National Center for Immunization & Respiratory Diseases

Vaccines in the Pipeline: Norovirus and Respiratory Syncytial Virus (RSV)

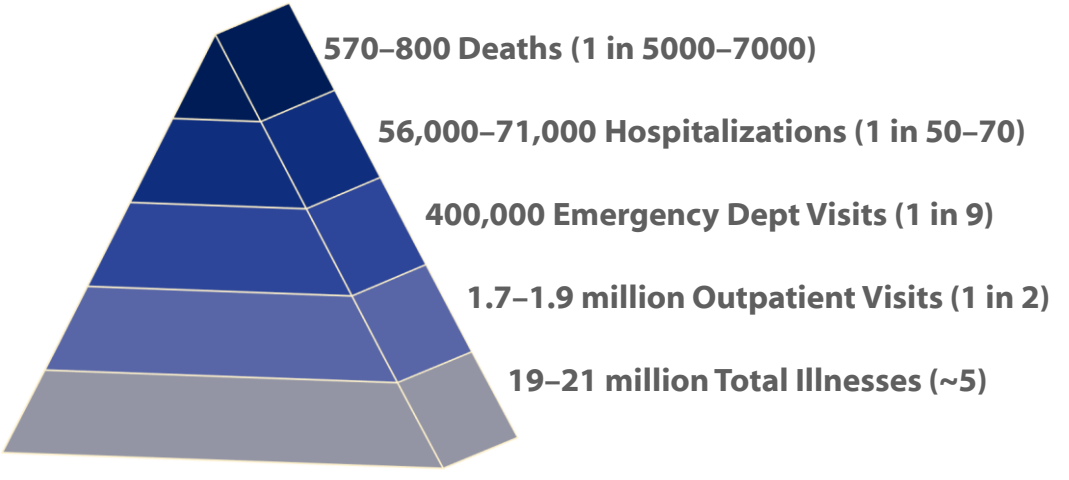
Aron J. Hall, DVM, MSPH, Dipl ACVPM

(RSV slides courtesy of Sue Gerber, MD)

CDC Division of Viral Diseases

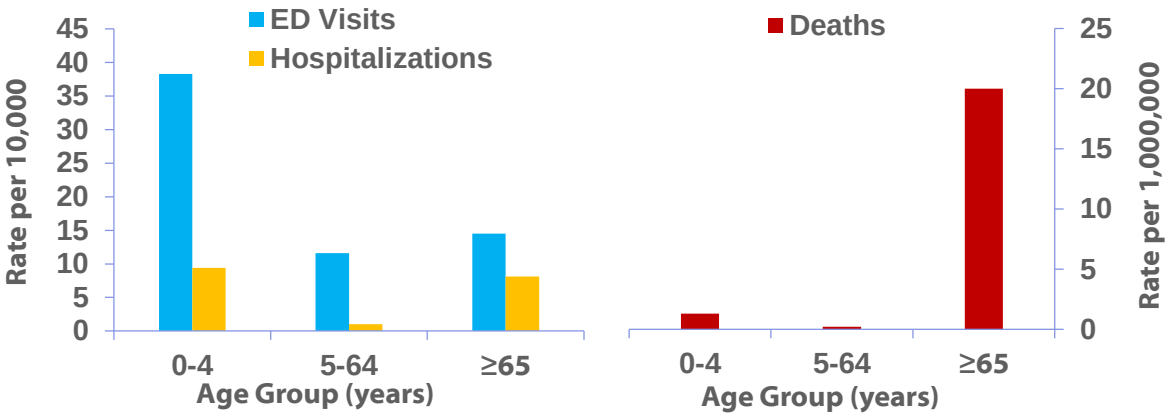
National Adult and Influenza Immunization Summit, Atlanta, GA
May 10, 2017

Annual Burden (Lifetime Risk) of Norovirus Disease in the United States



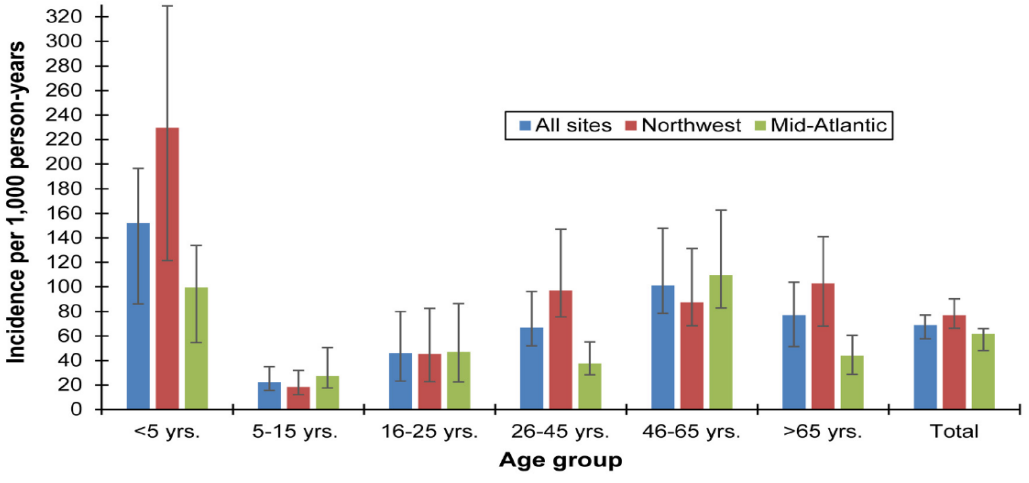
Hall 2013 EID

Severe Norovirus-associated Disease Rates by Age



Hall 2013 EID

Community Norovirus Incidence, Kaiser Permanente Member Populations, 2012-2013



Grytdal 2016 PLoS One

Global Disease Burden of Norovirus

- WHO Foodborne Disease Burden Epidemiology Reference Group (FERG)
- Global and regional age-stratified estimates of illnesses, deaths, and DALYs caused by speicific foodborne hazards
- Total norovirus burden annually:
  - 685 million illnesses and 212, 489 deaths
  - 29% of illnesses and 26% deaths in children <5
  - 85% of illnesses and 99% of deaths in developing countries
  - Total societal cost of $60 billion

Pires 2015 PLoS One
Kirk 2015 PLoS Med
Hall 2016 Exp Rev Vac
Bartsch 2016 PLoS One

Age-based Target Groups for Norovirus Vaccines

Target population	High disease burden	High transmission risk	Characteristics
Young children	Yes	Yes	• Highest overall norovirus incidence rate and hospitalization rate • Globally, norovirus is leading cause of pediatric acute gastroenteritis requiring medical attention in countries using rotavirus vaccines • Highest R_0 of any age group
Elderly	Yes	No	• Greatest burden of fatal disease • Higher hospital charges per case compared with children • Nursing homes have higher rates of deaths during norovirus outbreak periods

Aliabadi 2015 Exp Rev Vac

Occupational Target Groups for Norovirus Vaccines

Target population	High disease burden	High transmission risk	Characteristics
Healthcare workers	No	Yes	• Most common setting for norovirus outbreaks • Infected healthcare workers can propagate infection to vulnerable patient populations
Food handlers	No	Yes	• Most foodborne illnesses in US with identified agent caused by norovirus • Implicated source in majority of foodborne norovirus outbreaks in US • Poor compliance with hand hygiene and exclusion while ill
Military	Yes	No	• Norovirus common cause of acute gastroenteritis in deployed troops • Lost duty time, decreased reserve readiness

Aliabadi 2015 Exp Rev Vac

Specific Sub-population Target Groups for Norovirus Vaccines

Target population	High disease burden	High transmission risk	Characteristics
Travelers	Yes	No	• 9–16% of traveler's diarrhea attributable to norovirus • Numerous leisure settings implicated
Immuno-compromised patients	Yes	Yes	• Suffer severe clinical complications • Persistent viral shedding, up to months or years • Potential reservoir for new strain emergence • Poor immune response likely limits efficacy of vaccination

Aliabadi 2015 Exp Rev Vac

Norovirus Vaccine Candidates

	P particle	Transgenic plant-vaccine	Trivalent noro-rota combo	Bivalent VLP	Adenoviral vector
Norovirus antigen	2-3 norovirus P domains	Norwalk virus (GI.1) VLP	GII.4 and GI.3 VLP	GI.1 and GII.4 consensus VLP	GI.1 VP1
Other antigen	Rotavirus VP8 Influenza, Hepatitis E	None	Rotavirus VP6	None	Adenovirus vector
Route of administration	Intranasal	Intranasal	Intramuscular and intranasal	Intramuscular, previously intranasal	Oral (pill)
Commercial partner			UMN Pharma	Takeda	Vaxart
Status	Preclinical	Preclinical	Preclinical	Phase 2	Phase 1

Human Challenge Efficacy Trials of Norovirus Vaccines

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ORIGINAL ARTICLE

Norovirus Vaccine against Experimental Human Norwalk Virus Illness

Robert L. Atmar, M.D., David I. Bernstein, M.D., Clayton D. Harro, M.D., Mohamed S. Al-Ibrahim, M.B., Ch.B., Wilbur H. Chen, M.D., Jennifer Ferreira, Sc.M., Mary K. Estes, Ph.D., David Y. Graham, M.D., Antone R. Opekun, P.A.-C., Charles Richardson, Ph.D., and Paul M. Mendelman, M.D.

N Engl J Med 2011; 365:2178-2187 | December 8, 2011 | DOI: 10.1056/NEJMoa1101245

GI.1 intranasal

The Journal of Infectious Diseases

Norovirus Vaccine Against Experimental Human GII.4 Virus Illness: A Challenge Study in Healthy Adults

David I. Bernstein[1], Robert L. Atmar[2], G. Marshall Lyon[3], John J. Treanor[4], Wilbur H. Chen[5], Xi Jiang[1], Jan Vinjé[6], Nicole Gregoricus[6], Robert W. Frenck Jr[1], Christine L. Moe[7], Mohamed S. Al-Ibrahim[8], Jill Barrett[9], Jennifer Ferreira[9], Mary K. Estes[2], David Y. Graham[2], Robert Goodwin[10], Astrid Borkowski[11], Ralf Clemens[11] and Paul M. Mendelman[10]

GI.1/GII.4 intramuscular

IN Monovalent (GI.1) Vaccine Challenge Per Protocol Efficacy Analysis

Endpoint	Vaccine (N=43)	Placebo (N=41)	% Reduction (95% CI)
NV infection	60.5%	82.1%	26% (1%, 45%)
Viral AGE	36.8%	69.2%	47% (15%, 67%)

Atmar 2011 NEJM

IM Bivalent (GI.1/GII.4) Vaccine Challenge Per Protocol Efficacy Analysis

Illness Severity Infected	Vaccine (N=50)	Placebo (N=48)	% Reduction (95% CI)
Any	20.0%	37.5%	47% (-4%, 73%)
Mod-severe	6.0%	18.8%	68% (-11%, 91%)
Severe	0%	8.3%	100%

Bernstein 2015 JID

Current Human Clinical Trials of Norovirus Vaccines

- GI.1/GII.4 bivalent VLP vaccine
  - Phase II: Safety and Immunogenicity in an Elderly population
  - Phase II: Safety and Immunogenicity in Children
  - Phase IIb: Efficacy and Immunogenicity in Adults (Military recruits)

- GI.1 Adenoviral vectored vaccine
  - Reportedly met all safety and immunogenicity endpoints

Clinicaltrials.gov

Challenges for a Norovirus Vaccine

- Role of prior infection history?
- Duration of protection?
- Protection against multiple genotypes?
- Need to be updated to keep up with viral evolution?
- Need for different vaccine formulation for certain groups?
- Variation in human genetic susceptibility?

http://www.cdc.gov/norovirus/downloads/global-burden-report.pdf

Respiratory Syncytial Virus (RSV)

- Common cause of acute respiratory infections
  - Most infected in 1st year of life
  - Virtually all children infected by 2 years of age
  - Repeat infections affect older children and adults
- Most common cause of lower respiratory tract infections among infants
  - Including bronchiolitis or pneumonia

Glezen 1986 AJDC
Nair 2010 Lancet
Hall 2009 NEJM
Jain 2015 NEJM

RSV Clinical Manifestations – Primary Infection

- Most have upper respiratory tract symptoms
- 20–30% develop lower respiratory tract disease
  - Bronchiolitis and/or pneumonia
    - Symptoms can include tachypnea, cough, labored breathing, wheezing, crackles
  - Most do not require hospitalization
- Fever may be absent
- Young infants may present with apnea, irritability, poor feeding
- Relationship with subsequent development of recurrent wheezing unclear

Glezen 1986 AJDC
AAP 2015 Red Book

RSV in Adults

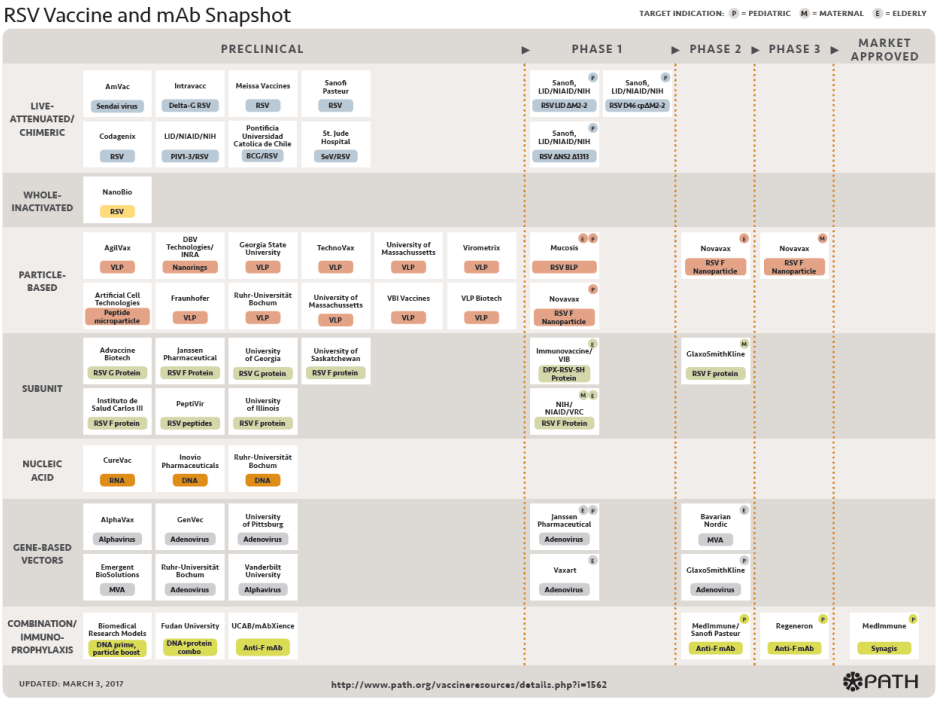
- Repeat infections affect adults
- Most often upper respiratory tract illnesses
  - Symptoms often more severe than common cold
  - Less fever and fewer systemic symptoms compared to influenza
- Lower respiratory tract illnesses can occur
  - Especially among immunocompromised, underlying cardiopulmonary disease, elderly
  - Manifests as pneumonia and exacerbations of asthma, COPD, and congestive heart failure

Falsey 2005 NEJM

Burden of RSV in Older US Adults (≥65 years)

- Importance first recognized with outbreaks in long-term care facilities for older adults
- Estimated 177,000 hospitalizations and 14,000 deaths annually
  - Based on extrapolation from prospective study in Rochester, NY over 4 consecutive winter seasons
- Average annual RSV hospitalization rate of 15 per 10,000 residents
  - Prospective study over 3 winter seasons
  - 1 county (Davidson County, Nashville, TN)
  - Similar hospitalization rate for influenza

Falsey 2005 NEJM
Widmer 2012 JID



Conclusions

- Norovirus and RSV exact a substantial disease burden, prompting development of multiple vaccine candidates currently in clinical trials
- Multiple potential target groups for candidate vaccines
  - Norovirus: pediatric, elderly, specific occupational/risk groups
  - RSV: pediatric, elderly, maternal
- Considerations for potential use of norovirus vaccines
  - Incidence and disease severity
  - Transmission risk to others
  - Compliance and other programmatic challenges

Questions?

ajhall@cdc.gov

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.