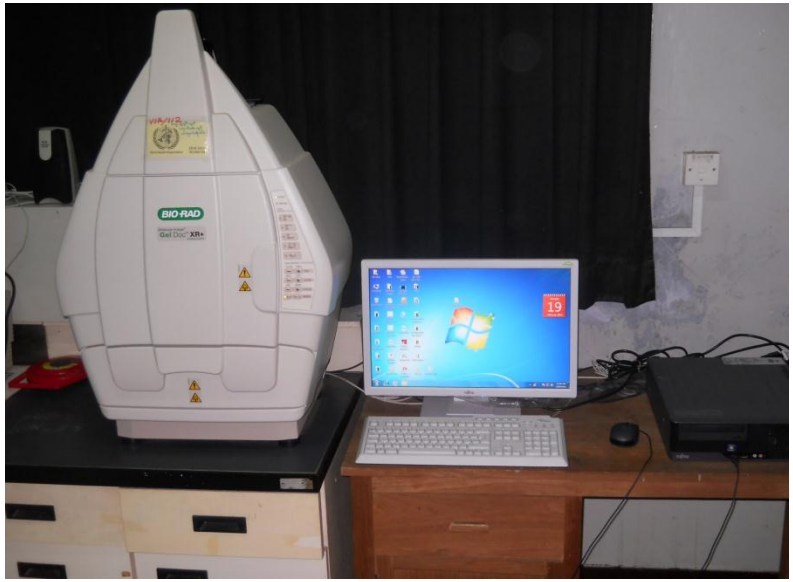






RT-PCR for genotyping





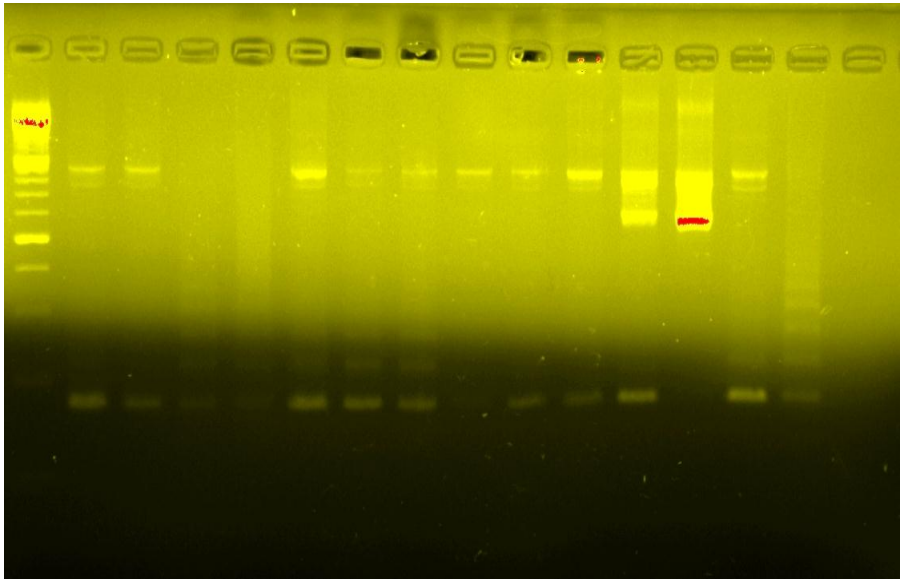


Table (1) PCR primers and cycling conditions used for VP7 genotyping of rotavirus strains

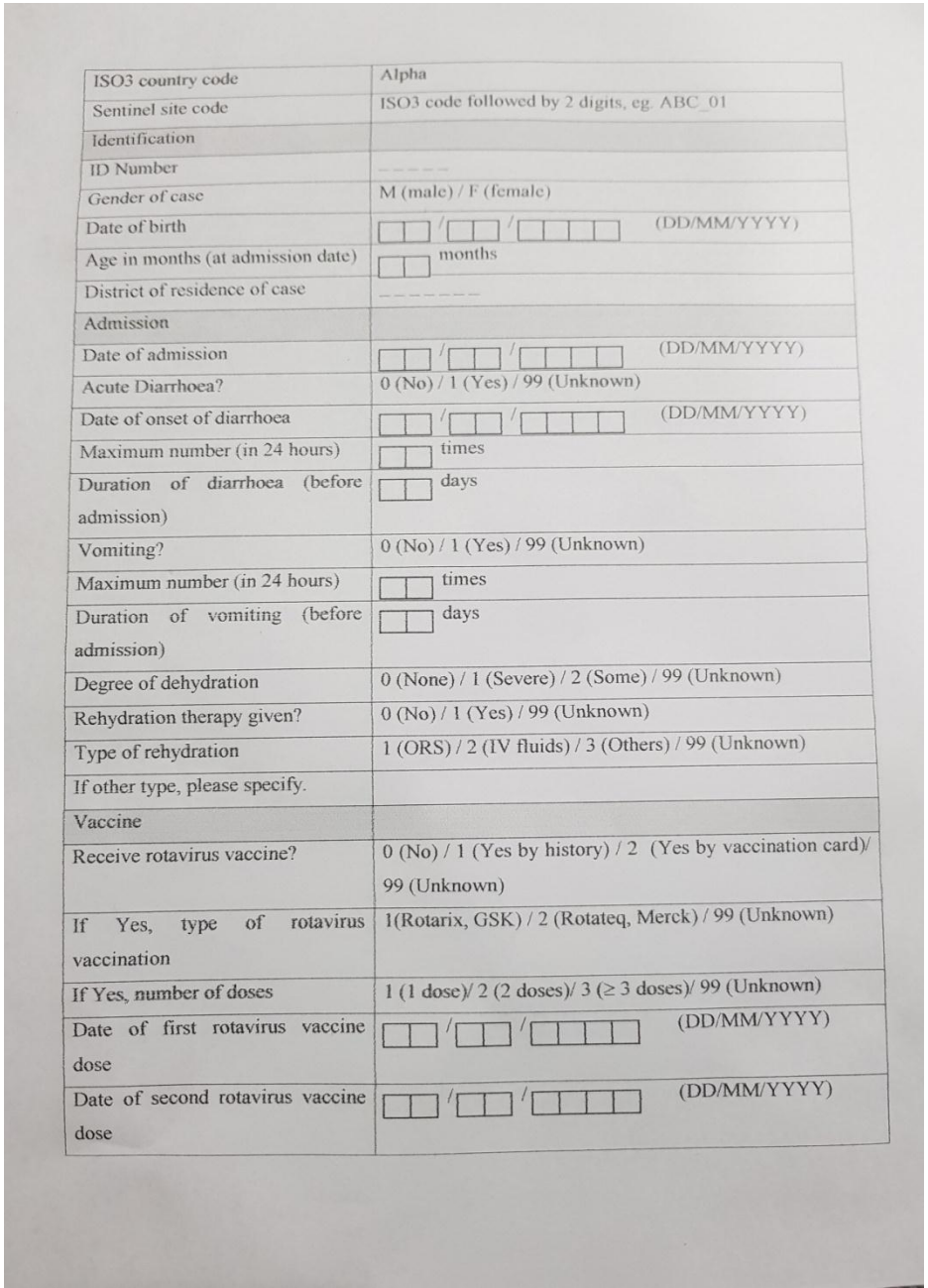
PCR	Cycling Conditions	Primer	Primer sequence	Amplicon Size
VP7 1st round	42 °C - 30min 95 °C – 15 min 94 °C – 1 min 52 °C – 1 min 72 °C – 1 min 72 °C – 7 min (X 35) 15 °C – hold	VP7/F VP7/R	5' ATG TAT GGT ATT GAA TAT ACC AC 3' 5' AAC TTG CCA CCA TTT TTT CC 3'	881 bp
VP7 2nd round	94 °C – 4 min 94 °C – 1 min 42 °C – 2 min 72 °C – 1 min 72 °C – 7 min (X 30) 15 °C – hold	VP7/R G1 G2 G3 G4 G8 G9 G10 G12	 5' CAA GTA CTC AAA TCA ATG ATG G 3' 5' CAA TGA TAT TAA CAC ATT TTC TGTG 3' 5' ACG AAC TCA ACA CGA GAG G 3' 5' C GT TTC TGG TGA GGA GTT G 3' 5' GTCACACCATTTGTAAATTCG3' 5′ CTT GAT GTG ACT AYA AAT AC 3' 5′ ATG TCA GAC TAC ARA TAC TGG 3' 5' CCGATGGACGTAACGTTGTA 3'	 618 bp 521 bp 682 bp 452 bp 756 bp 179 bp 266 bp 396 bp

Table (2) PCR primers and cycling conditions used for VP4 genotyping of rotavirus strains

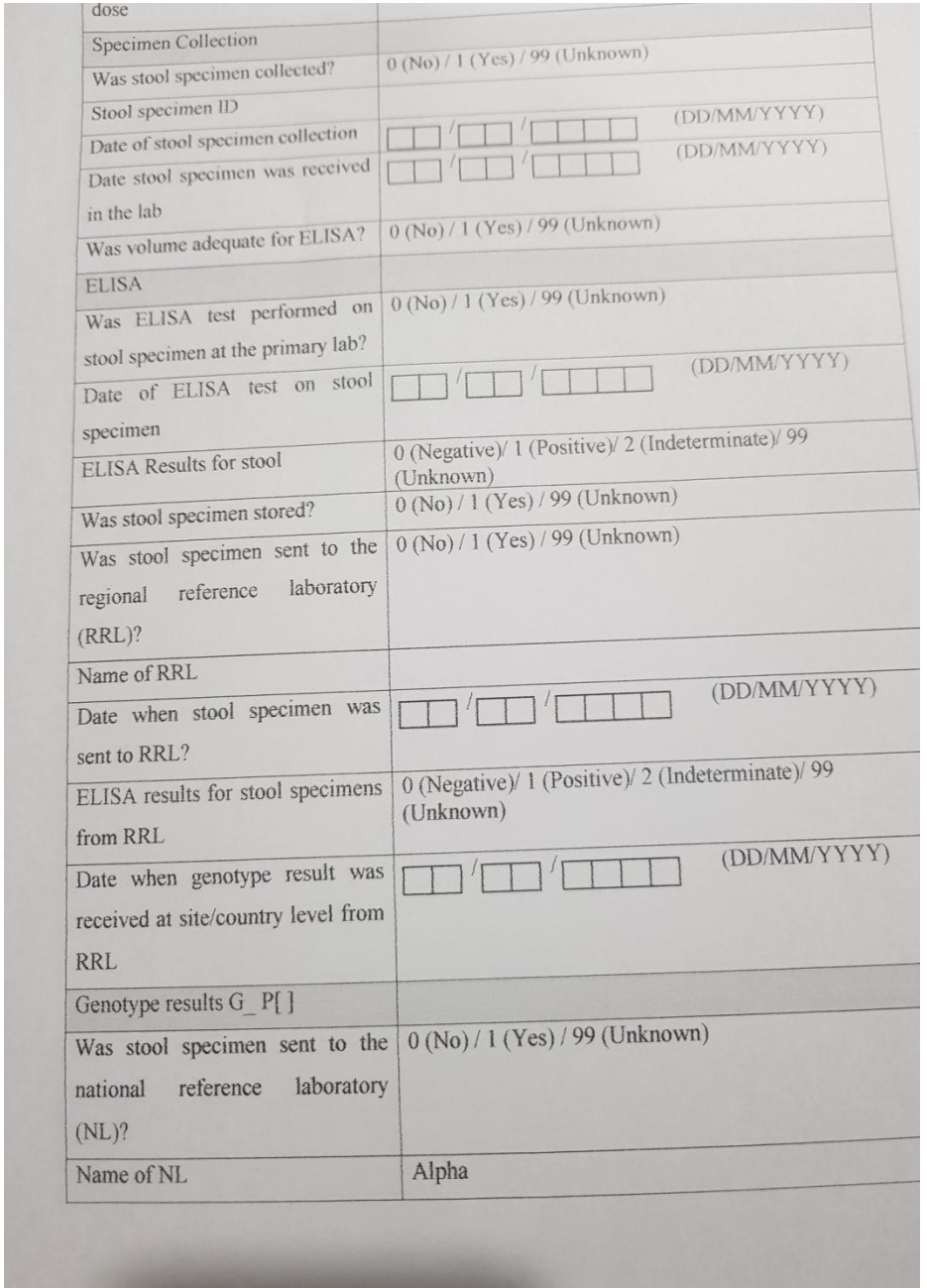
PCR	Cycling Conditions	Primer	Primer sequence	Amplicon Size
VP4 1st round	42 °C - 30min 95 °C – 15 min 94 °C – 1 min 52 °C – 1 min X 72 °C – 1 min 35 72 °C – 7 min 15 °C – hold	Con 3 Con 2	5' TGG CTT CGC CAT TTT ATA GAC A 3' 5' ATT TCG GAC CAT TTA TAA CC 3'	876 bp
VP4 2nd round	94 °C – 2 min 94 °C – 1 min 42 °C – 2 min X 72 °C – 1 min 30 72 °C – 7 min 15 °C – hold	Con 3 P[4] P[6] P[8] P[9] P[10] P[11]	 5' CTA TTG TTA GAG GTT AGA GTC 3' 5’ TGT TGA TTA GTT GGA TTC AA 3’ 5’ TCT ACT GGR TTR ACN TGC 3’ 5' TGA GAC ATG CAA TTG GAC 3' 5' ATC ATA GTT AGT AGT CGG 3' 5’ GTA AAC ATC CAG AAT GTG 3’	 483 bp 267 bp 345 bp 391 bp 583 bp 312 bp

Statistical Analysis

• Data entry - Microsoft Excel (WHO format)



ISO3 country code	Alpha
Sentinel site code	ISO3 code followed by 2 digits, eg. ABC_01
Identification	
ID Number	_ _ _ _ _
Gender of case	M (male) / F (female)
Date of birth	☐☐/☐☐/☐☐☐☐ (DD/MM/YYYY)
Age in months (at admission date)	☐☐ months
District of residence of case	_ _ _ _ _ _ _
Admission	
Date of admission	☐☐/☐☐/☐☐☐☐ (DD/MM/YYYY)
Acute Diarrhoea?	0 (No) / 1 (Yes) / 99 (Unknown)
Date of onset of diarrhoea	☐☐/☐☐/☐☐☐☐ (DD/MM/YYYY)
Maximum number (in 24 hours)	☐☐ times
Duration of diarrhoea (before admission)	☐☐ days
Vomiting?	0 (No) / 1 (Yes) / 99 (Unknown)
Maximum number (in 24 hours)	☐☐ times
Duration of vomiting (before admission)	☐☐ days
Degree of dehydration	0 (None) / 1 (Severe) / 2 (Some) / 99 (Unknown)
Rehydration therapy given?	0 (No) / 1 (Yes) / 99 (Unknown)
Type of rehydration	1 (ORS) / 2 (IV fluids) / 3 (Others) / 99 (Unknown)
If other type, please specify.	
Vaccine	
Receive rotavirus vaccine?	0 (No) / 1 (Yes by history) / 2 (Yes by vaccination card)/ 99 (Unknown)
If Yes, type of rotavirus vaccination	1(Rotarix, GSK) / 2 (Rotateq, Merck) / 99 (Unknown)
If Yes, number of doses	1 (1 dose)/ 2 (2 doses)/ 3 (≥ 3 doses)/ 99 (Unknown)
Date of first rotavirus vaccine dose	☐☐/☐☐/☐☐☐☐ (DD/MM/YYYY)
Date of second rotavirus vaccine dose	☐☐/☐☐/☐☐☐☐ (DD/MM/YYYY)



dose	
Specimen Collection	
Was stool specimen collected?	0 (No) / 1 (Yes) / 99 (Unknown)
Stool specimen ID	
Date of stool specimen collection	☐☐/☐☐/☐☐☐☐ (DD/MM/YYYY)
Date stool specimen was received in the lab	☐☐/☐☐/☐☐☐☐ (DD/MM/YYYY)
Was volume adequate for ELISA?	0 (No) / 1 (Yes) / 99 (Unknown)
ELISA	
Was ELISA test performed on stool specimen at the primary lab?	0 (No) / 1 (Yes) / 99 (Unknown)
Date of ELISA test on stool specimen	☐☐/☐☐/☐☐☐☐ (DD/MM/YYYY)
ELISA Results for stool	0 (Negative)/ 1 (Positive)/ 2 (Indeterminate)/ 99 (Unknown)
Was stool specimen stored?	0 (No) / 1 (Yes) / 99 (Unknown)
Was stool specimen sent to the regional reference laboratory (RRL)?	0 (No) / 1 (Yes) / 99 (Unknown)
Name of RRL	
Date when stool specimen was sent to RRL?	☐☐/☐☐/☐☐☐☐ (DD/MM/YYYY)
ELISA results for stool specimens from RRL	0 (Negative)/ 1 (Positive)/ 2 (Indeterminate)/ 99 (Unknown)
Date when genotype result was received at site/country level from RRL	☐☐/☐☐/☐☐☐☐ (DD/MM/YYYY)
Genotype results G_ P[ ]	
Was stool specimen sent to the national reference laboratory (NL)?	0 (No) / 1 (Yes) / 99 (Unknown)
Name of NL	Alpha

- **Data analysis - SPSS version 15.0.**

- **Number and Percentage : for descriptive analyses**

- **Chi-square test: to determine statistically significant differences regarding characteristics, clinical and outcome between RVGE and non-RVGE groups**

- **p-value <0.05 was considered significant.**

Ethical Consideration

The study was conducted after getting approval from the Ethics Review Committee (Department of Medical Research) and followed its guidelines.

The Government of the Republic of the Union of Myanmar
Ministry of Health and Sports
Department of Medical Research
No. 5, Ziwaka Road, Dagon Township, Yangon 11191
Tel : 95-1-375447, 95-1-375457, 95-1-375459 Fax : 95-1-251514

ERC Number: 010815
Approval Number: Ethics/DMR/2015/108AE
Date of Approval: 19 October, 2016 (valid up to 18 October, 2017)

Project Title: **Surveillance of rotavirus diarrhea in children under five years of age admitted to Yangon Children Hospital and 550 bedded Mandalay Children Hospital**

Principal Investigator: Dr. Theingi Win Myat
Department of Medical Research

Documents Accepted:

1. Ethical Approval from Department of Medical Research Dated 11 December, 2016
2. Request for Modification of the protocol version 1.0 Dated 4 October, 2016
3. Amended Full Protocol version 2.0 Dated 19 September, 2016
4. Informed Consent Form (English & Myanmar) version 2.0 Dated 19 September, 2016
5. Information for taking biological specimen (English & Myanmar) version 2.0 Dated 19 September, 2016
6. Consent for keeping biological specimen (English & Myanmar) version 2.0 Dated 19 September, 2016

The Ethics Review Committee on Medical Research Involving Human Subjects, Department of Medical Research, Ministry of Health and Sports approves to conduct the proposed research project as it is in full compliance with the Declaration of Helsinki, Council for International Organizations of Medical Sciences guidelines and International Conference on Harmonisation in Good Clinical Practice guidelines.

Prof. Pe Thet Khin
Chairperson
Ethics Review Committee
Department of Medical Research

IORG Number: IORG0007357 FWA Number: FWA00018816 IRB Number: IRB00008833

RESULTS

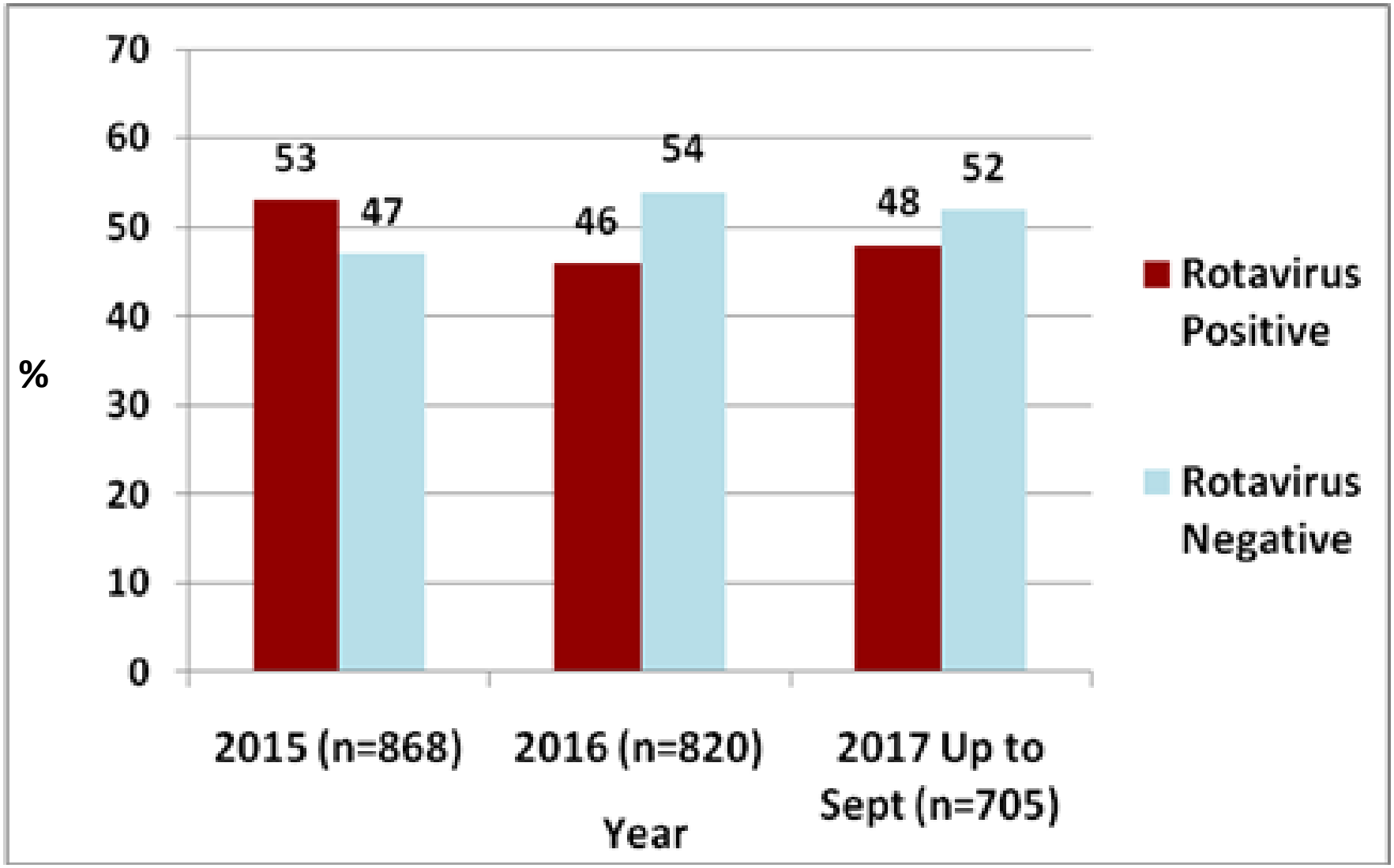


Fig (1) Proportion of Rotavirus positive cases tested by ELISA

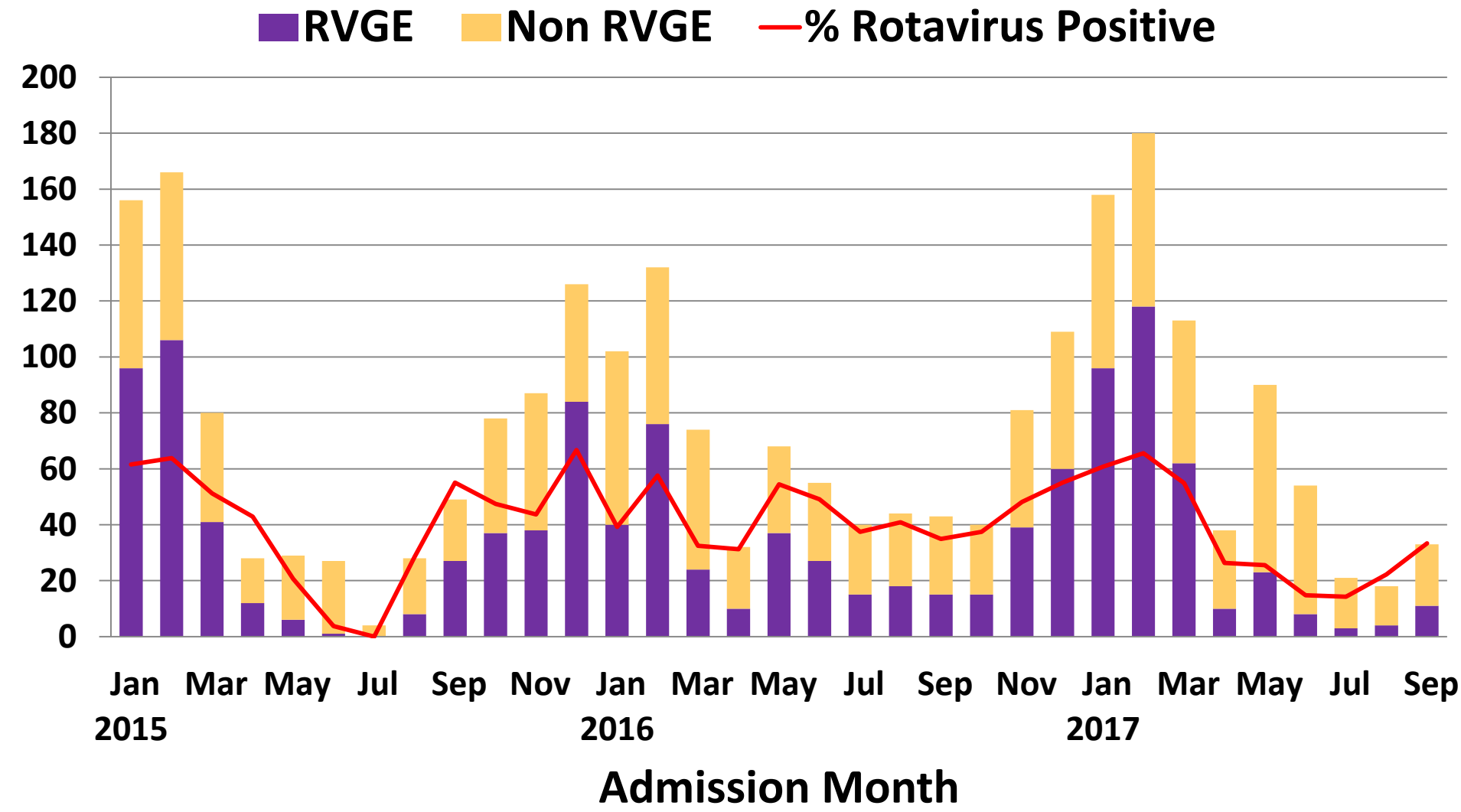


Figure (2) Seasonality of RVGE among hospitalized <5 years old children

Table (1) Characteristics, clinical presentations and outcome of hospitalized children with rotavirus gastroenteritis and non-rotavirus gastroenteritis, 2015-2017 Sept (N= 2393)

Characteristics	RVGE N (%)	Non RVGE N (%)	P value
	N=1167 (49%)	N=1226 (51%)	
Gender			
Male	721 (62%)	753 (61%)	0.855
Female	446 (38%)	473 (39%)	
Age group			
0-5 months	106 (9.1%)	198 (16.2%)	
6-23 months	**956 (81.9%)**	879 (71.6%)	**<0.01**
24-59 months	105 (9%)	149 (12.2%)	

Characteristics		RVGE N (%)	Non RVGE N (%)	P value
		N=1167 (49%)	N=1226 (51%)	
Clinical symptoms				
Vomiting	Yes	**986 (84.5%)**	895 (73%)	**<0.01**
	No	181 (15.5%)	331 (27%)	
Fever	Yes	**935 (80.1%)**	880 (71.8%)	**<0.01**
	No	232 (19.9%)	346 (28.2%)	
Dehydration	Yes	887 (76%)	900 (73.4%)	0.144
	No	280 (24%)	326 (26.6%)	
Vesikari scoring				
Mild	<7	24 (2.1%)	26 (2.1%)	
Moderate	7-10	216 (18.5%)	373 (30.4%)	**<0.01**
Severe	≥11	**927 (79.4%)**	827 (67.5%)	

Vesikari Clinical Severity Scoring System Parameters and Scores

	Score		
Parameter	1	2	3
Diarrhoea			
Maximum Number Stools per Day	1-3	4-5	≥6
Diarrhea Duration (Days)	1-4	5	≥6
Vomiting			
Max. No. vomiting Episodes per Day	1	2-4	≥5
Vomiting Duration (Days)	1	2	≥3
Temperature	37.1 - 38.4	38.5 – 38.9	≥39.0
Dehydration	N/A	1-5%	≥6%
Treatment	Rehydration	Hospitalization	N/A

Characteristics	RVGE N (%)	Non RVGE N (%)	P value
	N=1167 (49%)	N=1226 (51%)	
Hospital stay			
<2 days	93 (8%)	123 (10%)	
2-5 days	1039 (89%)	1079 (88%)	0.06
>5 days	35 (3%)	24 (2%)	
Outcome			
Recovery	1167 (100%)	1225 (99.9%)	NA
Expired	0	1(0.1%)	

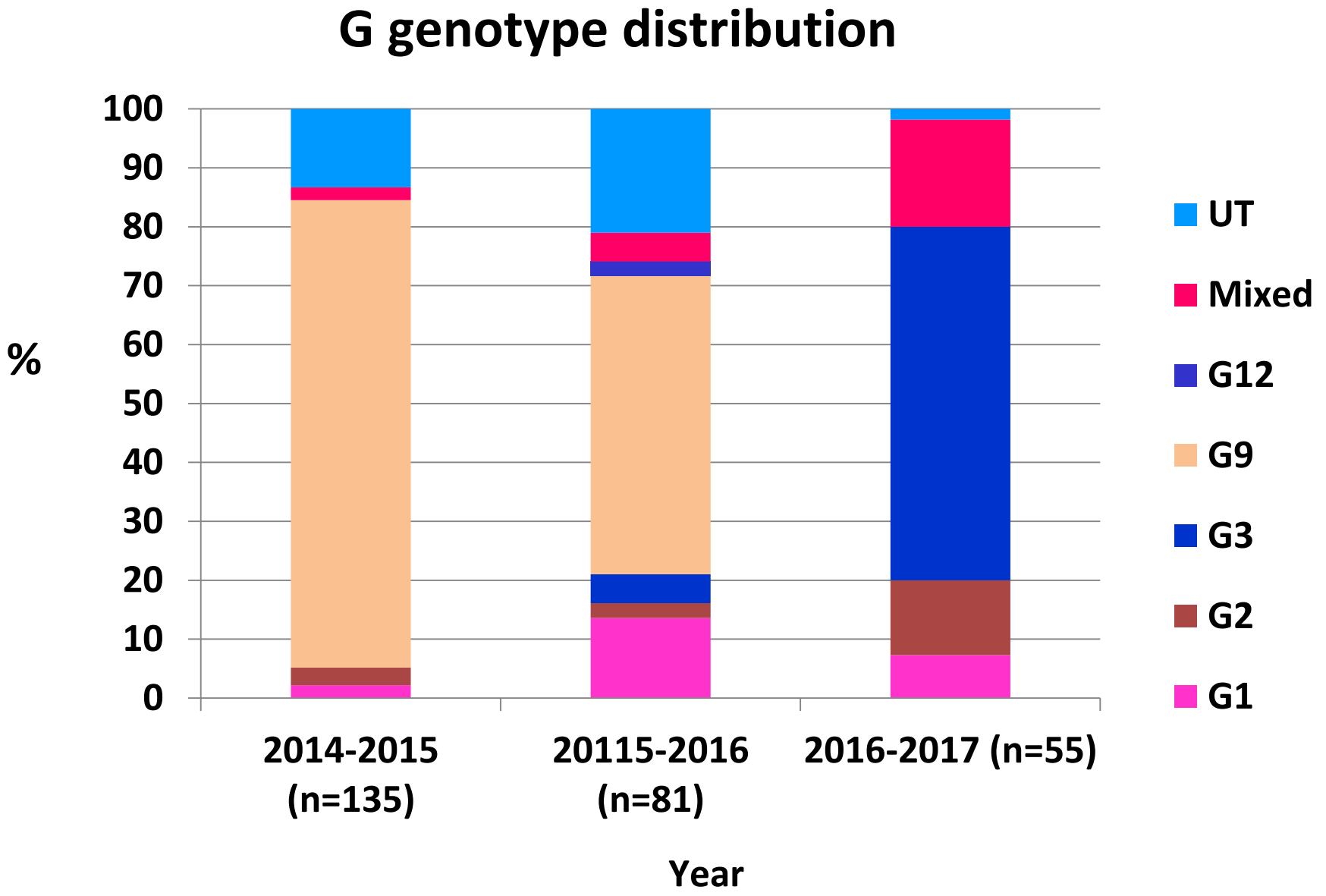


Figure (3) Distribution of rotavirus G genotype by seasonal year

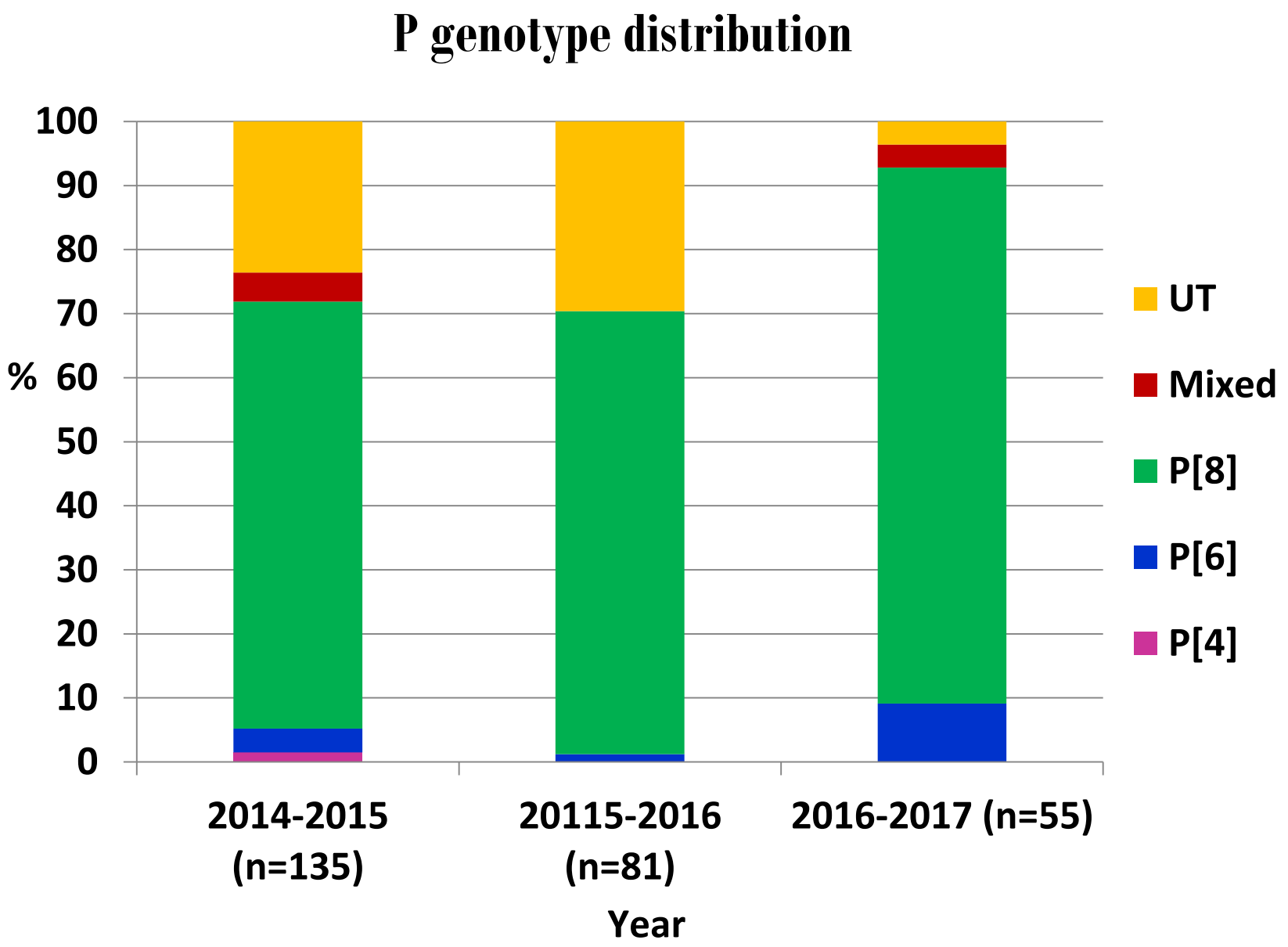


Figure (4) Distribution of rotavirus P genotype by seasonal year

Table (2) Distribution of rotavirus strains (combination of G and P genotypes)

	2014-2015 N (%)	2015-2016 N (%)	2016-2017 N (%)	Total
G1P[8]	3 (2.2)	8 (9.9)	2 (3.6)	13
G2P[4]	2 (1.5)	0	0	2
G2P[6]	0	1 (1.2)	4 (7.3)	5
G2P[8]	2 (1.5)	1 (1.2)	2 (3.6)	5
G3P[8]	0	4 (4.9)	**32 (58.2)**	**36**
G9P[6]	4 (3.0)	0	0	4
G9P[8]	**72 (53.3)**	**25 (30.9)**	0	**97**
G12P[8]	0	1 (1.2)	0	1
Mixed	7 (5.2)	4 (4.9)	12 (21.8)	23
Partially Typed	41 (30.4)	34 (42)	3 (5.5)	78
Untypable	4 (3.0)	3 (3.7)	0	7
Total	**135 (100)**	**81 (100)**	**55 (100)**	**271**

DISCUSSION

Prevalence of RVGE in Myanmar and other countries

Study Year	Country	Prevalence of RVGE
2012-2013	Philippines	43.5%
2011-2013	India (Kolkata)	53.4%
2008-2012	Bangladesh	42%
2000-2006	US	43%
2015-2017	Myanmar	49%
2009-2014	Myanmar	49.9%

Prevalence of RVGE before and after vaccine introduction

Country	Prevalence before vaccine	Prevalence after vaccine
Fiji	41% (2006-2011)	21% (2013)
US	43% (2000-2006)	9% (2009)
Rwanda	50% (2011)	20% (2013)
Malawi	50.3% (2011-2012)	39.6% (2013)

2. Gender Distribution of RVGE

- **Present study - male preponderance (male to female ratio of 1.6:1, 62% Vs 38%)**
- **in accordance with the findings of other studies**
- **(male RVGE accounted for 60% in Lahore[13], 61% in Uganda[14], 1.2:1 in Tunisia[15])**

3. Distribution of RVGE cases by age groups

- **Almost all studies around the world like this study found that 6-23 month age group is the most commonly affected (81.9%%)**
- **>60% were infants and**
- **~90% of the cases were <2 year.**
- **Thus, the WHO recommendation (2013) stated that the first dose of RV should be started as soon as after 6 weeks and all doses to be completed by 24 weeks of child age.**

4. Seasonal trend of RVGE

- **Strong seasonal trend with peak in winter seasons**
- **Peak detection of rotavirus (60-80%) of hospitalized AGE cases in January and February**
- **Such strong seasonal trend is also occurred in other tropical countries**

5. Clinical presentations

- **Vomiting, fever and severe clinical vesikari score - significantly associated with rotavirus positivity.**

  (also in line with the findings of other studies)

- **Of enrolled children, only one patient expired who was a 7 months-old male admitted in April 2016 and presented with high fever, severe dehydration and shock and tested rotavirus negative.**

6. Genotype distribution

Seasonal Year	Most Prevalent Genotype	N (%)	Total genotyped
2008-2009	G1P[8]	15 (35%)	43
2009-2010	G12P[8]	50 (61.7%)	81
2010-2011	G12P[8]	103(75.2%)	137
2011-2012	G12P[8]	45 (26%)	173
2012-2013	G2P[4]	22 (73.3%)	30
2013-2014	G1P[8]	31 (41.9%)	74
2014-2015	G9P[8]	72 (53.3%)	135
2015-2016	G9P[8]	25 (30.9%)	81
2016-2017	G3P[8]	32 (58.2%)	55

- **The immense diversity and changing trends in the circulating rotavirus strains underlines the need for vigilance and sustained surveillance**

- **to monitor efficacy of vaccine and**

- **study the evolution of vaccine escape strains in post-vaccination era.**

CONCLUSION

1.	Prevalence of RVGE (~50%)	• Indicator of considering RV introduction to reduce diarrhea hospitalization as well as RVGE
2.	Epidemiological Information (Age distribution, Seasonal variation etc.)	• platform to consider target population, timing and dosage schedule for vaccination
3.	Diversity of circulating rotavirus Strains	• Selection of appropriate vaccine, to monitor the effectiveness of vaccine

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