The Ruth Bishop Lecture

One person's journey through the land of pathogenic enteric viruses

Harry Greenberg MD

15th International Rotavirus Symposium
Sabin Vaccine Institute
Cape Town, South Africa
10/30/2025- 11/2/2025

My current Industry Interaction Disclosures (2025)

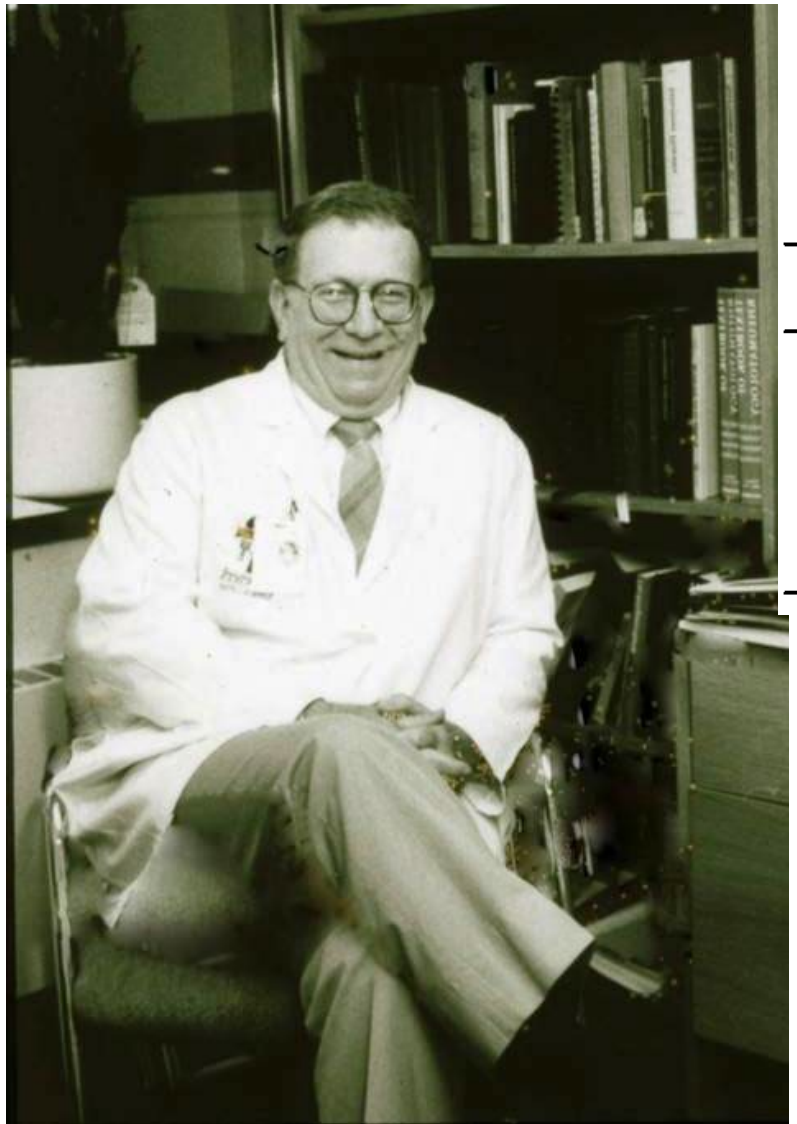
- Vaxart
- GSK
- Flugen

Harry Greenberg: Educational & Professional Chronology

- 1944 Born NYC,NY (AKA: The silent generation)
- 1966- BA- Dartmouth College
- 1970- MD- Columbia P & S ***1st Virology Research Experience***
- 1970-1972- 2 Yr Medical Residency, Bellevue Hospital, NYU, NY
- **1972-1974- USPHS, NIH, NIAID, Laboratory of Infectious Disease**
- 1974- 1976- GI Fellow, Stanford University Medical School ***2d Virology Research Experience***
- **1976-1983 – Back to NIH, USPHS, NIAID, LID** ***3d Virology Research Experience***
- 1983- 2023- Back to Stanford, Professor of Medicine and Microbiology and Immunology
- 1999-2001- Senior Associate Dean for Research, Stanford Medical School
- **1999- 2015- Member Indo/US VAP- Part of the team that developed ROTAVAC**
- **2001 & 2002- LOA- Chief Scientific Officer at Aviron, local vaccine company start-up**
  4th Virology Research Experience
- 2002- 2018- Senior Associate Dean for Research, Stanford Medical School
- 2008-2023- Director& PI: NIH funded Stanford Center for Clinical & Translational Research
- **2023- 2025- Retired, Emeritus faculty**

"Australia Antigen" (HBsAg) Detection in Infectious Blood Donors (A Modified proof of "Kock's Postulates")

Dr. David J. Gocke: 1st Mentor Par Excellence



Summary of 168 Patients Who Received Hepatitis Antigen Containing Transfusions

Blood Infused	# of Patients	Hepatitis	Antigen Only	Antibody	Well
Positive	42	22	3	6	11
Negative	126	8	...	...	118

60%

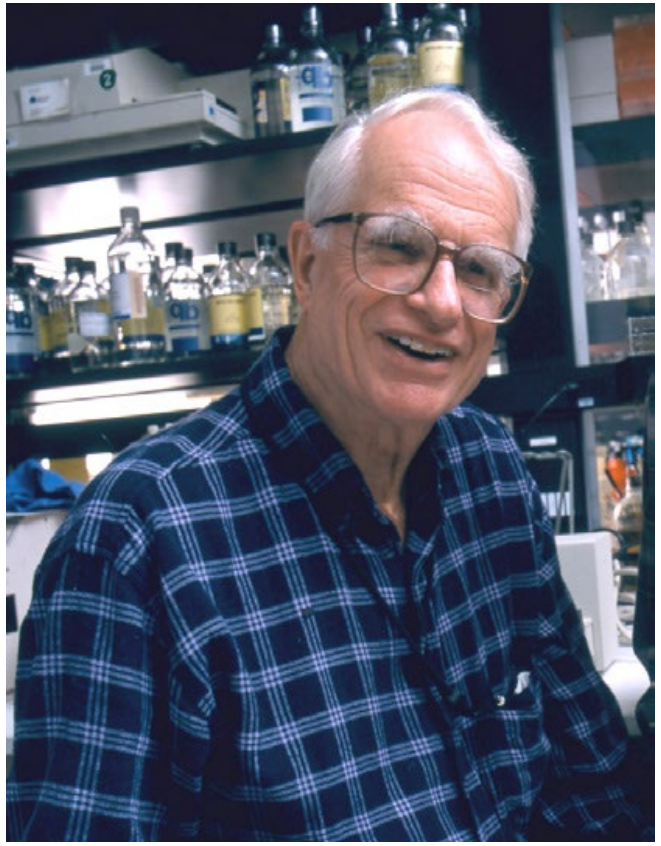
6%

Transfusions of HBsAg containing blood were strongly associated with subsequent development of hepatitis (B).

Importance of having an early successful research experience

Lancet , 1969, JAMA,1970

NIH Career Mentors Par Excellence
1972-1974; 1976-1983



Bob Chanock



Al Kapikian

Stanford GI Fellowship -1974-1976

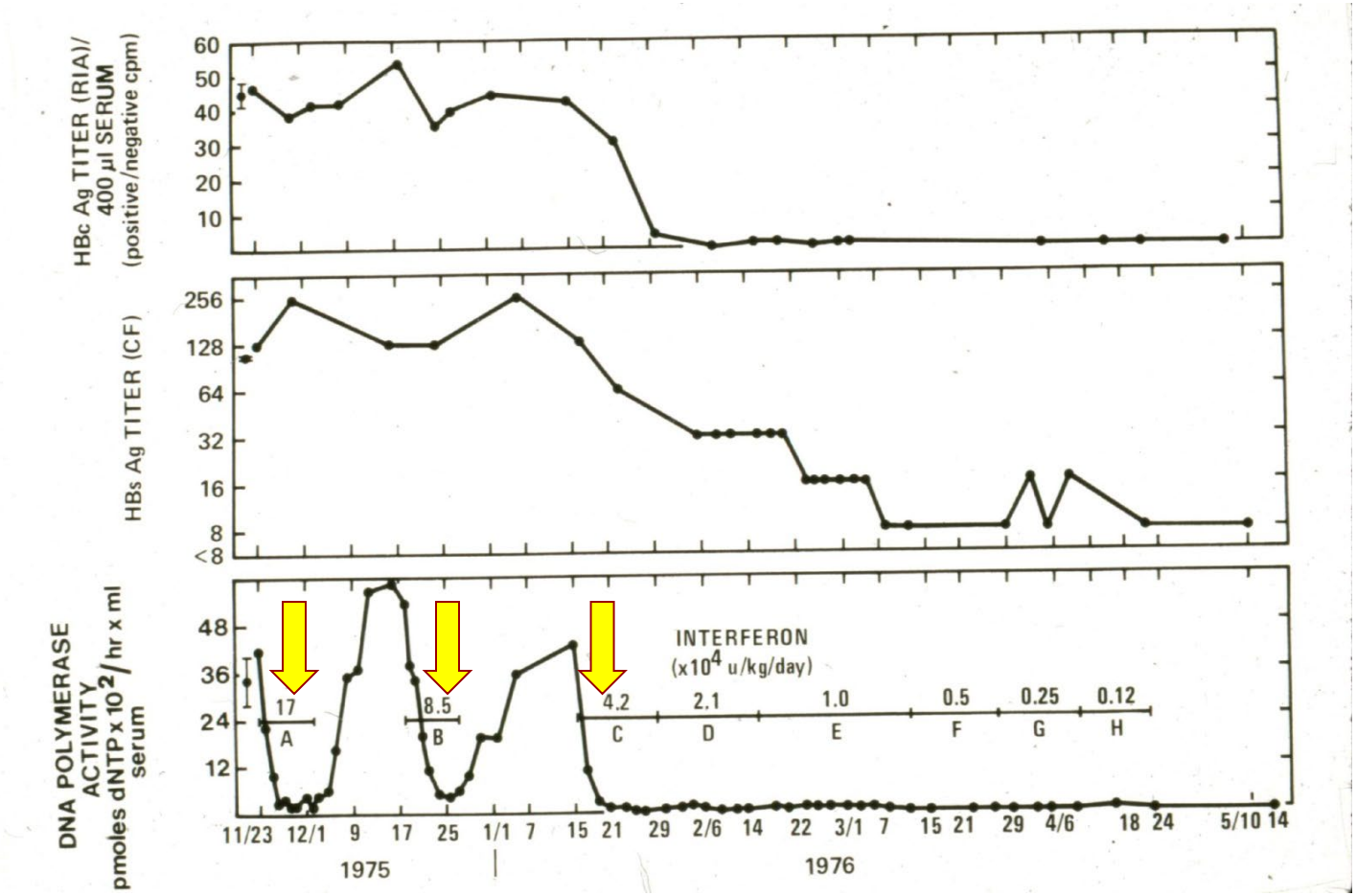
First effective antiviral therapy for chronic Hepatitis B Virus

Tom Merigan



Bill Robinson

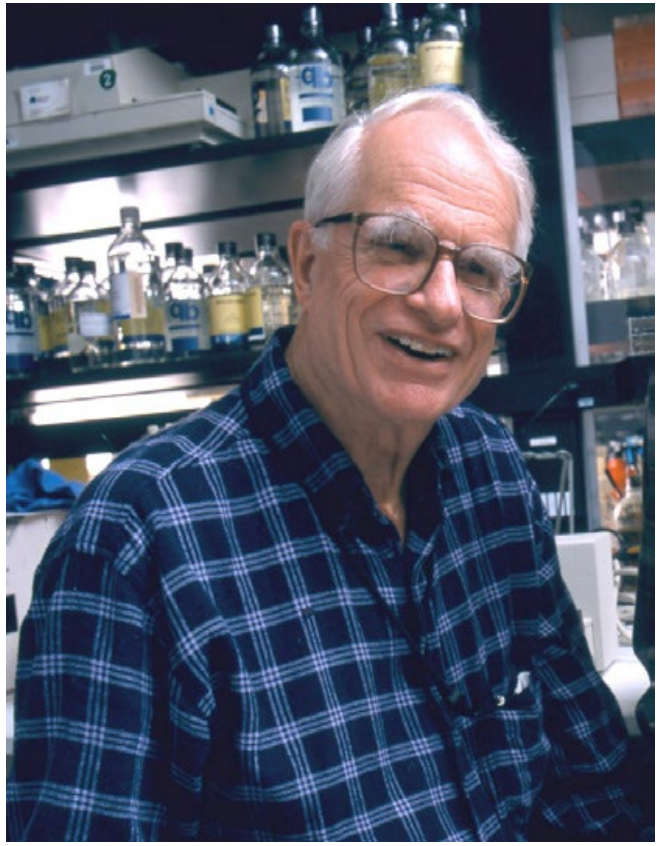




Importance of good luck, of applying novel technology to study a research question, and most important, *having great mentors*

Greenberg H, et al, NEJM,1976

NIH Career Mentors Par Excellence
1972-1974; 1976-1983



Bob Chanock



Al Kapikian

The Lancet, 1973
A VERY SIMPLE EXPERIMENT
changed everything!

VIRUS PARTICLES IN EPITHELIAL CELLS OF DUODENAL MUCOSA FROM CHILDREN WITH ACUTE NON-BACTERIAL GASTROENTERITIS

RUTH F. BISHOP G. P. DAVIDSON

Department of Gastroenterology, Royal Children's Hospital, Melbourne, Australia

I. H. HOLMES B. J. RUCK

Department of Microbiology, University of Melbourne, Australia

Summary Electron microscopy of duodenal mucosa from nine children with acute non-bacterial gastroenteritis revealed virus particles in epithelial cells from six patients. The morphology of the virus particles was identical in each of the six children. The virus belonged to the orbivirus group. No virus particles were observed in duodenal mucosa obtained from three of these children after clinical recovery. This orbivirus is believed to have been an important cause of sporadic gastroenteritis in children in Melbourne during the 3 months of the survey.



Noroviruses in a fecal specimen aggregated by convalescent immune sera

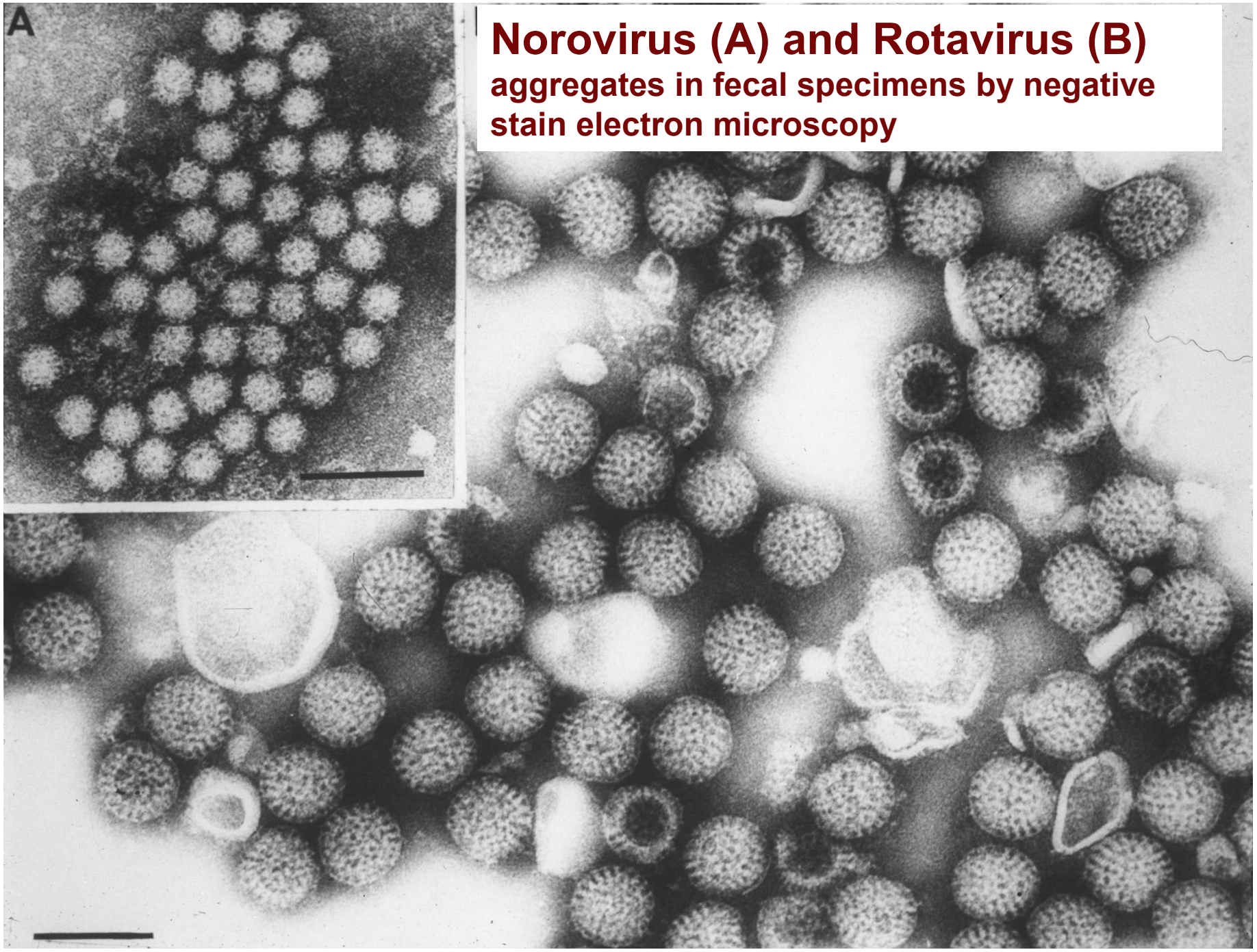
ANOTHER IMPORTANT DISCOVERY!

A. Kapikian

T. Flewett

R. Bishop

1972/ 1973



Norovirus (A) and Rotavirus (B)

aggregates in fecal specimens by negative stain electron microscopy

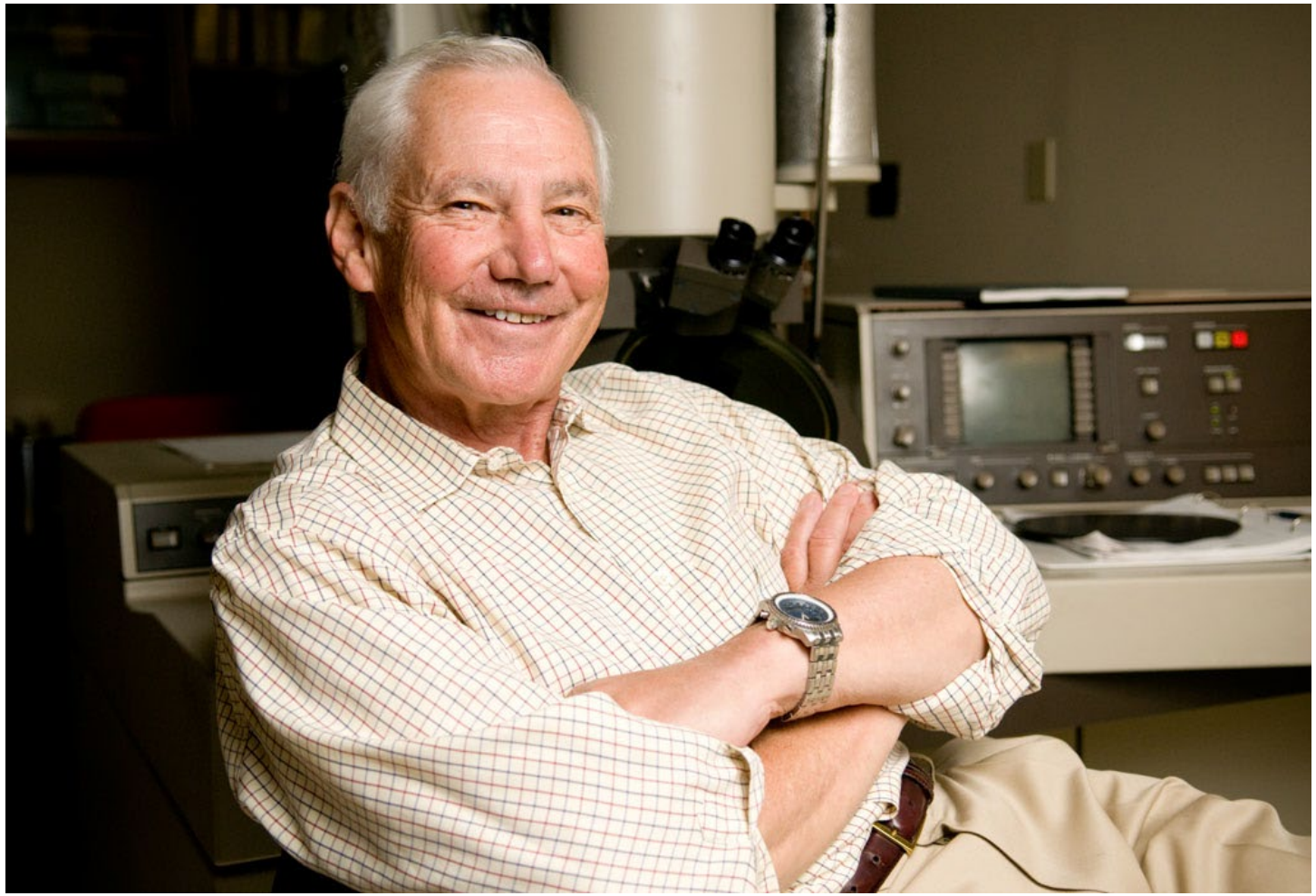
Note: large number of RV particles in diarrheal a specimen No antisera needed

Dr. Stanley Falkow (Chair of Department of M&I)

Stan gave me a joint appt. in the M&I Dept

Offered me lab space in Fairchild following the Loma Prieta earthquake

Taught me the power of humor as a major teaching skill

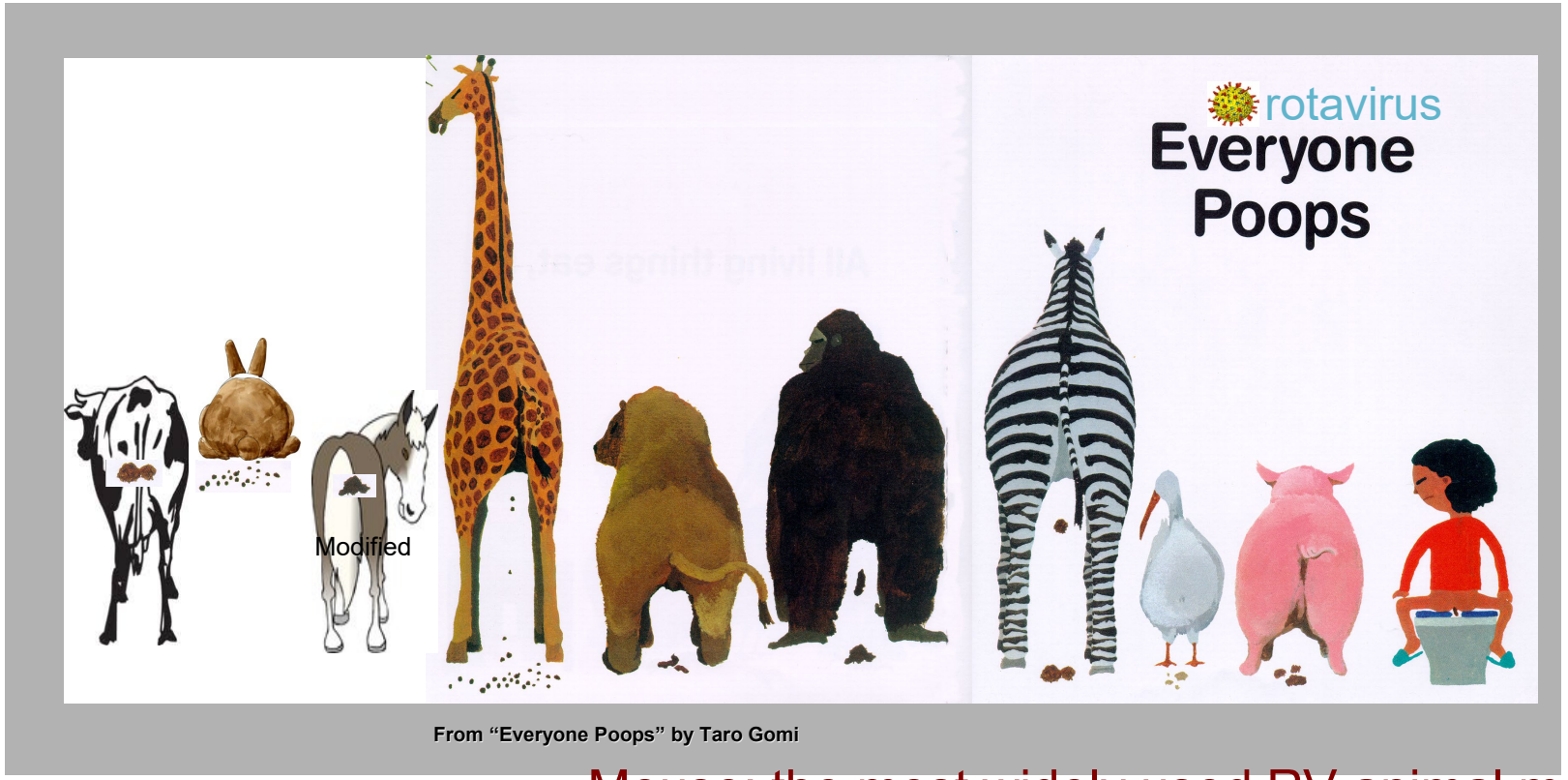


Gifted Microbiologist

Spectacular Mentor & Teacher

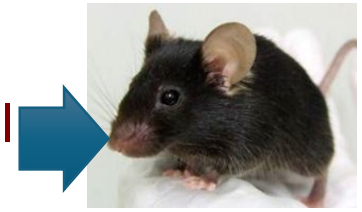
II- WHAT IS THE BASIS OF RV HOST RANGE RESTRICTION?

Genetically and antigenically distinct RVs strains infect specific mammalian and avian species



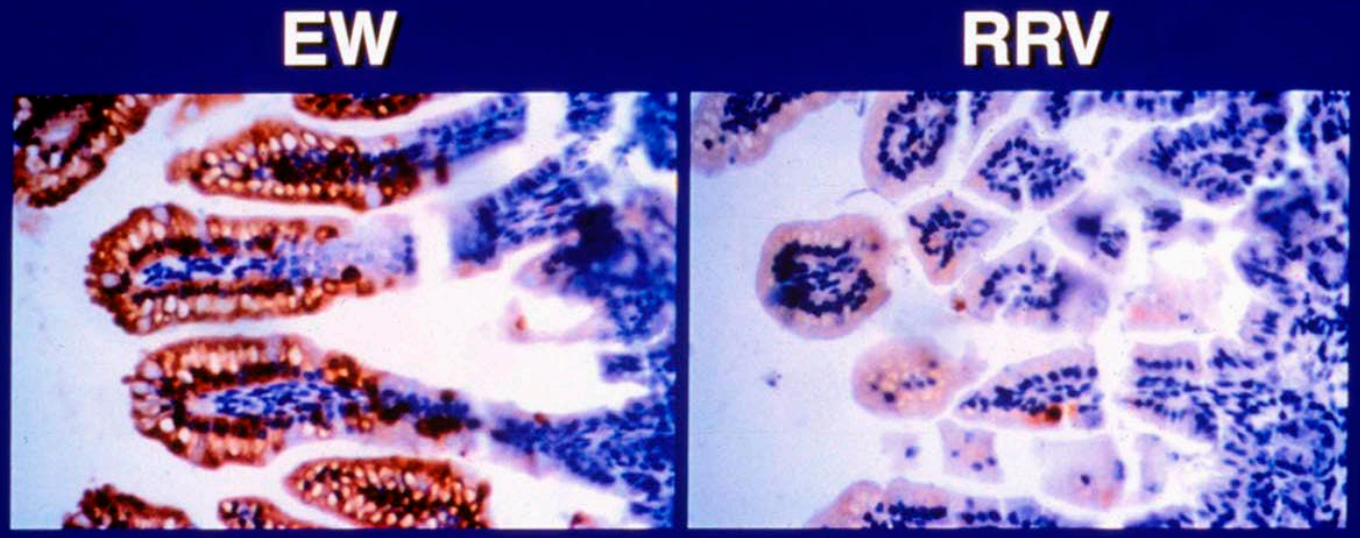
From "Everyone Poops" by Taro Gomi

Mouse: the most widely used RV animal model

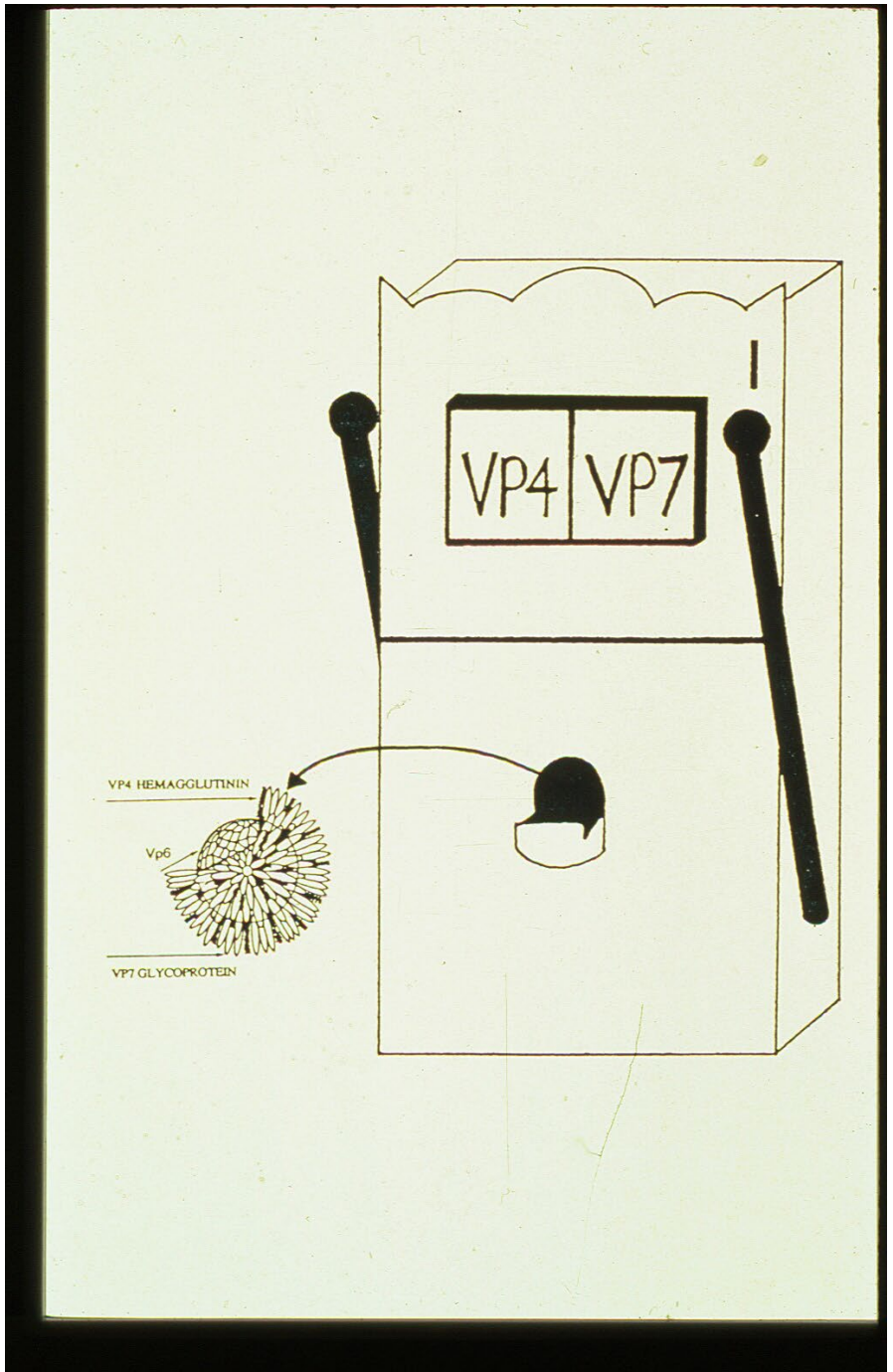


Specific RV infection strongly associated with diarrheal disease in the young of a specific species, despite the fact that RVs have segmented genomes and undergo gene reassortment at high frequency

4ILE Ileum from 4-day old suckling mice infected with either murine (EW) or simian (RRV) rotavirus and stained with Ab to rotavirus VP6



Rotavirus replication *in the small bowel* is also highly host-range restricted which has served as a basis for vaccine attenuation in several instances.



Animal models (mostly mice and pigs) have been very useful

Based on a variety of immunization and passive transfer studies in mice, B cell derived antibodies to either VP4 or VP7 were sufficient to provide protection from RV disease. On the other hand, immune RV protein specific CD8+ T cells could speed the resolution of RV infection and diarrheal disease but were not efficient at providing protection from infection or disease.

An Experimental Basis for Developing a Rotavirus Vaccine

- Mexican children have several rotavirus infections in the first years of life, **but the first was frequently the most severe**
- The first rotavirus infection induced **substantial immunity** against subsequent severe rotavirus (RV) gastroenteritis

# of previous RV infections	% efficacy (95% CI) by disease severity	
	Any	Mod. to severe
1	77	87
2	83	100

- Natural immunity is both serotype-specific and heterotypic

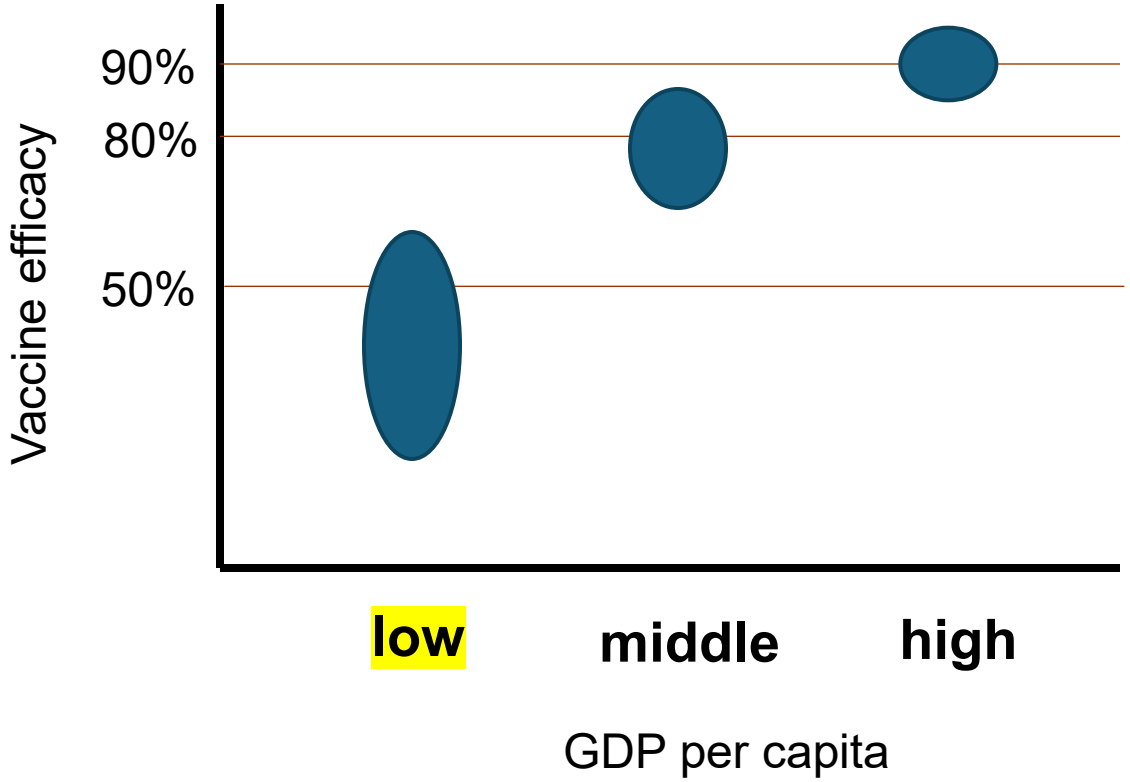
A second severe illness caused by any serotype was uncommon

Velazquez et al, N Engl J Med 1996;335:1022-8.

How well have live oral rotavirus vaccines worked in low-, middle-, and high- income countries?

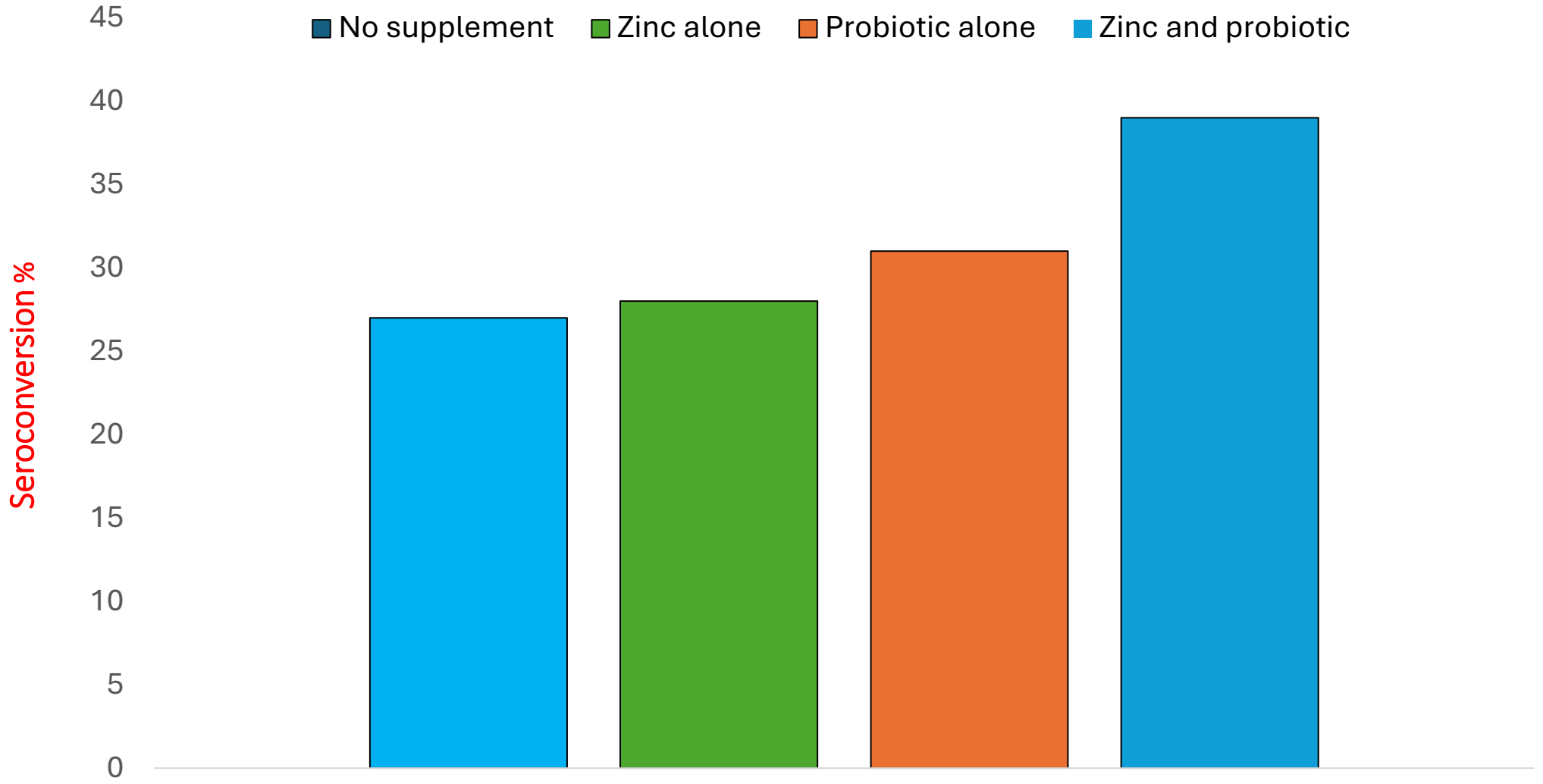
Summary Data

Rotavirus vaccine efficacy and the wealth of nations



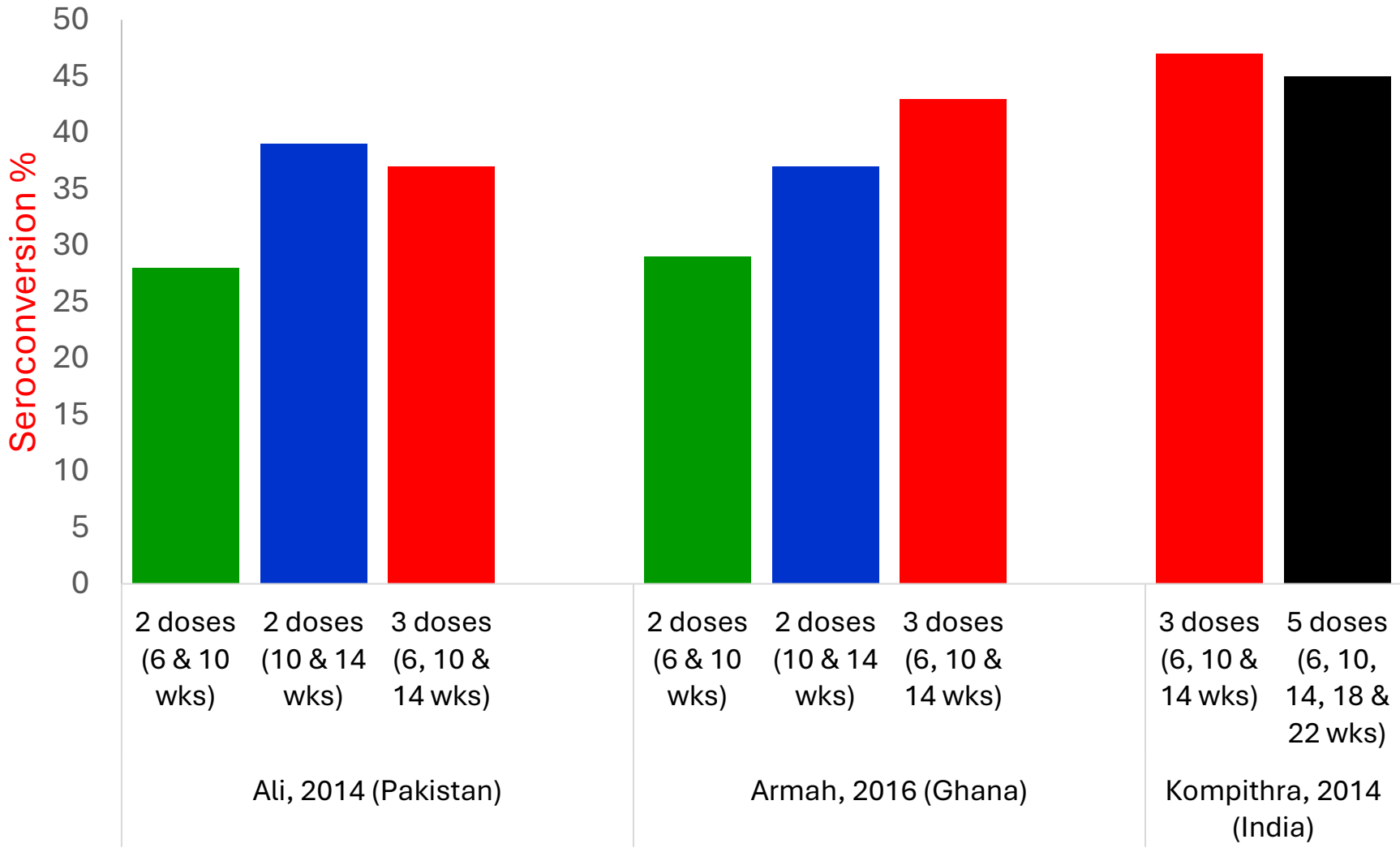
slide provided by Dr U. Parashar

Supplementing with both zinc and probiotics only slightly improved the vaccine immune response



Lazarus et al, Vaccine, 2018 (Slide provided by Dr. U Parashar)

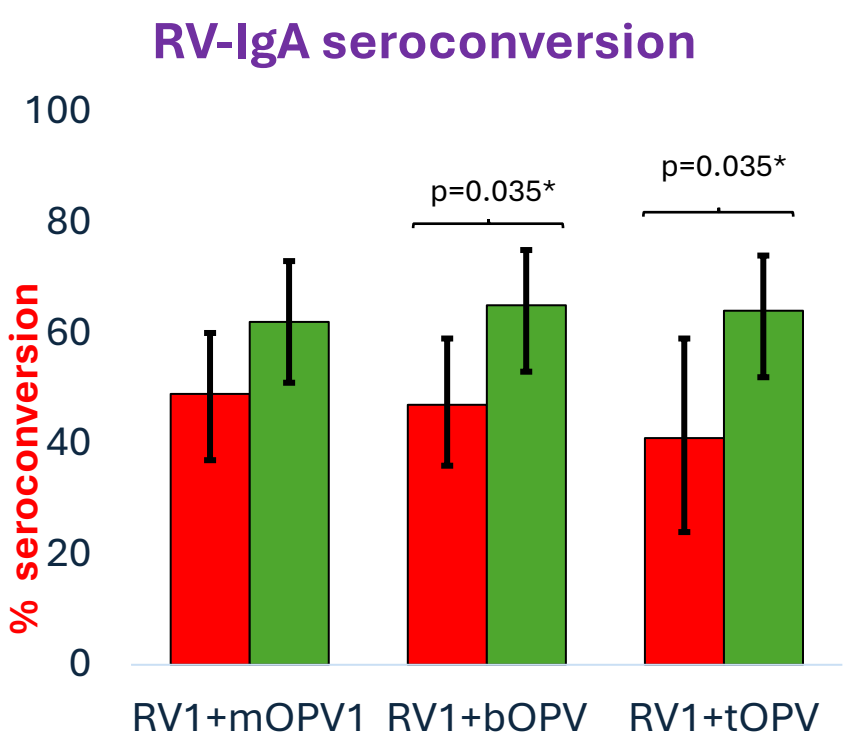
Delaying 2-dose Rotarix schedule or adding additional doses only slightly improved vaccine sero-response rate in several settings

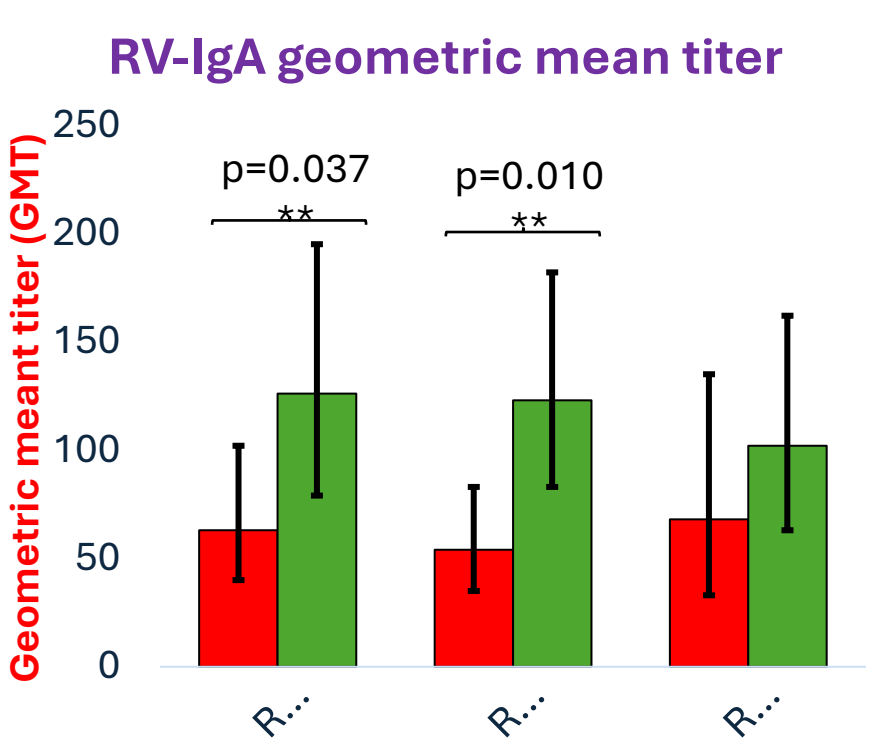


(Slide provided by Dr U Parashar)

Withdrawal of OPV improved rotavirus vaccine immunogenicity

Concomitant OPV and rotavirus vaccine
Separated OPV and rotavirus vaccine





Emperador D et al. CID 2016
(slide provided by Dr U Parashar)

If you want a widely available rotavirus vaccine in India- develop it, manufacture it, test it, and market in India *

A few members of the Indian RV Vaccine development team- Early days at the first Bharat manufactory site in Hyderabad



MISSING DRS. RAJ BHAN (Indian government official), Gates foundation representation, & MANY OTHERS

THE LANCET
2014

Efficacy of a monovalent human-bovine (116E) rotavirus vaccine in Indian infants: a randomised, double-blind, placebo-controlled trial

Nita Bhandari, Temsunaro Rongsen-Chandola, Ashish Bavdekar, Jacob John, Kalpana Antony, Sunita Taneja, Nidhi Goyal, Anand Kawade, Gagandeep Kang, Sudeep Singh Rathore, Sanjay Juvekar, Jayaprakash Muliyil, Alok Arya, Hanif Shaikh, Vinod Abraham, Sudhanshu Vrati, Michael Proschan, Robert Kohberger, Georges Thiry, Roger Glass, Harry B Greenberg, George Curlin, Krishna Mohan, G V J A Harshavardhan, Sai Prasad, T S Rao, John Boslego, Maharaj Kishan Bhan, for the India Rotavirus Vaccine Group†*

Product name: Rotavac

Endpoints	ROTAVAC N= 4354	Placebo N= 2187	Vaccine Efficacy % (95% CI)	p value
Severe RV GE requiring hospitalization# or supervised rehydration therapy$				
Till 2 yrs of age	92 (2%)	102 (5%)	**55.6%** (40.5, 66.8)	<0.0001
Till 1 yr of age	57 (1%)	65 (3%)	**56.3%** (36.7, 69.9)	<0.0001



India takes the lead in developing new, effective & economically feasible RV vaccines in Asia



- 2 New Vaccines from India
  - Rotavac licensed 2014 (100,000,000 just given)
  - ROTASIIL, Serum Institute of India, licensed 2017



Prime Minister Modi

"Government of India will provide a rotavirus vaccine to all Indian children"

Some questions the answer to which might hasten development of better RV approaches for prevention of RV disease in LICs

1) Why are natural RV infections & current oral RVs vaccines highly effective in preventing severe RV diarrhea in the USA/Europe but only 40-60% effective in LIC?

2) Is parenteral immunization with inactivated RV TPL(s), recombinant TLPs, recombinant RV proteins, RV RNAs w/o adjuvants (mucosal/ systemic) a more effective approach to enhance vaccine efficacy in L/MICs?

3) Is a birth immunization of a live attenuated RV vaccine (RV VLP or protein) useful/ and how useful?

4) Could a viral/bacteria/yeast produced enteric or parentally delivered vaccine that expresses selected RV protein(s) be more protective and but still safe?

5) Which of the RV vaccine/prevention approaches above (or others) might be best explored using a human CHIM approach?

6) Are there highly predictive *in vitro* (organoids/other) or *in vivo* (small animals/other) ways to test and compare experimental RV vaccines strategies for potential efficacy in humans?

7) Is giving another oral live attenuated RV vaccine between 7 and 9 months of age (when maternal immunity is basically gone) capable of boosting immunity and enhancing protection at end of year 1 & year 2?

Some potential rotavirus prevention strategies for further exploration/ implementation (2025)

- 1) Birth Dose
- 2) Inactivated whole RV virions or engineered TLPs delivered parenterally +/- adjuvant
- 3) Engineered recombinant RV protein(s)/or RNAs administered parenterally to enhance their immunogenicity (+/-existing or novel adjuvants)
- 4) genetically modified RV particles for enhanced immunogenicity
- 5) Rotavirus used as a vector for Norovirus, other enteric pathogen targets
- 6) Long (> 6 mo) and safe acting monoclonal Abs that block or significantly restrict replication of RV in the GI tract
- Long acting (> 6 mo) rotaviral antivirals that could significantly suppress RV GI tract replication

Three Basic Principles Derived from the prior Rotavirus Vaccine Development and Implementation Saga

- Vaccine Development is a Team Sport

- Effective Implementation and Delivery of a Vaccine Takes a Village

- The development and subsequent implementation of a new vaccine is often most effectively caried out by the country that needs it most