GLOBAL ENTERIC MULTI-CENTER STUDY ("GEMS")
Diarrheal Disease in Infants and Young Children In Developing Countries

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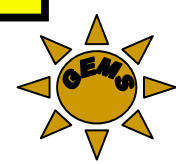
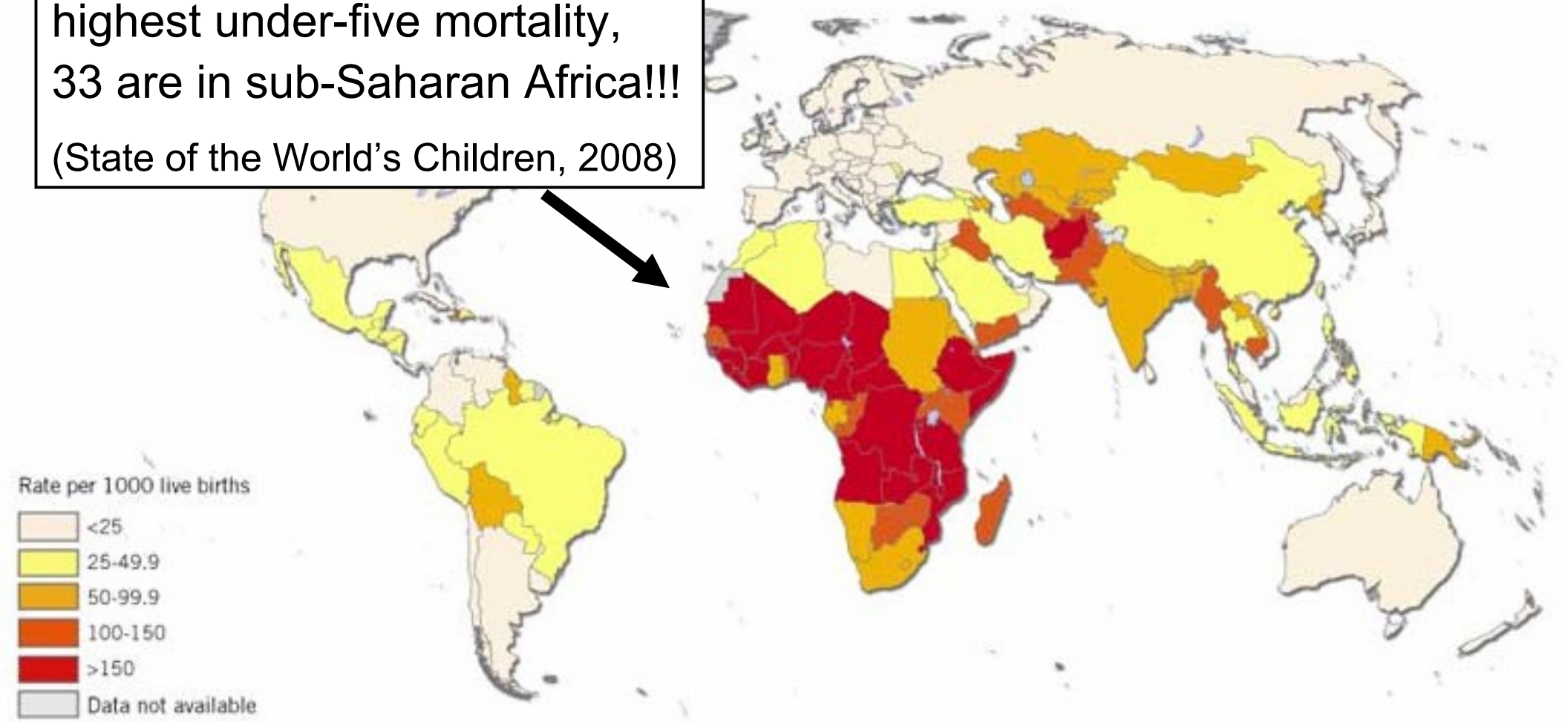
CVD



UN Millenium Development Goal # 4 aims to diminish mortality in children < 5 years of age by 67% by 2015

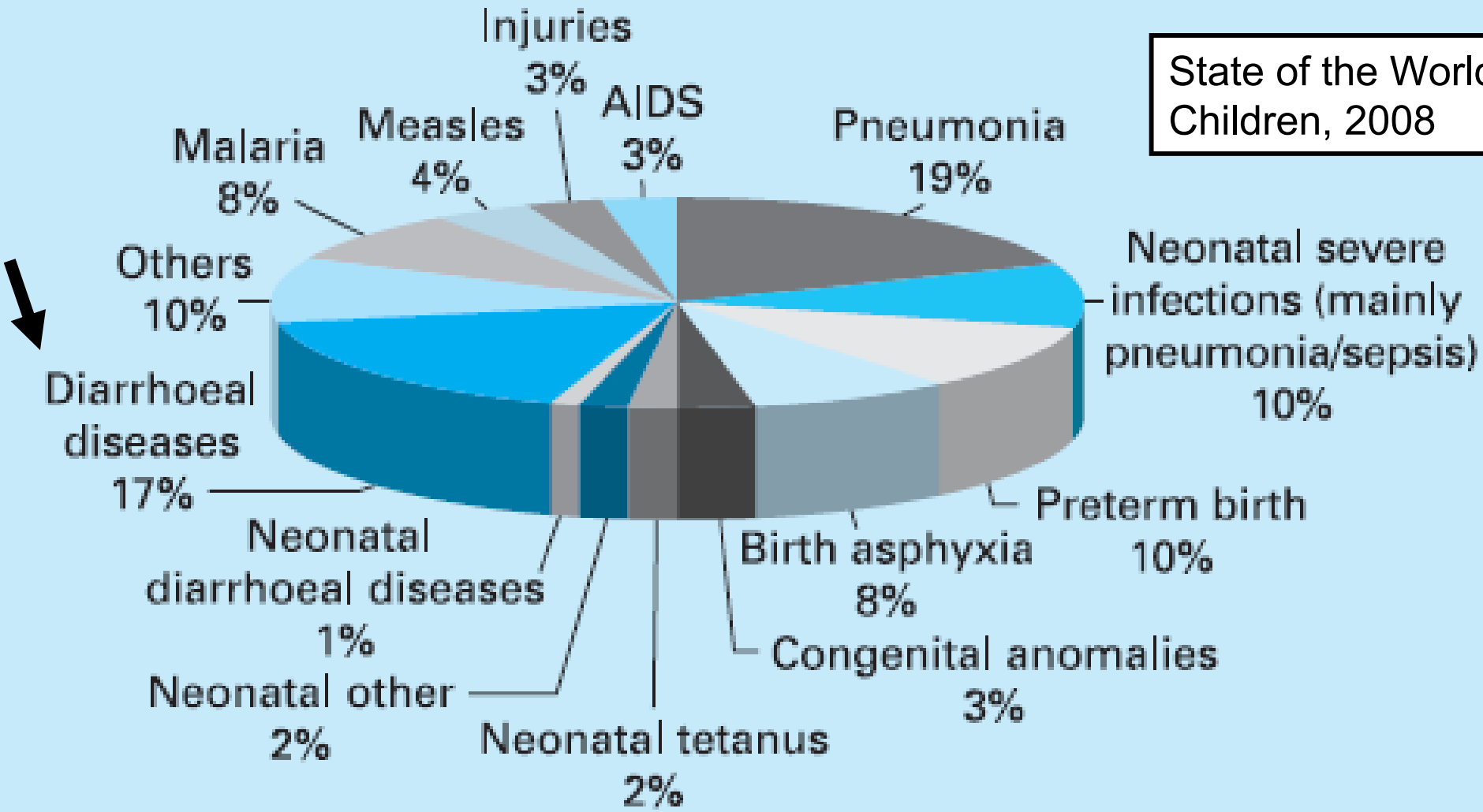
Of the 35 countries with the highest under-five mortality, 33 are in sub-Saharan Africa!!!

(State of the World's Children, 2008)



Deaths among children < 5 yrs of age, developing countries

State of the World's Children, 2008



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Knowledge gaps before GEMS

- *Lack of agreement on the major etiologic agents associated with severe and fatal diarrheal disease in areas of high <5 MR*
- *Is the global "burden" of enteric infections sufficiently quantified to set priorities?*
  - What enteric vaccines are most needed?
  - Serotype & antigenic differences by region?
- *Paucity of data from sub-Saharan Africa*
- *Doubt whether the diagnostic microbiologic methods exist (or could be rapidly prepared & validated) to fill the above knowledge gaps*

Some limitations of earlier studies

- Few studies from countries with **high child mortality**
- Very few studies from **sub-Saharan Africa**
- Typically only **one site** studied per report
- Often limited to **children < 24 months of age**
- Most had **short surveillance** (only 6-24 calendar months; too limited to detect cyclical patterns)
- **Failure to enroll and study matched controls**
- **Lack of census data** or linkage to a DSS (can't calculate population-based incidence rates)
- **Health care utilization** patterns not known
- **Incomplete survey** of etiological agents
- **Insensitive** microbiological methods
- **Strains not characterized** for serotype, genotype, etc.
- **No follow-up** of cases & controls

GLOBAL ENTERIC MULTI-CENTER STUDY ("GEMS")
Diarrheal Disease in Infants and Young Children In Developing Countries

Project Funded by Bill & Melinda Gates Foundation

Coordinating Investigator

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Principal Investigator, microbiology

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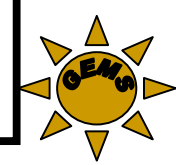


- **Common protocol** to study **moderate & severe diarrhea**
- Rigorous epidemiologic **case/control** & microbiologic design
- **Defined population** under **demographic surveillance**
- **3 age strata: 0-11 mos; 12-23 mos; 24-59 mos**
- Health Services Utilization & Attitudes Survey **(HUAS);** 1000/site
- 600 analyzable **cases** & $\geq$ 600 analyzable **matched controls** per age group, per each of 7 sites, over 3 years
- Record all **severe/moderate** cases coming to sentinel sites
- **Even sampling** throughout the year (8-9 cases per age stratum, per fortnight, throughout the enrollment period)
- AFRICA & ASIA; rural & urban; high & low HIV; high & low malaria
- Record specific **clinical syndromes**
- Utilize modern **molecular diagnostic tools**
- **Expanded etiology**; serotypes; antigenic types; genotypes
- **60-DAY FOLLOW-UP VISITS** of cases & controls
  - Detect **deaths**; nutritional consequences; (persistent diarrhea)$_{CVD}$
- **Water/sanitation risk factor** data & **economic burden** data
- **SPECIMEN & STRAIN REPOSITORY**

4 GEMS Sites in Sub-Saharan Africa

CVD-Mali: Bamako, Mali **PI – Samba Sow** 

MRC Unit, Basse, Gambia **PI – Debasish Saha** 

CISM, Manhiça, Mozambique **PI – Pedro Alonso** 

CDC/KEMRI, Kisumu, Kenya **PI – Robert Breiman** 

3 GEMS Sites in South Asia

Aga Khan University, Pakistan **PI – Anita Zaidi** 

NICED, Kolkata, West Bengal, India **PI- Dipika Sur** 

ICDDR,B: Mirzapur, Bangladesh **PI- ASG Faruque** 

Study Coordination & Advisories

Epidemiology/Clinical Issues Steering Committee

- Karen Kotloff, Dilruba Nasrin, Tamer Farag, Site Epi PIs,
- Fred Binka (Ghana), Eric Mintz (CDC), Paul Stolley (UM), John Clemens (IVI), Halvor Sommerfelt (Bergen)

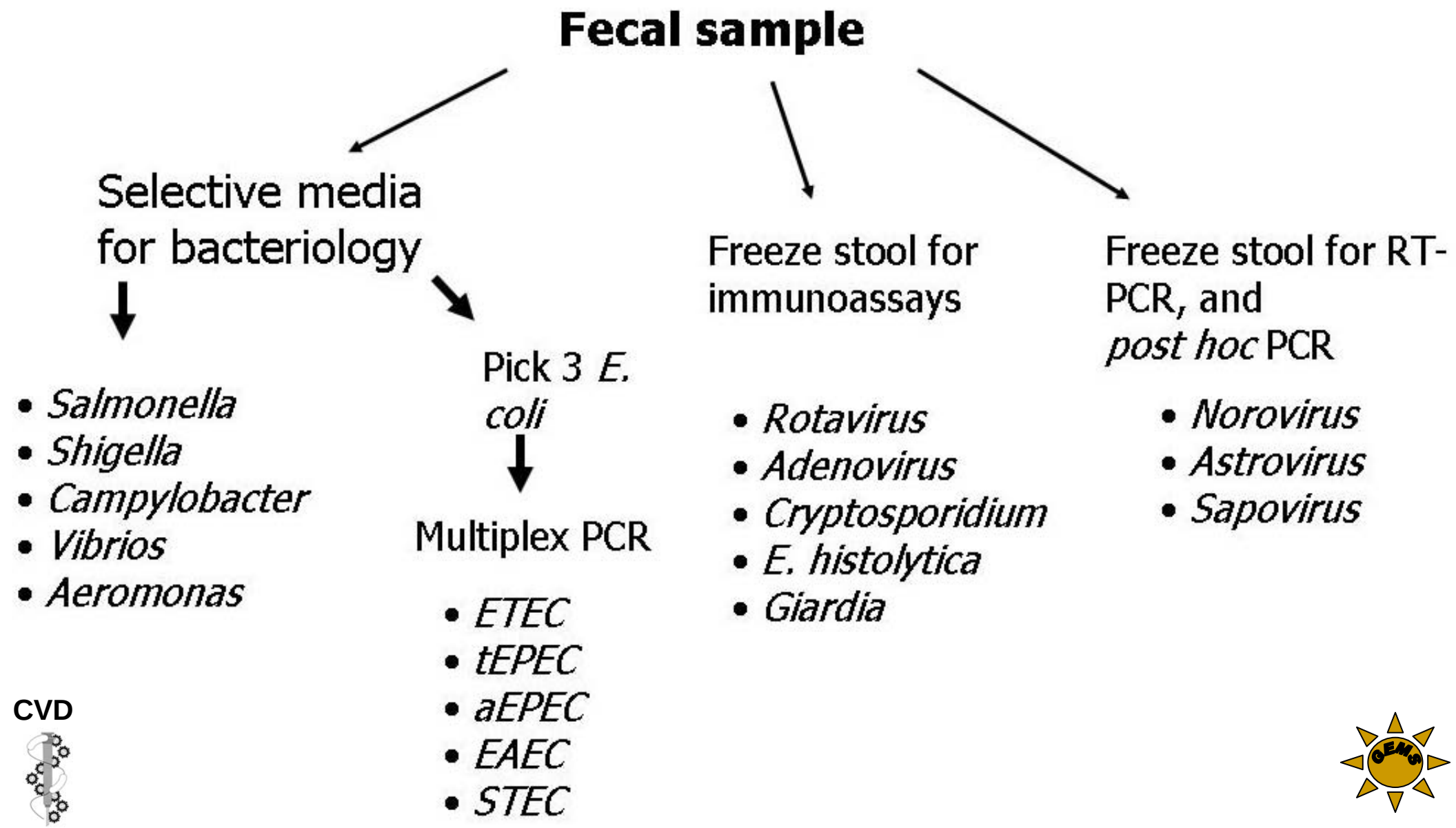
Microbiology Steering Committee

- Jim Nataro, Sandra Panchalingam, Site Microbiologists
- Patrick Murray (NIH), Roy Robins-Browne (U of Melbourne), Philippe Sansonetti (l'Institut Pasteur)

Consensus Approach

- The case/control study protocol & the microbiologic methodologies were finalized after extensive consultation with the Steering Committees and the site PIs. These constitute **consensus approaches**.

Microbiology work flow



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GEMS Reference Laboratories

Shigella

- CDC (WHO *Shigella* Reference Center)
  - Nancy Strockbine

ETEC

- University of Goteborg (Ann Mari Svennerholm)
- University of Chile (Roberto Vidal, Valeria Prado)

Cryptosporidium, Entameba, Giardia

- University of Virginia (William Petri, Eric Houpt)

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GEMS Reference Laboratories

Rotavirus, Norovirus & Astrovirus Genome Typing

- WHO Reference Laboratory Network (liaison, Duncan Steele)
- CDC (John Gentsch & Jan Vinje)
- Fogarty Institute (liaison, Roger Glass)

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Health Care Utilization & Attitudes Survey: diarrhea in previous 2 weeks (random sample of ~ 1000 per site)

	Gambia	Mali	Moz	Kenya	India	Bangl	Pakist
No. in DSS (<60 mo.)	145,469 (27,800)	210,425 (31,583)	84,206 (14,100)	145,825 (21,600)	199,054 (18,000)	292,000 (48,000)	148,000 (27,000)
% MSD	20.9	7.9	2.0	17.4	6.2	6.5	30.7
% MSD sought care at SHC	39.4	30.4	85.7	36.1	12.1	19.2	23.5

MSD= Moderate to severe diarrhea; DSS = Demographic surveillance survey

SHC = Sentinel health center (site of case-control study)

Case eligibility & enrollment

- Age 0-59 mos. & from DSS
- Seeking care at a sentinel HC
- Diarrhea (≥3 loose stools in previous 24h)
- Diarrhea-free for 7 days before current episode
- Episode began within 7 days of enrollment
- Diarrhea is moderate-severe, *i.e.*, has ≥ 1 of:
  - Sunken eyes
  - Loss of skin turgor
  - IV rehydration administered
  - Dysentery
  - Hospitalized

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Selection of controls

- Community controls randomly selected using DSS database
- 1-3 controls/case
- Matched to case by:
  - Age (strata are respected)
    - 0-11 mos: ±2 months
    - 12-59 mos: ±4 months
  - Gender
  - Same or nearby village
  - Within 14 days of presentation of case
- No diarrhea within 7 days of enrollment
- Provides stool sample
- Informed consent

Data collection (cases & controls)

- Enrollment
  - Demographic
  - Clinical
  - Epidemiologic
  - Anthropometrics

- Memory aid for 14 days
- Single fresh, well-preserved stool sample
- **60-day follow-up visit to the home**
  - Clinical sequelae; death
  - Nutritional outcome (anthropometrics)
  - Direct observation of environmental risks

Memory Aid to Record the Presence of Diarrhea

Site	Center	Child ID	Day	Month	Year
☐	☐☐	☐☐☐☐☐☐	☐☐	☐☐☐	☐☐☐☐

Please complete this form every day for each of the next 14 days.

1. Each morning when you wake up, decide whether your child had diarrhea during the previous day. *Diarrhea* means that your child passed 3 or more loose or watery stools that were not normal for him or her on that day.
2. Go to the correct day. "☼" means today, "☼☼" means tomorrow, and so on. A day begins when you wake up in the morning and ends when you wake up the next morning.
3. If your child had diarrhea that day, mark "X" in the dark box for that day [X]. If your child did not have diarrhea, mark "X" in the white box for that day [X]. **Each day, make only one "X".**
4. If you forget for a few days, try to start again on the correct day.
5. Keep this form in a safe place. We will come to your house to collect it in 60 days.

DIARRHEA

NORMAL

		DIARRHEA	NORMAL
(1)	☼ (today)		
(2)	☼☼		
(3)	☼☼☼		
(4)	☼☼☼☼		
(5)	☼☼☼☼☼		
(6)	☼☼☼☼☼☼		
(7)	☼☼☼☼☼☼☼		
(8)	☼☼☼☼☼☼☼☼		
(9)	☼☼☼☼☼☼☼☼☼		
(10)	☼☼☼☼☼☼☼☼☼☼		
(11)	☼☼☼☼☼☼☼☼☼☼☼		
(12)	☼☼☼☼☼☼☼☼☼☼☼☼		
(13)	☼☼☼☼☼☼☼☼☼☼☼☼☼		
(14)	☼☼☼☼☼☼☼☼☼☼☼☼☼☼		

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No. from DSS presenting to health centers, eligible, and enrolled

	ASIA			AFRICA		
Age group (mos.)	0-11	12-23	24-59	0-11	12-23	24-59
No. presenting	46,593	24,118	37,766	56,448	45,836	59,812
No. diarrhea	6,462	4,439	3,171	7,937	6,711	3,319
% of presenting kids	14%	18%	8%	14%	15%	6%
% with dysentery	8%	11%	13%	2%	4%	7%
No. eligible	1,339	1,064	718	2,625	1,929	1,044
% of diarrhea	21%	24%	23%	33%	29%	21%
No. enrolled	1,030	770	501	1,310	981	706

Clinical presentation		ASIA (n=2,207)	AFRICA (n=2,870)
Maximum no. loose stools per day			
≤ 6		36%	83%
7-10		41%	16%
≥10		23%	2%
Vomiting ≥3 x/ day		37%	48%
Fever		64%	63%
Sunken eyes		58%	90%
Oral mucosa:	Somewhat dry	50%	66%
	Very dry	4%	6%
Skin pinch:	Slow return	16%	29%
Rectal prolapse		0.4%	0.6%

Percent of children who received various treatments before visiting the sentinel health care facility

	ASIA N=2,207	AFRICA N=2,870
ORS	50.1%	14.2%
Zinc	7.6%	0.9%
Antibiotic	16.2%	7.5%

Preliminary, informally analyzed data

- These are **incomplete data** representing only ~ 50% of the study duration (18 of 36 study months)
- No adjustments for site differences
- No adjustments for multiple pathogens
- Meant to illustrate broad trends
- Some examples of analytical challenges

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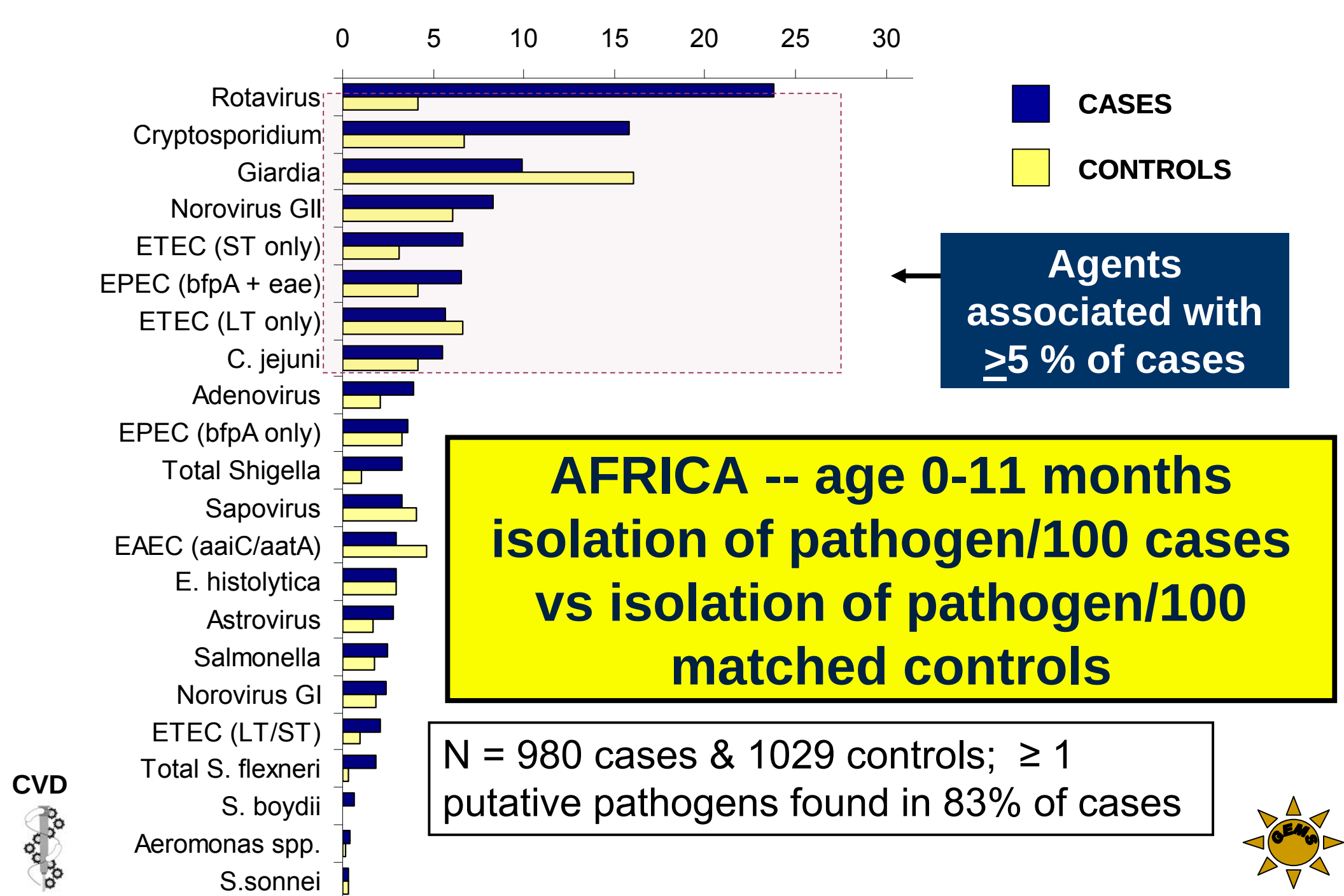
0
5
10
15
20
25
30
Rotavirus
Cryptosporidium
Giardia
Norovirus GII
ETEC (ST only)
EPEC (bfpA + eae)
ETEC (LT only)
C. jejuni
Adenovirus
EPEC (bfpA only)
Total Shigella
Sapovirus
EAEC (aaiC/aatA)
E. histolytica
Astrovirus
Salmonella
Norovirus GI
ETEC (LT/ST)
Total S. flexneri
S. boydii
Aeromonas spp.
S.sonnei
CASES
CONTROLS
Agents associated with ≥5 % of cases
AFRICA -- age 0-11 months
isolation of pathogen/100 cases
vs isolation of pathogen/100
matched controls
N = 980 cases & 1029 controls; ≥ 1 putative pathogens found in 83% of cases
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Pathogenicity Index (PI) = Odds Ratio

odds of isolation in cases / odds of isolation in controls

Calculated as:

(rate of isolation in cases / rate of non-isolation in cases

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rate of isolation in controls / rate of non-isolation in controls)

PI >1 suggests pathogenicity, *i.e.*, an ability of the agent to cause disease

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Excess Rate of Isolation (ERI) = isolation rate per 100 cases minus the isolation rate per 100 controls

↓

ERI will be used as an adjustment in the calculation of agent-specific incidence and of the burden of diarrheal disease in the population under demographic surveillance

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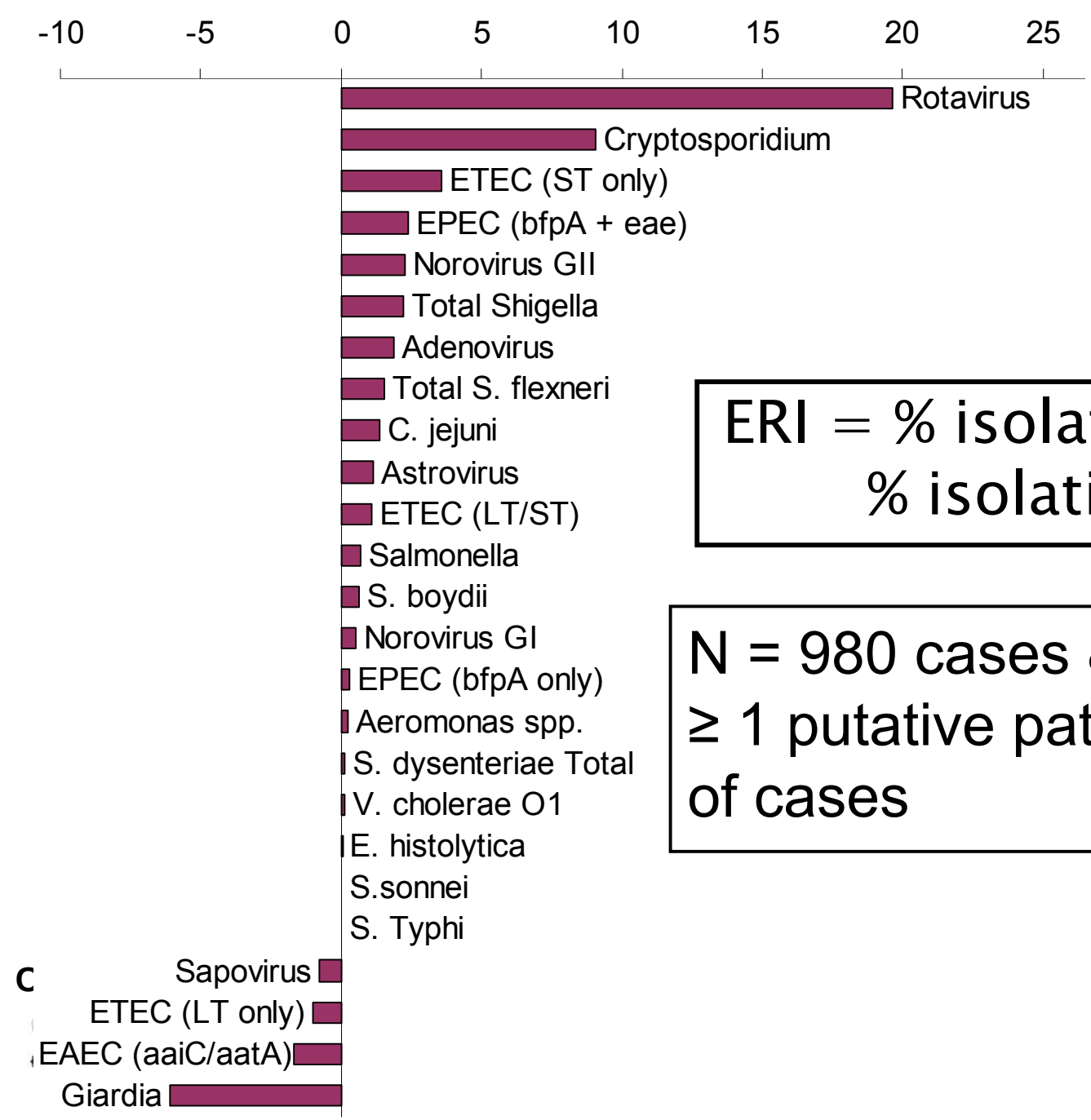
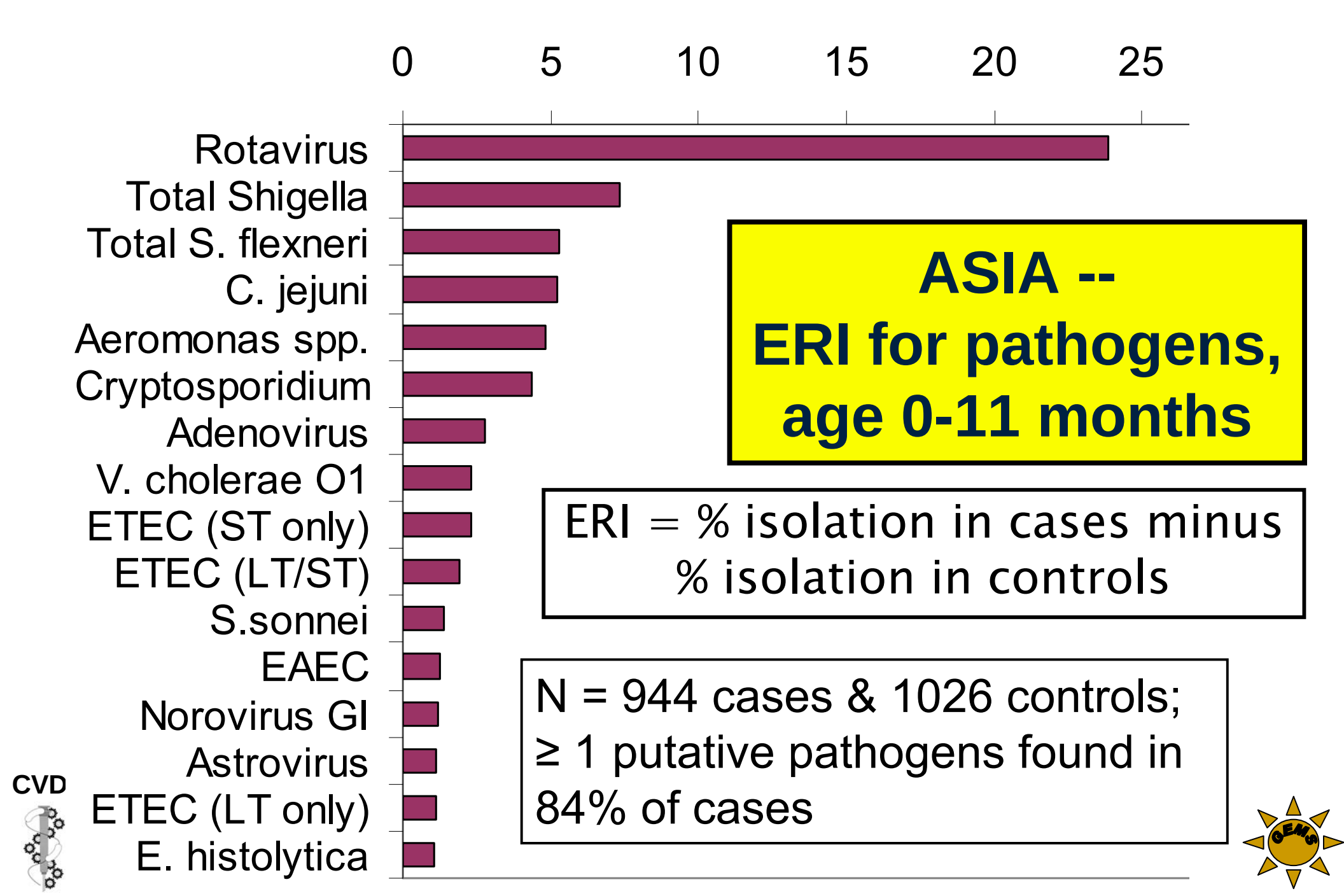


AFRICA -- ERI of pathogens, age 0-11 mos.

ERI = % isolation in cases minus % isolation in controls

N = 980 cases & 1029 controls;
≥ 1 putative pathogens found in 83% of cases


0
5
10
15
20
25
Rotavirus
Total Shigella
Total S. flexneri
C. jejuni
Aeromonas spp.
Cryptosporidium
Adenovirus
V. cholerae O1
ETEC (ST only)
ETEC (LT/ST)
S.sonnei
EAEC
Norovirus GI
Astrovirus
ETEC (LT only)
E. histolytica
ASIA --
ERI for pathogens,
age 0-11 months
ERI = % isolation in cases minus
% isolation in controls
N = 944 cases & 1026 controls;
≥ 1 putative pathogens found in
84% of cases
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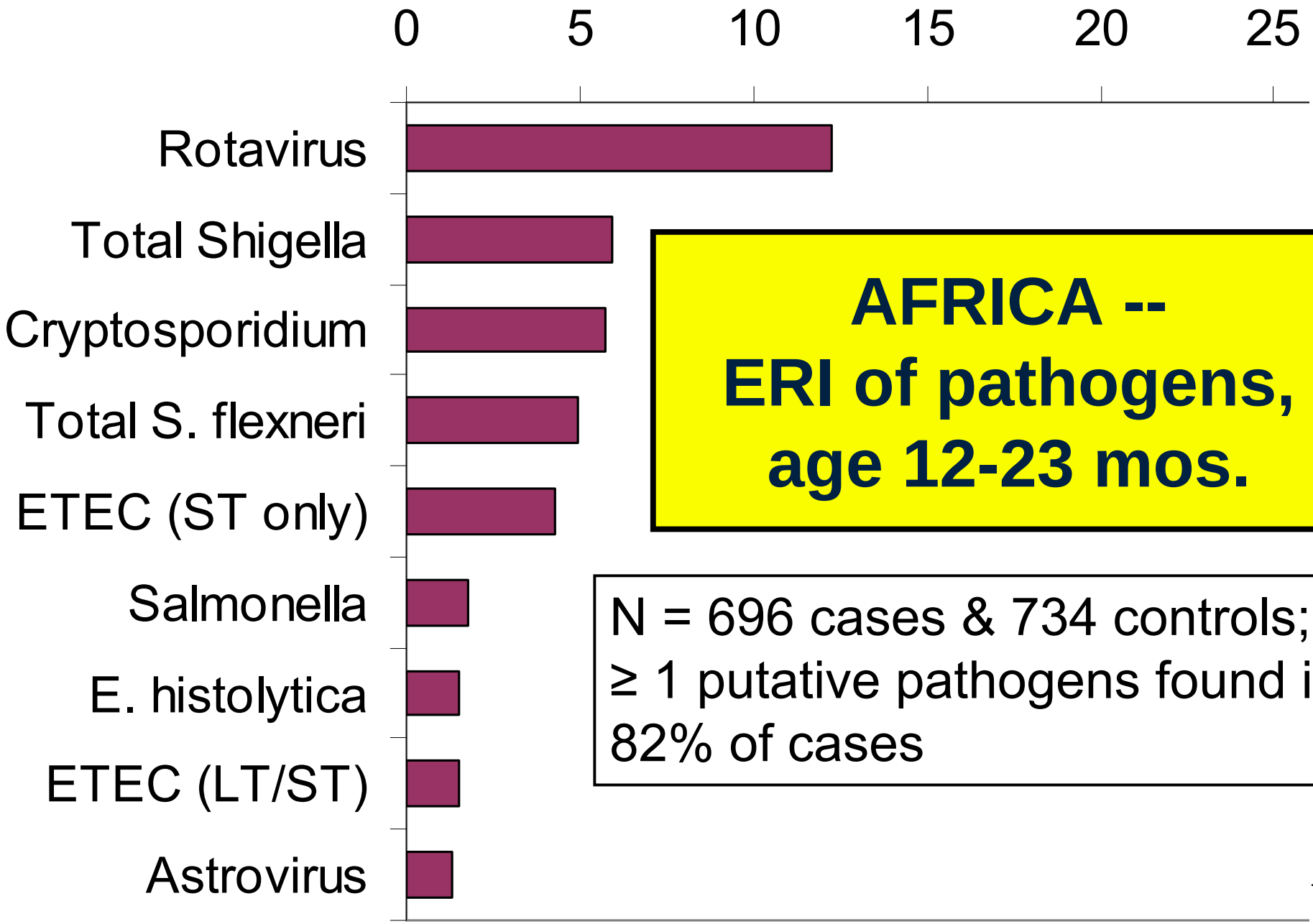

AFRICA -- ERI of pathogens, age 12-23 mos.

N = 696 cases & 734 controls;
≥ 1 putative pathogens found in 82% of cases

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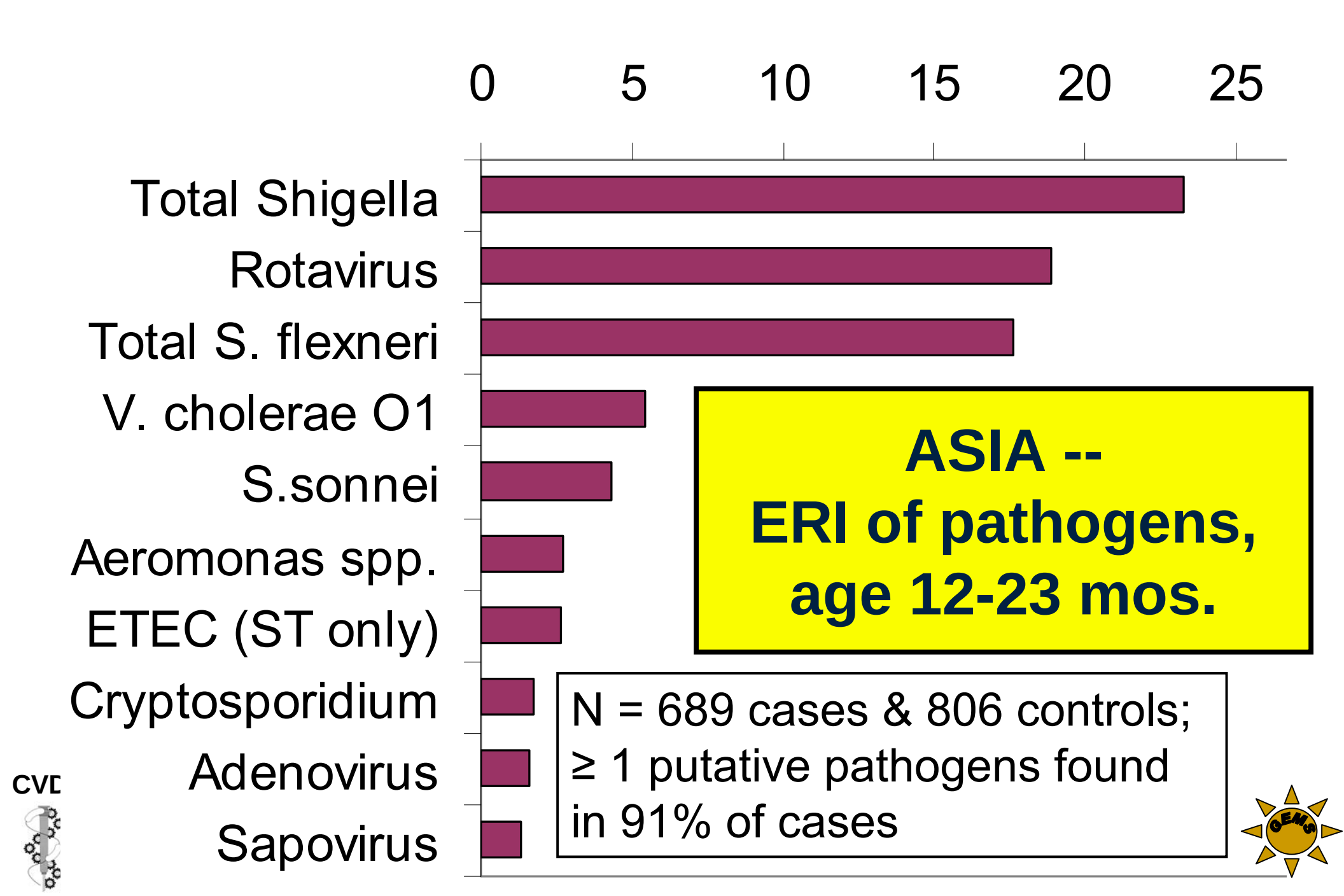
0
5
10
15
20
25
Total Shigella
Rotavirus
Total S. flexneri
V. cholerae O1
S.sonnei
Aeromonas spp.
ETEC (ST only)
Cryptosporidium
Adenovirus
Sapovirus
ASIA --
ERI of pathogens,
age 12-23 mos.
N = 689 cases & 806 controls;
≥ 1 putative pathogens found
in 91% of cases
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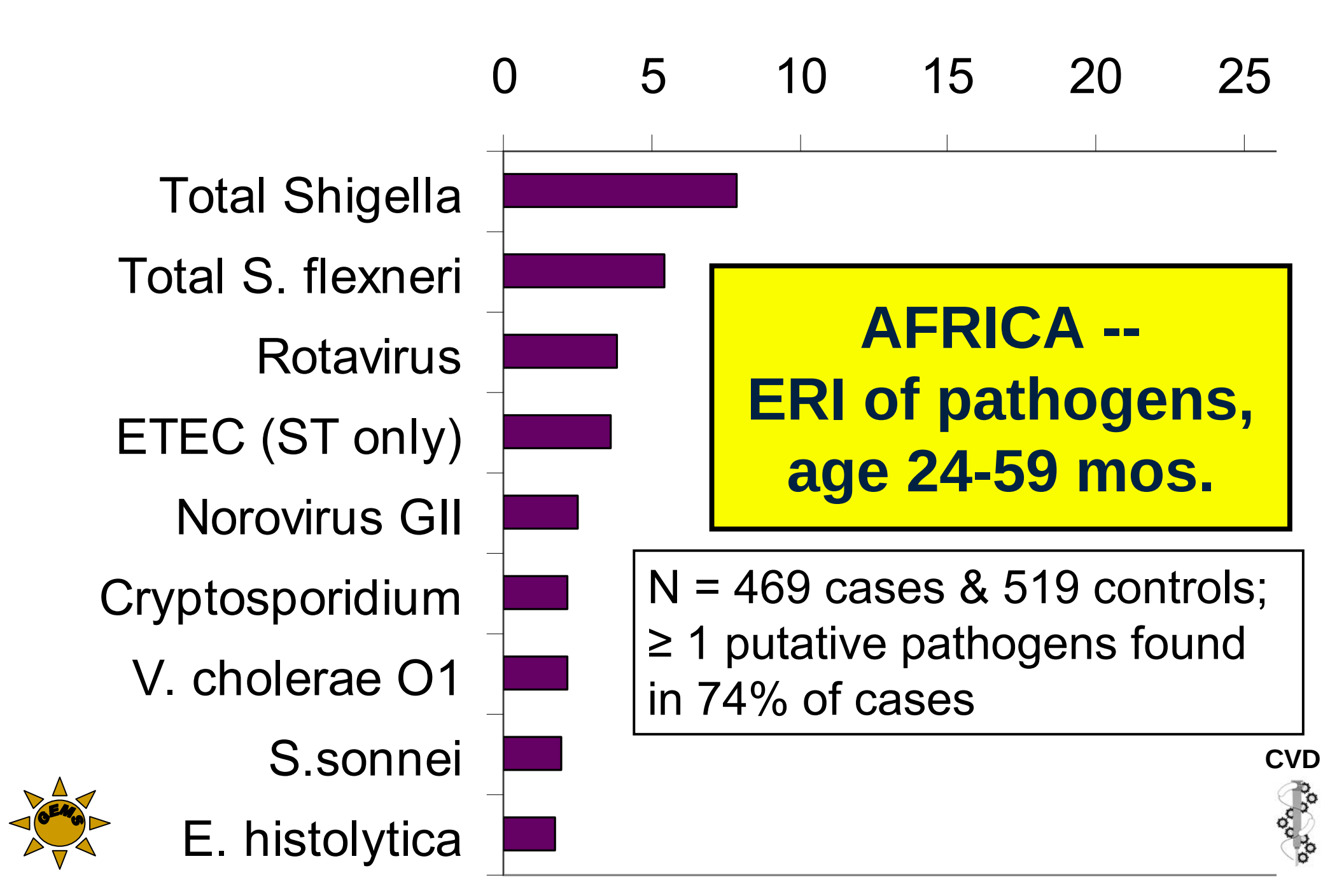
0
5
10
15
20
25
Total Shigella
Total S. flexneri
Rotavirus
ETEC (ST only)
Norovirus GII
Cryptosporidium
V. cholerae O1
S.sonnei
E. histolytica
AFRICA --
ERI of pathogens,
age 24-59 mos.
N = 469 cases & 519 controls;
≥ 1 putative pathogens found
in 74% of cases
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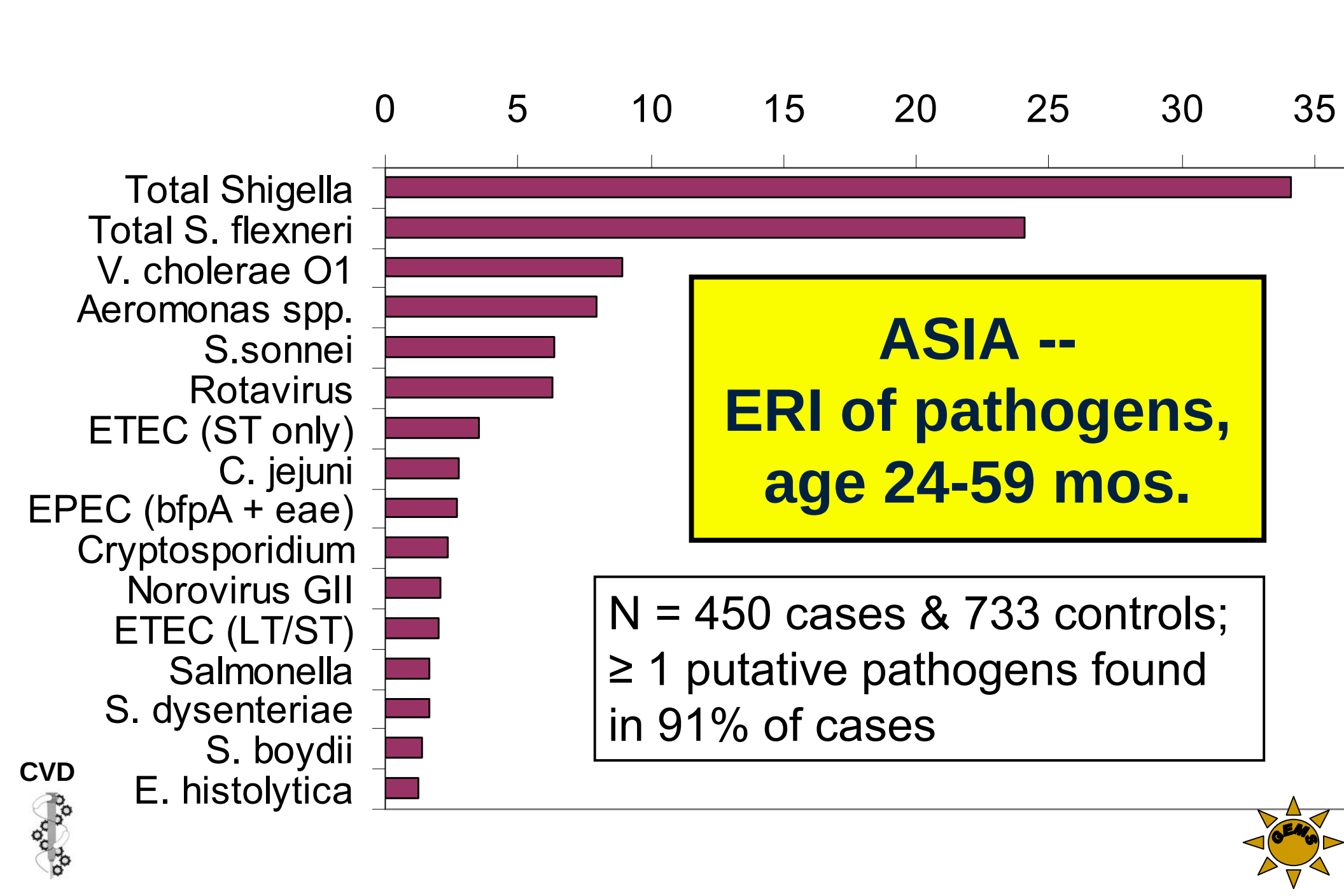
0
5
10
15
20
25
30
35
Total Shigella
Total S. flexneri
V. cholerae O1
Aeromonas spp.
S.sonnei
Rotavirus
ETEC (ST only)
C. jejuni
EPEC (bfpA + eae)
Cryptosporidium
Norovirus GII
ETEC (LT/ST)
Salmonella
S. dysenteriae
S. boydii
E. histolytica
ASIA --
ERI of pathogens,
age 24-59 mos.
N = 450 cases & 733 controls;
≥ 1 putative pathogens found
in 91% of cases
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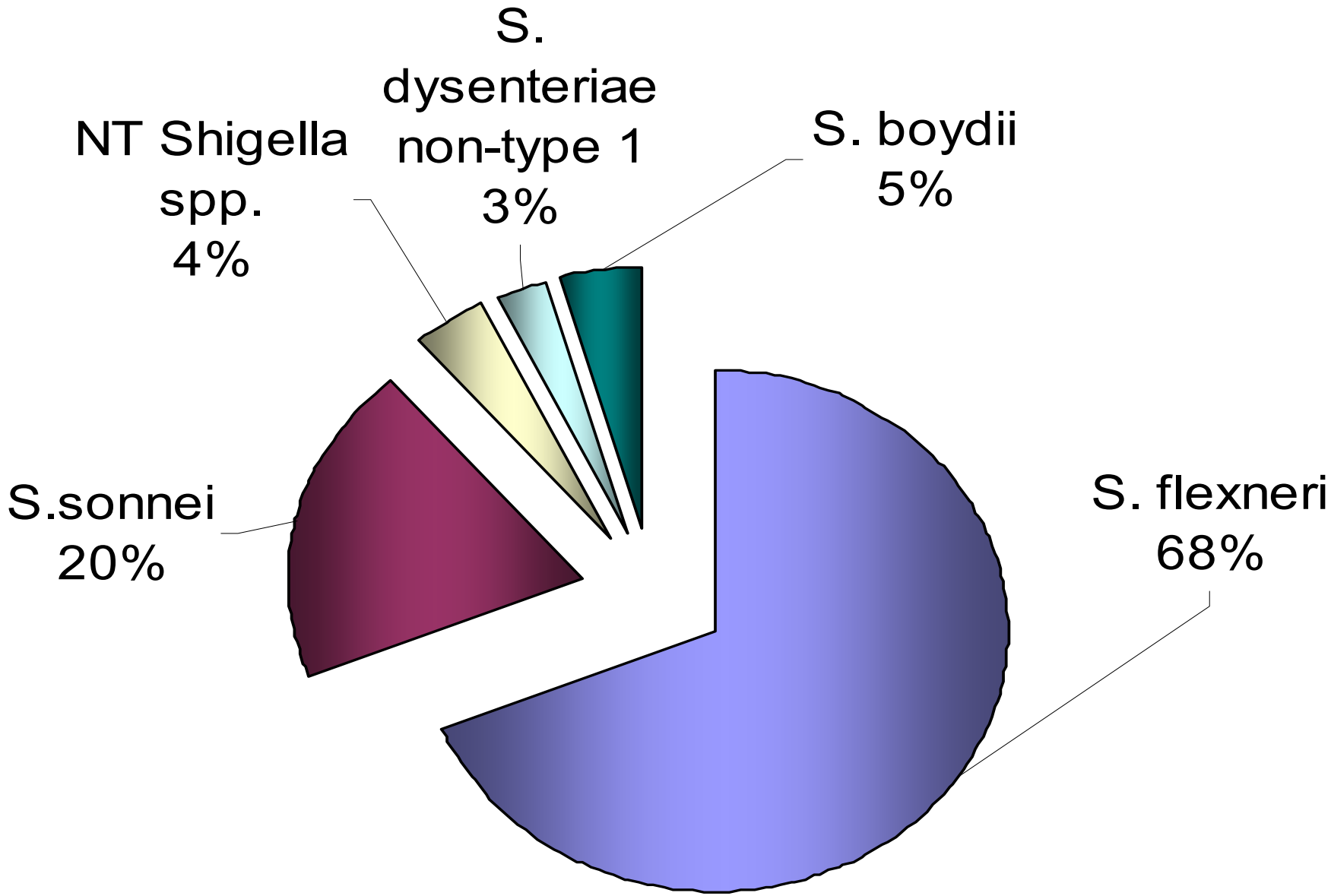
Shigella serogroup in 481 cases



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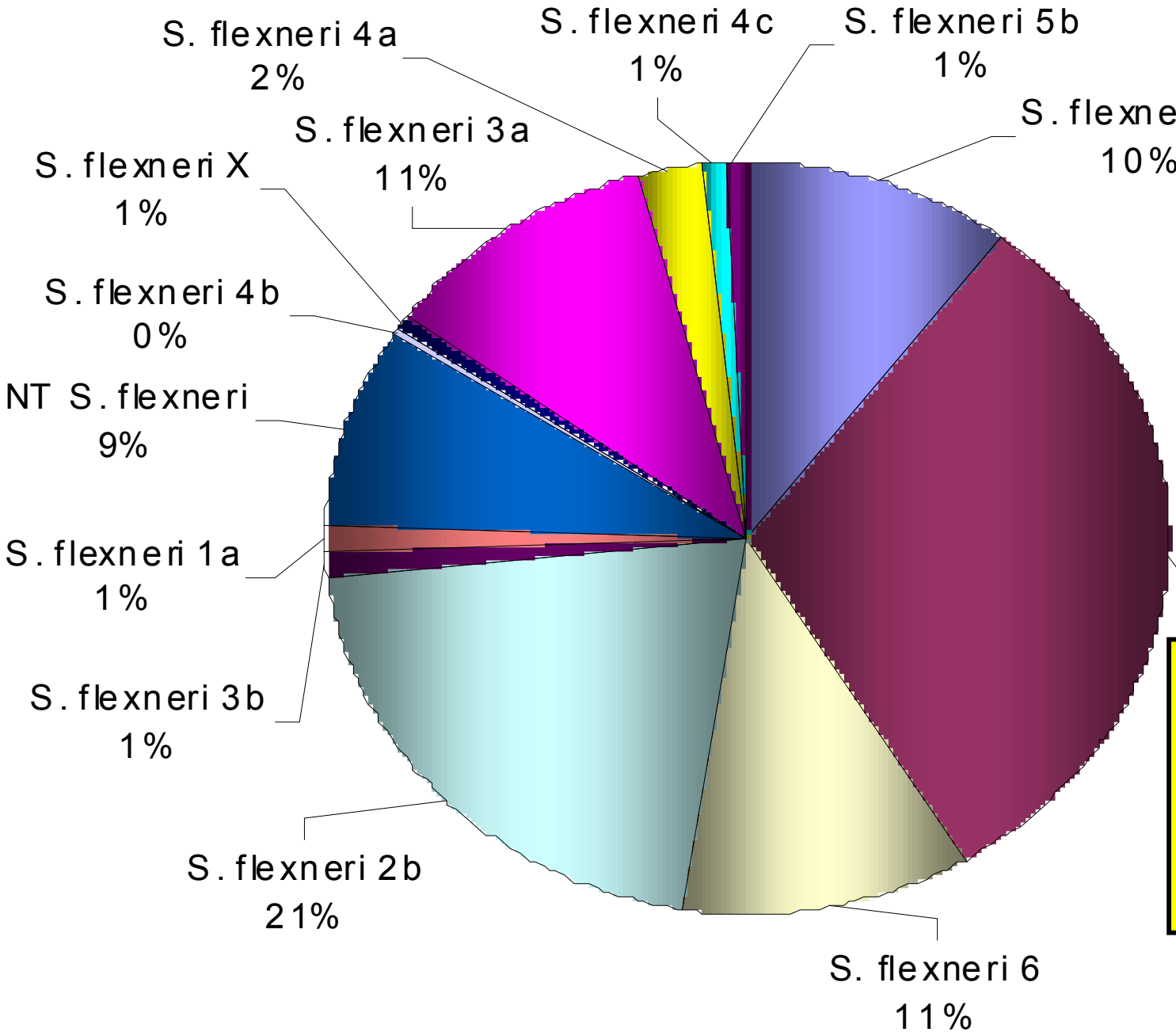

Shigella flexneri serotypes in 327 cases

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GEMS subject in Pakistan

Before Rehydration

After Rehydration

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Detecting deaths

- Enrolled children
  - During hospitalization
  - 60-day follow-up
- Non-enrolled children
  - DSS
- Verbal autopsy requested for all deaths among children age < 60 mos

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Deaths among study children

Country	Study	
	Cases (CFR)	Controls (CFR)
Bangladesh	4 (0.5%)	1 (0.1%)
India	2 (0.3%)	1 (0.1%)
Pakistan	10 (1.7%)	1 (0.1%)
Gambia	21 (3.2%)	2 (0.3%)
Mali	13 (1.4%)	2 (0.1%)
Mozambique	32 (7.0%)	3 (0.4%)
Kenya	38 (4.6%)	6 (0.7%)
Total	120 (2.4%)	16 (0.3)*

*(p<0.001); CFR= case fatality rate

Deaths among cases

Country	No. deaths (% of enrolled) by age (mos.)			
	0-11	12-23	24-59	Total
Bangladesh	3 (0.9)	-	1(0.5)	4 (0.5)
India	2 (0.6)	-	-	2 (0.3)
Pakistan	7 (2.2)	2 (1.2)	1 (1.0)	10 (1.7)
Gambia	10 (3.9)	10 (3.6)	1 (0.9)	21 (3.2)
Mali	7 (1.9)	5 (1.6)	1 (0.4)	13 (1.4)
Mozambique	15 (6.1)	12 (9.8)	5 (6.0)	32 (7.0)
Kenya	20 (5.4)	10 (4.4)	8 (3.5)	38 (4.6)
Total (% enrolled)	**64 (2.9%)**	**39 (2.3%)**	**17 (1.5%)**	**120 (2.4%)**

Timing and setting of deaths in study children

- 38% (45/120) of cases died within 7 days of enrollment in the study
- 66% (79/120) of cases died at home

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Economic data analysis

- Richard Rheingans, Rollins School of Public Health, Emory University
- Damian Walker, Bloomberg School of Public Health, John Hopkins University

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Data management

Cooperative Studies Program Coordinating Center,

Veterans Administration Medical Center Perry Point, MD

Kousick Biswas, Karen Lawson, Joseph Collins

Statistical analysis

William Blackwelder, CVD

Yukun Wu, CVD

Kousick Biswas, Perry Point VAMC

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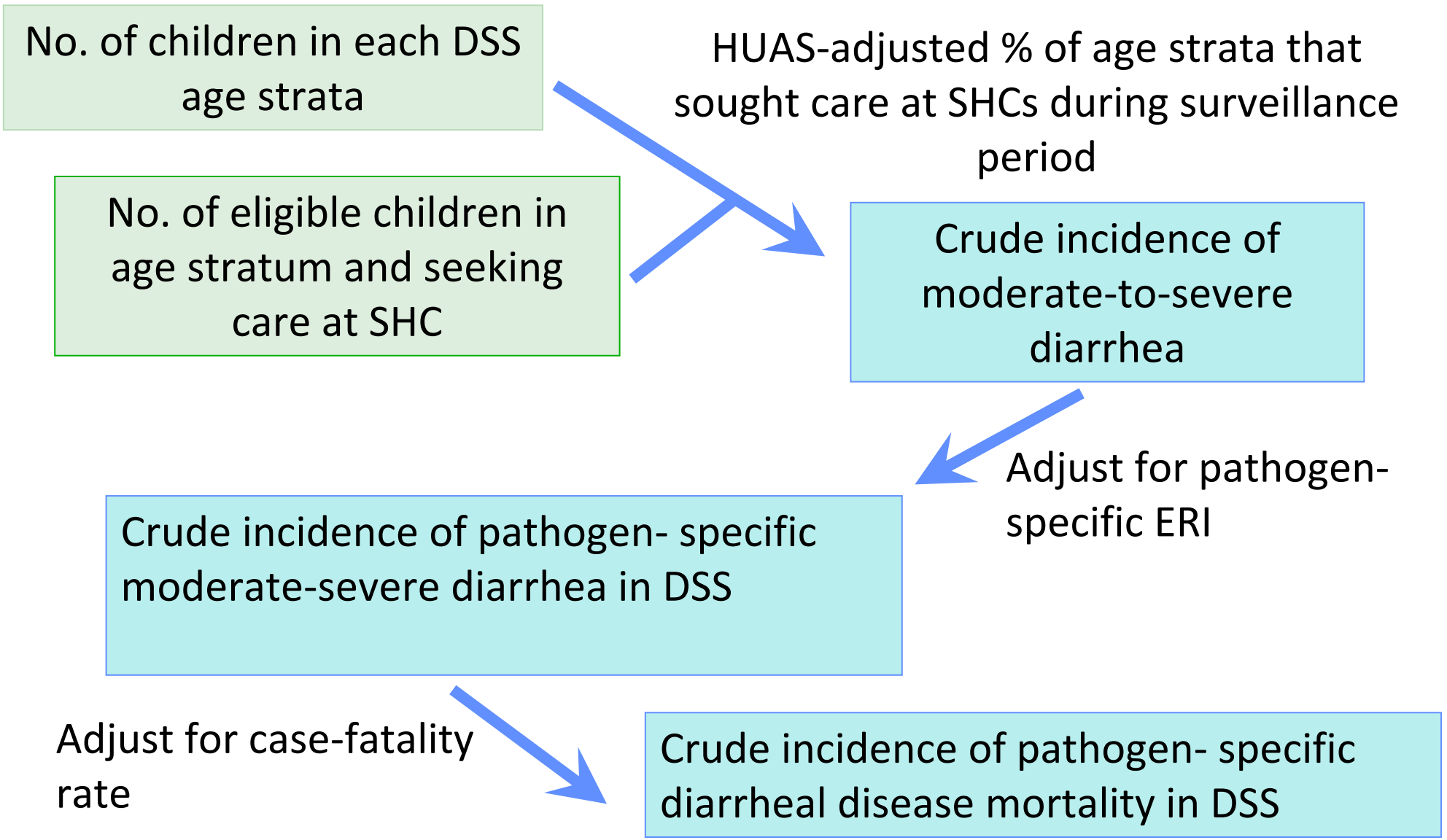
Calculation of crude incidence rate for pathogen-specific moderate-to-severe diarrhea & death in the DSS



GEMS water, sanitation & hygiene (W/S/H) strategy

- Collect W/S/H data from cases & matched controls
- Analyze W/S/H data from individual GEMS sites to identify risk factors for developing moderate/severe diarrhea (MSD), & protective factors
- Analyze data to identify risk factors for enhanced transmission of specific pathogens, and protective factors.
- Utilize site-specific, pathogen-specific data to **design highly focused environmental microbiologic studies**.
- Design large-scale interventions to assess the impact of WSH improvements, including on transmission of pathogens.

- *Carry out the intervention studies*
- *Propose large-scale implementation and assess impact and sustainability*.

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Statistical method: Conditional Logistic Regression Modeling

Model: $\log_e(\text{odds}) = \alpha + \beta x$

Conditional: takes matching into account

$\log_e$(odds) = natural logarithm of odds

odds = p/(1-p), where p is probability of **moderate or severe diarrhea (MSD)**

x = potential risk or protective factor (1=present, 0=absent)

α **and** β are coefficients to be estimated

e^{β} = antilogarithm of β

= odds ratio

= odds of MSD when x is present / odds of MSD when x is absent

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Open public well for drinking water

Manhiça, Mozambique

Basse, Gambia

Kolkata, India

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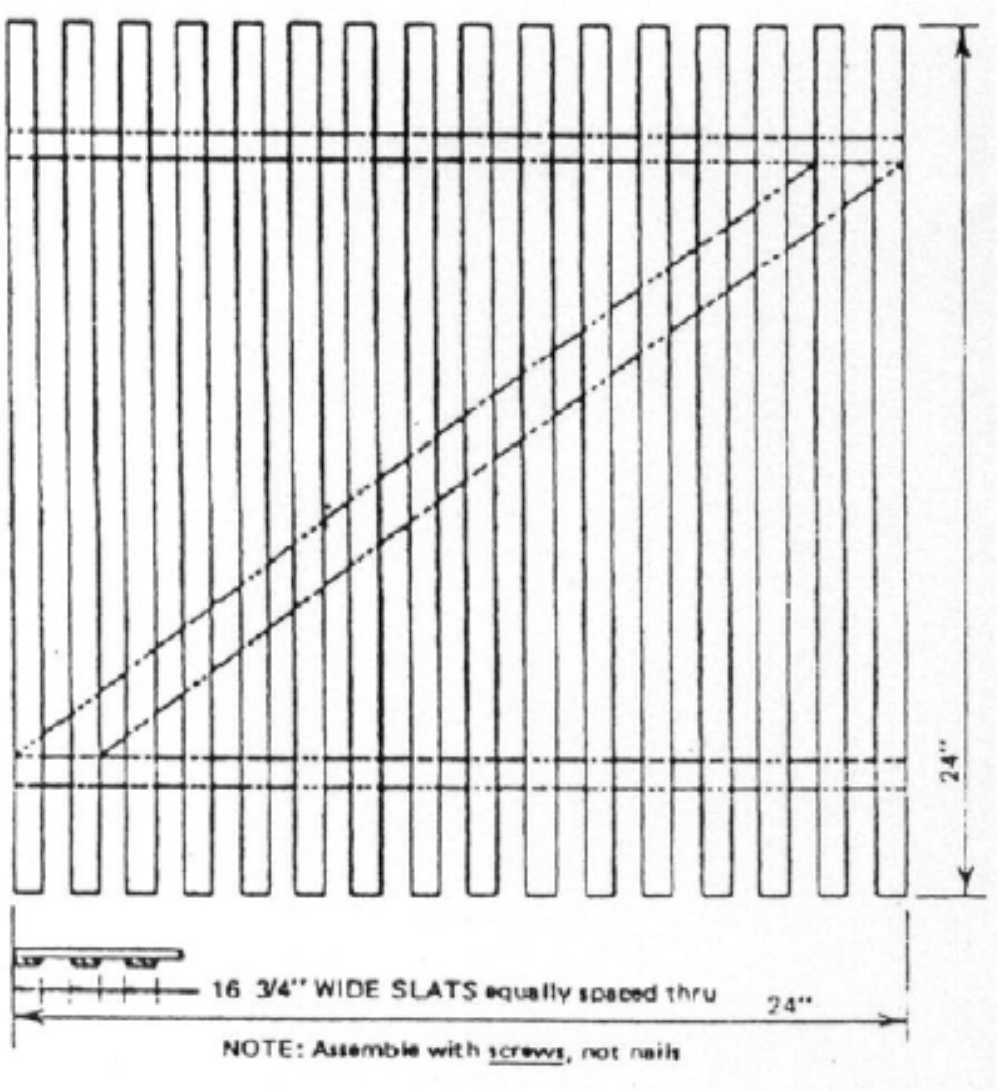
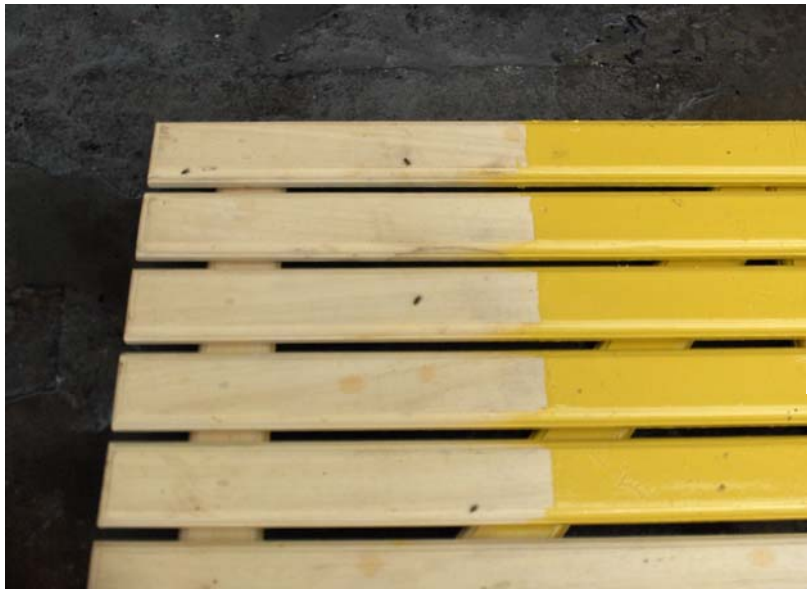
Filtering drinking water through a cloth, Basse, Gambia

Scudder grill for counting flies

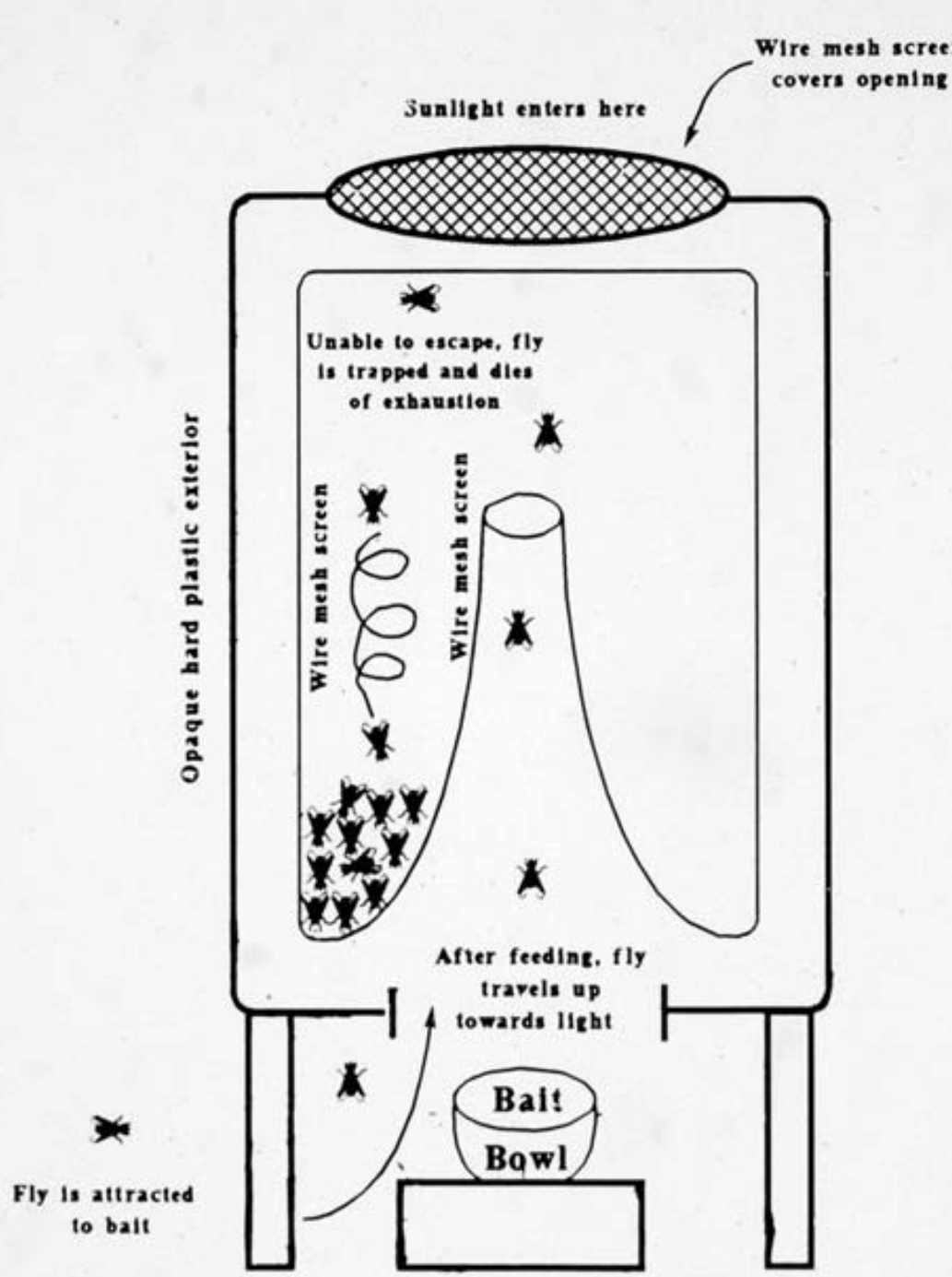


Mali

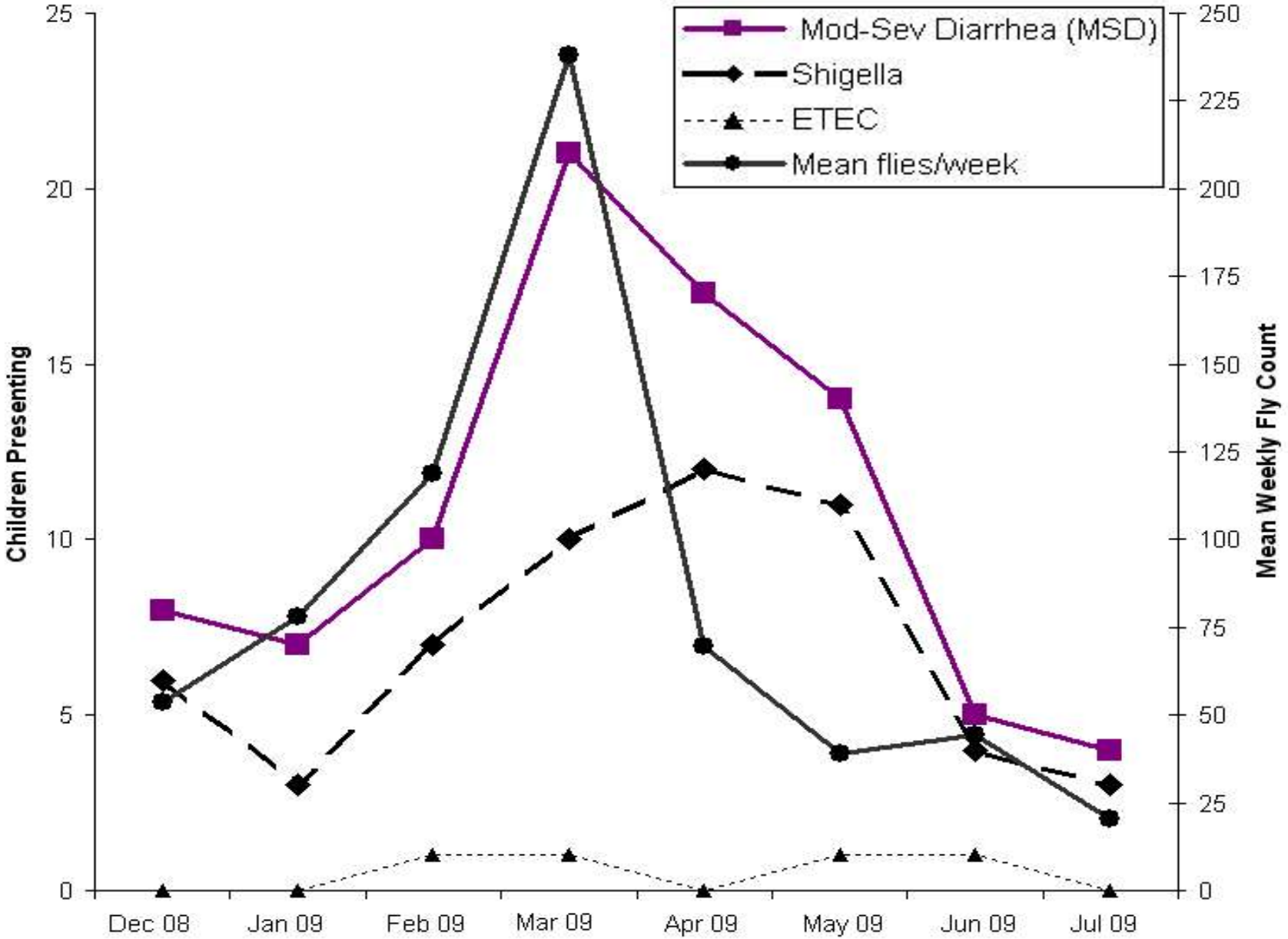


Bangladesh

Arbico® fly trap



Bangladesh, 24-59 months, *Shigella* and ETEC



What GEMS can provide

- Data to **prioritize** control efforts based on:
  - Pathogen-associated diarrhea **morbidity burden**
  - Pathogen-associated diarrhea **mortality burden**
- Incrimination of specific agents as diarrheal disease pathogens (**Pathogenicity Index**)
- **Correlation** of pathogens with distinct clinical syndromes
- A **network of field sites** with sophisticated laboratory capability where interventions can be evaluated in controlled trials
- Paves the way for sustainable, **low-tech water & sanitation interventions**

CVD

3rd GEMS Investigators' Meeting, Seattle, 2008

GEMS Investigators' Meeting, Kolkata, 2009

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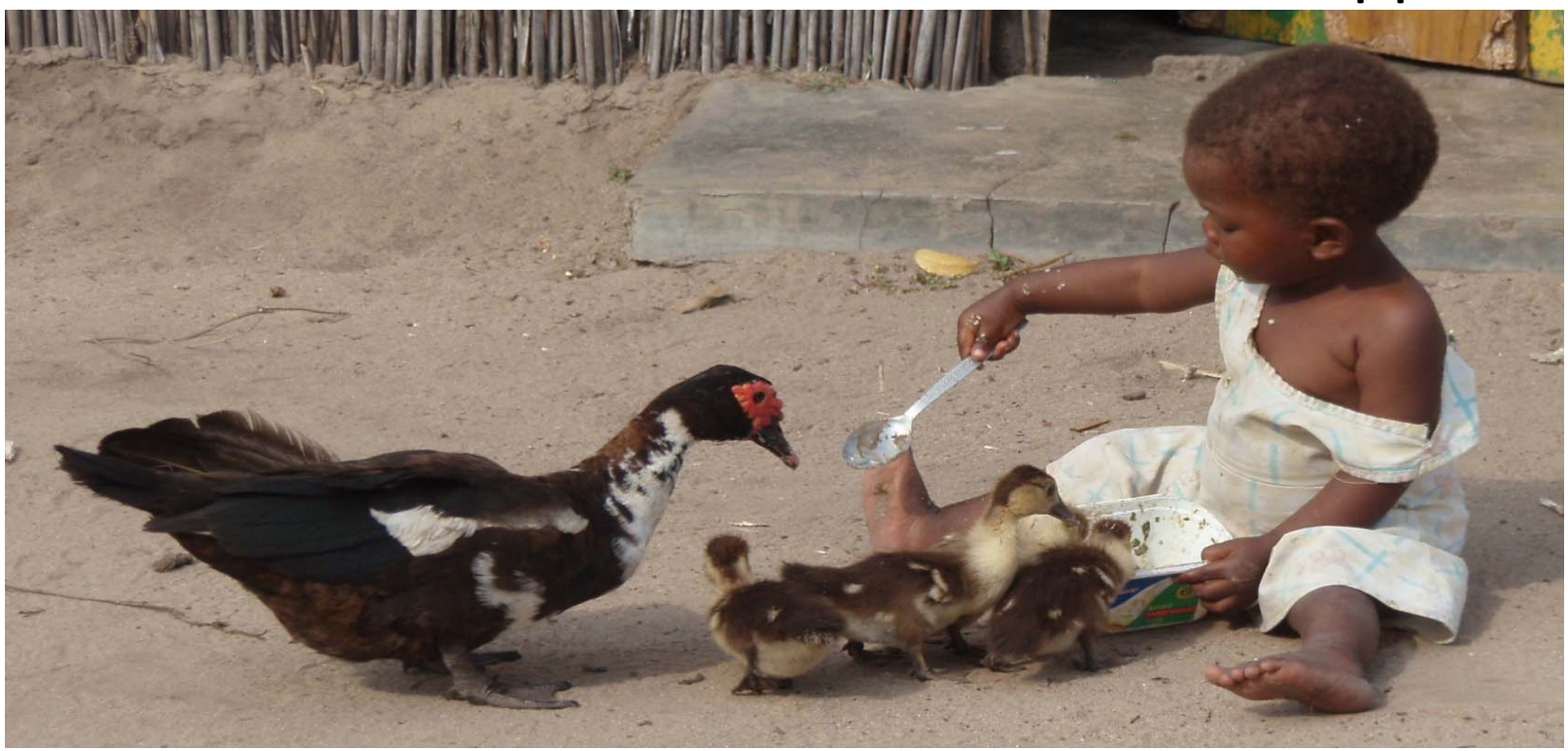

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