



Pivotal role for Human Challenge Trials (HCT) in the development of a candidate norovirus vaccine

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2nd Human Challenge Trials in Vaccine Development

Norovirus Vaccine and Human Infection Challenge Model



- Vaccines and the human infection challenge model studies have been extremely important advancing knowledge of this important human pathogen

Rationale for use of vaccine and human infection challenge model studies for Noroviruses



- Human proof of concept to de-risk Phase 3 studies
 - Show vaccine effect prior to investment in large field studies
- Selection of vaccine candidates with or without novel adjuvants
 - No animal model is available for human norovirus
 - Humans are the only 'animal' model available for human norovirus
- Assessing disease mechanism and correlates/surrogates of protection
 - Illness and infection attack rates
 - Pre-and post-exposure biologic samples, immune response profiles
 - Breadth of protection with heterologous strains
 - Viral shedding profiles as a surrogate for transmission

'Norovirus - the perfect human pathogen'



- Highly contagious
- Environmentally stable
- Rapidly and prolifically shed
- Genetic and antigenic diversity
- Recurrent illness - evokes limited natural immunity
- May be fatal in the elderly and very young

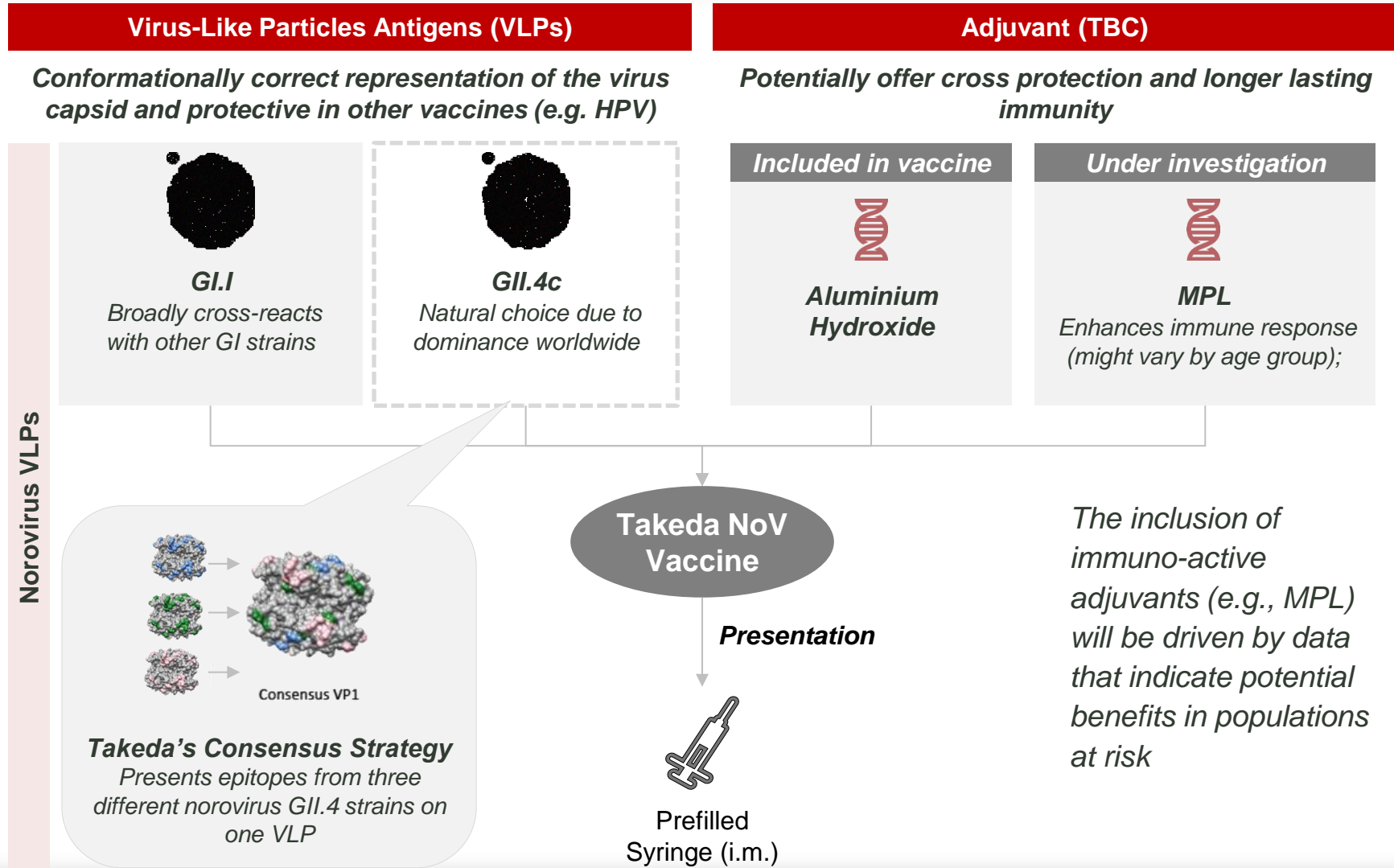
(Hall AJ J Infect Dis 2012;205:1622-4.)

- Leading cause of the world's infectious gastroenteritis burden

(Ahmed SM, et al. Lancet Infect Dis 2014;14:725-30.)

- Nearly one out of every five GE episodes is due to norovirus
- No efficient cultivation system

Takeda's Vaccine Candidate is Based on Virus-like Particle Antigens Representing Two Major Genogroups



Two Human Challenge Studies Show Vaccine Protection is Possible



GI.1 – homologous challenge

- *Atmar RL, et al. N Engl J Med 2011;365:2178-87.*

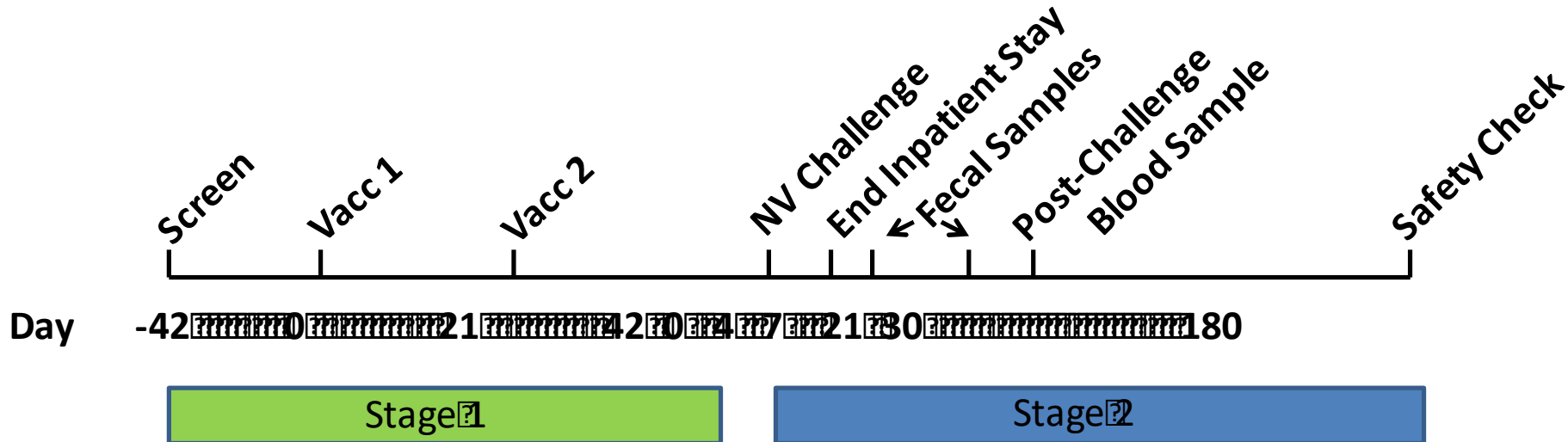
GII.4 – heterologous challenge

- *Bernstein DI, et al. J Infect Dis 2015;211:870-8.*
- First observations of vaccine association with reduction in norovirus symptoms and severity
- Indication of serologic correlate/surrogate with decreased disease

Norwalk GI.1 VLP Vaccine and Human Challenge Trial



- **Proof of concept study (LV01-103) - RDBPC**
 - *Atmar RL, et al. N Engl J Med 2011;365:2178-87.*
- **Two stages:**
 - Stage 1: Vaccine or placebo (Norwalk virus VLPs)
 - Stage 2: Homologous virus challenge (~10 HID_{50} of Norwalk virus)



Takeda Norovirus Challenge Studies: LV01-103 (GI.1)

- Interventional (nasal GI.1 monovalent VLP vaccine) study with subsequent GI.1 challenge
 - Vaccinated 98, challenged 84, with 77 subjects in PPS
 - Vaccine associated with significant reduction in infection and illness
 - First evidence of protection against norovirus illness

(Atmar et al. *N Engl J Med* 2011;**365**:2178-87)

	Per Protocol Analysis			
	Vaccine (n=38)	Placebo (n=39)	Relative Reduction	p value (Fisher's Exact)
Outcome	Number of Cases (%)		% (95% CI)	
Norovirus GI.1 Infection and Illness	14 (37)	27 (69)	47% (15 - 67)	0.006
Norovirus GI.1 Infection (PCR)	23 (61)	32 (82)	26% (1 - 45)	0.046

Another GII.4 Challenge Virus - Dose Finding Study was conducted



- 1st GII.4 challenge study in humans confirmed secretor status is important for susceptibility to GII.4 infection

Predicting Susceptibility to Norovirus GII.4 by Use of a Challenge Model Involving Humans

(Frenck R, et al. J. Infect Dis 2012; 206:1386-93)

- 2nd GII.4 Challenge study (unreported) **informed the challenge dosage** of 4.4×10^6 3 RT-PCR units as similar rates of infection (26/34, 76.5%) and illness (19/34, 55.9%) was observed as a 10 fold higher dose

Takeda Norovirus Challenge Studies: LV03-105 (GII.4)

- Interventional (IM bivalent GI.1/GII.4 VLP vaccine) study with subsequent GII.4 challenge
 - Vaccinated 132, challenged 109, with 98 subjects in PPS
 - Vaccine associated with reduction in disease severity and symptoms of vomiting and diarrhea
 - Primary endpoint not met, post-hoc analysis of vomiting and diarrhea symptoms:

Gastroenteritis Symptom independent of PCR confirmation	Vaccine (%) n=50	Placebo (%) n=48	% Reduction (95% CI)	p value (Fisher's Exact)
Severe vomiting AND/OR diarrhea	0 (0.0%)	4 (8.3%)	100.0% (-, -)	0.054
Moderate or severe vomiting AND/OR diarrhea	3 (6.0%)	9 (18.8%)	68.0% (-11.2, 90.8)	0.068
Mild, moderate or severe vomiting AND/OR diarrhea	10 (20.0%)	20 (41.7%)	52.0% (8.3, 74.9)	0.028

(Bernstein DI, et al. *J Infect Dis* 2015;**211**:870-8.)

History of Human Gastroenteritis Infection Challenge Model Studies



- Gordon (NY State DoH)
 - stool filtrates from outbreaks of gastroenteritis
 - (*J Exp Med* 1947;86:409)
- Dolin (NIH)
 - stool filtrates from Norwalk, OH outbreak
 - (*J Infect Dis* 1971;123:307)
- Wyatt (NIH)
 - other strains
 - (*J Infect Dis* 1974;129:709)
- Other sites
 - Boston (*N Engl J Med* 1973;288:1318)
 - Rochester (*Gastroenterology* 1980;78:1495)
 - Houston (*J Infect Dis* 1985;50:261)

Identification of a non-bacterial gastroenteritis agent in human infection challenge model



- Confirmed infectiousness of a filterable agent

Transmission of epidemic gastroenteritis to human volunteers by oral Administration of fecal filtrates

(Gordon I, et al. J. Exp Med 1947;86:409)

- Outbreak from 16 Dec 1946—initially 261/589 patients (44%) until 31 Jan 1947 with 589 of 2623 (22%) patients and 115 of 354 (32%) staff developed illness at Marcy State Hospital, near Utica, New York with 7 deaths
- Illness was reproduced and transmitted in series of volunteers after oral administration of stool suspensions
- Illness occurred after ***unfiltered and filtered*** stool suspensions
- Responsible agent was shown to be filterable

Identification of a non-bacterial gastroenteritis agent in human infection challenge model

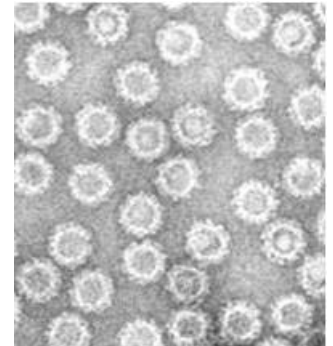


Transmission of Acute Infectious Nonbacterial Gastroenteritis to Volunteers by Oral Administration of Stool Filtrates

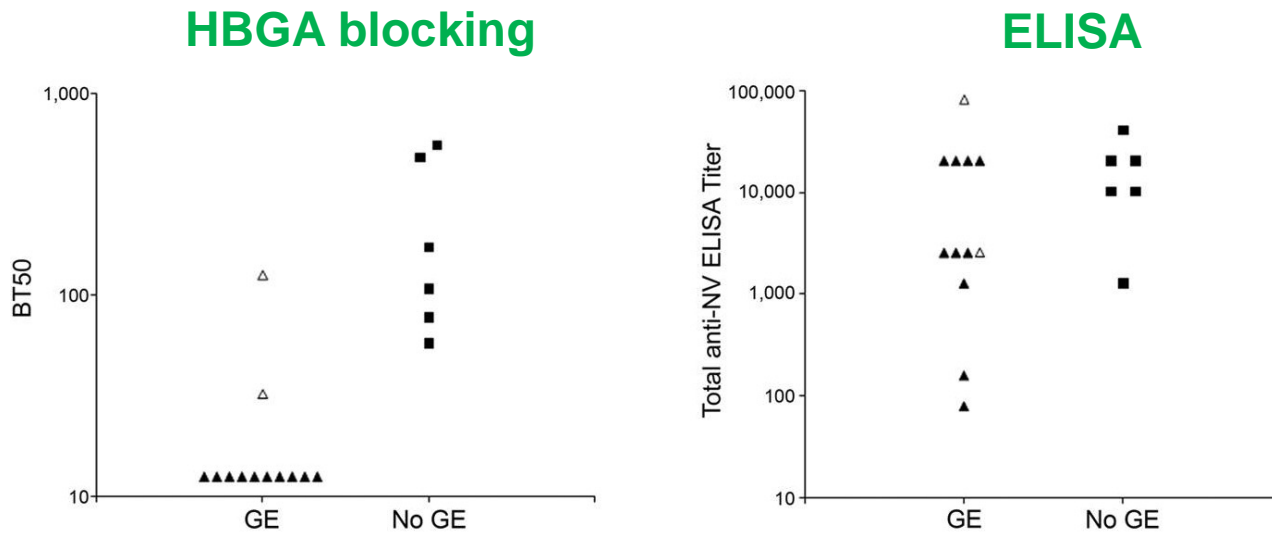
(Dolin R, et al. *J Infect Dis* 1971;**123**:307)

- Stool filtrates generated at NIH from four separate outbreaks in the late 1960s:
 - US Navy ship *Shenandoah in Carribean*, New Britain, Conn, Bethesda, MD, and elementary school in Norwalk Ohio
 - ***Only volunteers administered Norwalk samples became ill***
 - Two physicians processing Norwalk samples became ill
 - Each volunteer received **2 mL of gamma globulin IM** five days after oral challenge (for hepatitis risk)
- In the “Norwalk” school outbreak 50% of students developed illness
- Later identified as Norovirus GI.1

- **First viral cause of GE**
 - *Kapikian AZ, et al. J Virol 1972;10:1075-81.*
- **Norwalk virus is a calicivirus**
 - *(Jiang X, et al. Science 1990;250:1580)*
 - **Cloning → Capsid expression → VLPs**
 - *(Jiang X, et al. J Virol 1992;66:6527-32)*
 - **Cloning → Development of RT-PCR diagnostics**
 - *(Jiang X, et al. J Virol 1992;30:2529-34.)*
- **Norovirus Cultivation** → M. K. Jones, and S. M. Karst *et al*, **Human norovirus culture in B cells.** *Nat. Protoc.* 10, 1939–1947 (2015).
- K. Ettayebi and MK Estes *et al.*,
- **Replication of human noroviruses in stem cell–derived human enteroids.** *Science* 10.1126/science.aaf5211 (2016).



- **Genetic factor contributes to resistance to infection**
 - *Parrino TA, et al. N Engl J Med 1977;297:86-9.*
 - *Lindesmith L, et al. Nat Med 2003;9:548-53.,*
 - *Hutson, J Infect Dis 2002;185:1335 & J Med Virol. 2005;77:116)*
- **Potential correlate of protection identified**
 - *Reeck A, et al. J Infect Dis 2010;202:1212-8.*



Vaccine protection from challenge



- Increased pre-challenge levels of Norwalk GI.1 HBGA blocking antibodies correlated with protection against gastroenteritis and infection

Outcome	Per-Protocol Analysis			
	Antibody Titer <200 <i>no./total no. (%)</i>	Antibody Titer ≥200 <i>no./total no. (%)</i>	Odds Ratio (95% CI)	Relative Reduction (95% CI)
Viral gastroenteritis	38/60 (63)	3/17 (18)	8.1 (2.1–31.2)	72.1 (20.8–90.2)
Norwalk virus infection	49/60 (82)	6/17 (35)	8.2 (2.5–26.9)	56.8 (16.8–77.5)

- HBGA blocking antibody associated protection.

Atmar RL, et al. Clin Vaccine Immunol 2015;22:923-9.

Variability in the Norovirus Human Infection Challenge Model



- **HOST**
 - AGE
 - GENETICS
 - PRIOR NATURAL EXPOSURES
- **VIRUS**
 - CHALLENGE DOSE
 - HID 50
- **ATTACK RATE**
 - INFECTION RATE
 - ILLNESS RATE
 - INFECTION AND ILLNESS RATE
- **SAMPLE SIZE**
 - POWER
 - VACCINE EFFICACY
 - LB OF 95% CONFIDENCE INTERVAL

- Vaccine & challenge study requires 3 IND filings
 - One for vaccine
 - One for challenge virus
 - One for the vaccine & challenge trial
- Challenge strains used in last 10 years are limited:
 - Norwalk (GI.1) – two different pools derived from persons infected with original 8fIIa NIH strain
 - Snow Mountain (GII.2)
 - 1st GII.4 challenge virus – no longer available

- Resources
 - Availability and qualification of challenge strains
 - Further success in cultivation of norovirus
 - Development of viral neutralization assays
 - Dedicated contract human challenge facilities that can run larger waves of subjects in parallel
 - Large “pool” of volunteers with flexible work schedules to participate.
 - Regulatory endorsement of challenge studies as surrogate for clinical efficacy data

- For all of their co-operation and expertise, I thank each of the Norovirus experts, scientists, researchers, clinical investigators, adult volunteers, the children volunteers and their parents, the research staff at the many study centers, and at the research organizations, and my colleagues at Takeda Vaccines.