

Norovirus vaccines – time for reexamination?

LONDON, UK---24 September 2008---ExpertREACT. A forthcoming winter season coupled with a wider use of diagnostics and active surveillance may confirm that norovirus epidemics are growing in magnitude and severity. Like rotavirus, is it time for vaccine manufacturers to re-examine whether there is a future need for preventative norovirus vaccine?

Noroviruses (NVs), previously called “Norwalk-like viruses” are a group of single-stranded positive sense RNA viruses which, along with the genetically distinct *Sapoviruses* are members of the family *Caliciviridae* collectively known as human caliciviruses (1). The first single virus of the noroviruses, Norwalk virus was identified in 1972. Now other noroviruses including examples such as Desert Shield virus, Lordsdale virus and Mexico virus make-up a multitude of different strains.

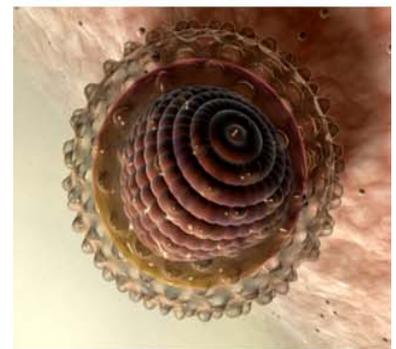
Noroviruses are transmitted from human-to human and are one of the most highly infectious viruses known. They are also environmentally stable being resistant to chlorination and heating to 60°C so remaining viable for several weeks despite infection control measures. Noroviruses are documented as the leading cause of epidemic acute gastroenteritis (AGE) otherwise known as “winter vomiting disease”, “vomiting or stomach bug” and “cruise ship virus”. According to the US Centers for Disease Control and Prevention (CDC), noroviruses are also responsible for ≤50% of all foodborne gastroenteritis outbreaks in the United States and are a major contributor to illness in nursing homes and hospitals (2). In hospitals, norovirus outbreaks are difficult to control with attack rates ranging from 30-60%. Other environments heavily impacted are commercial cruise ships and military naval vessels where the virus can affect the readiness of personnel.

In the community, noroviruses most commonly cause a self-limiting mild disease of short duration with gastrointestinal symptoms usually resolving after 1 to 3 days. However, it is the sheer volume of infections and burden on healthcare systems that presents the biggest challenge. In the US, which does not yet have active national surveillance, norovirus infections may account for 235,000 clinic visits, 91,000 emergency room visits and 23,000 hospitalizations among children <5 years of age (3). These figures are around 2-fold less than rotavirus, another major cause of AGE (4). In other countries such as Germany where norovirus is a notifiable illness the virus is estimated to cause around 50% of AGE cases in the elderly population as opposed to 0-4 yrs (~10% of cases) where rotavirus is more prevalent (5). Infection in elderly persons within long-term care facilities (LTCF) tends to be severe resulting in hospitalization (10-20% of the time) with chronic dehydration and electrolyte imbalance being the most common complications. In this group mortality has been estimated at ~2% (6). There is no specific treatment for norovirus-related infections with oral and intravenous rehydration being the most common option.

In terms of developing new treatments or even preventative vaccines, when comparing the burden of norovirus-related infections to other infectious pathogens, a key parameter is mortality and number of deaths. Rotavirus, for example is estimated to cause 20-60 infant deaths (4) per year in the US, enough for vaccine policy makers to implement recommended universal vaccination in 2006 at significant expense, and in the light of previous safety concerns with Wyeth’s Rotashield vaccine. Therefore, what is known about the direct mortality of norovirus-related infections despite their very high incidence? Are there new dynamics with norovirus-related infections that warrant a reexamination by industry to initiate vaccine based programs?

Among others, an article published in *Morbidity and Mortality Weekly Report* (MMWR), 2007 (7) and a recent literature review by **VacZine Analytics** (8) would suggest norovirus epidemics are growing in magnitude and severity. The MMWR article reporting on US activity during the 2006-2007 period equated a perceived increase of norovirus activity due to two new cocirculating GII.4 norovirus strains especially within long-term care facilities. More significantly, the report mentioned the first death in an individual aged 90 yrs where norovirus was confirmed as a direct cause. Another meeting report from a conference in Germany suggested that in the Netherlands, noroviruses might be responsible for up to 900 excess deaths in one year, a mortality rate comparable to influenza (9). In January 2008, the UK Health Protection Agency advised that they had observed double the number of norovirus cases reported for the same period the year before with a season starting uncharacteristically early (10). A similar pattern was observed in Germany (5).

CONTINUED.....



CONTINUED.....

As well as increasing severity and incidence of norovirus infections, the economic impact of norovirus-related infection must also be considered. Nosocomial outbreaks of acute gastroenteritis, similar to *Clostridium difficile* (C.diff) are a major burden on hospitals where lost-bed days due to ward closures and staff absence can be significant. For example, in the period 2002-2003 norovirus-related outbreaks were estimated to cost the English National Health Service (NHS) \$116m (11). In the US, a norovirus outbreak in a tertiary care hospital which affected 90 patients and 265 healthcare workers was associated with \$657,644 of additional cost (11). Again extrapolating such examples to the whole hospital system would equate to an economic burden >\$1 billion/annum.

In terms of vaccine development, there is only one known norovirus active program being developed by Montana-based Ligocyte who acquired intellectual property (IP) from Baylor College of Medicine and are supported by the U.S. Army Medical Research and Materiel Command. Ligocyte are developing an intranasal dry-powder formulation of norovirus virus like-particles (VLPs) in combination with GSK's proprietary 3-O-desacyl-4'-monophosphoryl lipid A, (MPL) adjuvant. Various lines of scientific evidence, and experience with other vaccines, e.g. polio, rotavirus and cholera suggest that a norovirus vaccine should ideally evoke mucosal and serum IgA/IgA for protective responses. Furthermore, because of yearly strain changes and short-lived immunity a norovirus vaccine might require reformulation/readministration each year.

According to Ligocyte the vaccine has completed Phase I safety testing and likely needs a partner to fund further development. However, a larger company needs convincing there is a viable market. Norovirus may cause thousands of deaths each year in children of the developing world, and with increased aging of the population there is a strong possibility it will become an ever prominent problem in the West. However, convincing people they need to take an annual vaccine for something mostly considered "self limiting" will be difficult. Manufacturers are recommended to "keep an eye" on a new US data through the National Outbreak Reporting System in 2008 which may confirm disease burden. Looking to future, could norovirus be the new rotavirus?

References:

- 1) US Centers for Disease Control and Prevention. Norovirus: Technical Fact Sheet. Available at: <http://www.cdc.gov/ncidod/dvrd/revb/gastro/norovirus-qa.htm>. Accessed: September 2008
- 2) References in: Widdenson., MA et al. Are noroviruses emerging? *Emerg Infect Dis*. Vol. 11, No. 5 May 2005. Available at: <http://www.cdc.gov/ncidod/eid/vol11no05/04-1090.htm>. Accessed: September 2008.
- 3) Patel., et al. MM et al. Systematic literature review of role of noroviruses in sporadic gastroenteritis. *Emerg Infect Dis*. 2008 Aug;14(8):1224-31
- 4) Rotavirus and Rotavirus Vaccine Epidemiology and Prevention of Vaccine-Preventable Diseases. National Center for Immunization and Respiratory Diseases Centers for Disease Control and Prevention Revised March 2008. Available at: www.cdc.gov. Accessed: September 2008.
- 5) German Federal Health Monitoring. Notifiable Diseases. Available at: <http://www.gbe-bund.de> Accessed: September 2008
- 6) Calderon-Margalit R et al. A large-scale gastroenteritis outbreak associated with Norovirus in nursing homes. *Epidemiol Infect*. 2005 Feb;133(1):35-40.
- 7) Morbidity and Mortality Weekly Report (MMWR). Norovirus Activity - United States, 2006-2007. August 24, 2007 / 56(33):842-846
- 8) Norovirus. **DiseaseINFOPACK** (Cat No: VADIP009). Published by VacZine Analytics, September 2008
- 9) Meeting report from the Third European Congress of Virology, 1-5 September 2007 in Nuremberg, Germany. *EuroSurveill*. 2007;12(12):pii=757
- 10) UK Health Protection Agency (HPA). Norovirus current situation, January 2008. Available at: http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1200660012274?p=1191942172970. Accessed: September 2008.
- 11) Lopman BA et al. Epidemiology and cost of nosocomial gastroenteritis, Avon, England, 2002-2003. *Emerg Infect Dis*. 2004 Oct;10(10):1827-34S
- 12) Johnston CP et al. Outbreak management and implications of a nosocomial norovirus outbreak. *Clin Infect Dis*. 2007 Sep 1;45(5):534-40

For more information about this research please visit www.vacZine-analytics.com
Or e-mail us at info@vacZine-analytics.com

About VacZine Analytics:

VacZine Analytics is a new strategic research agency based in the United Kingdom. Its aim is to provide disease and commercial analysis for the vaccine industry and help build the case for developing new vaccines.

© 2008 VacZine Analytics. All rights reserved.

