Chapter 1

Introduction
Acute gastroenteritis (AGE) is the third most frequent illness in the world and is the leading cause of childhood morbidity and mortality with annual estimated death rate of 2.2 million [WHO, 2001:1-2, Navaneethan and Giannella, 2008:637-647]. According to WHO estimates 2-4 billion episodes of infectious diarrhea occur annually in developing countries. Majority of the episodes are encountered by children <5 years of age [Kosek et al., 2003:197–204]. Diarrhea remains the primary symptom of AGE while other clinical manifestations usually include dehydration, nausea, vomiting, abdominal discomfort, anorexia, headache, malaise, low-grade fever or a combination of these. Dehydration is considered a prime cause of death. In worst cases of dehydration, symptoms progress from thirst, restlessness, decreased skin turgor and sunken eyes, diminished consciousness, rapid and feeble pulse and low or undetectable blood pressure (Fig 1.1).

Different etiological agents found associated with AGE include many species of bacteria, parasites and viruses [Nguyen et al., 2007:582-590]. Among bacteria, *Vibrio cholerae* is considered as the most common cause of AGE worldwide [Navaneethan and Giannella, 2008:637-647]. The pathogen is predominant in Indian subcontinent, South East Asia, Africa and South America [WHO, 1999: 249]. Other bacterial species associated with AGE are enteroaggregative *Escherichia coli*, enterohemorrhagic *Escherichia coli*, Salmonella, Shigella, Campylobacter. In
comparison, *Girdia lamblia, cryptosporidium, Entamoeba histolytica* are most common parasites found associated with AGE.

Viruses are considered as the important cause of non-bacterial AGE since 1940s [Kapikian, 1996:7-19; Parashar et al., 1998:561-570]. Over the time the frequency of identification of viruses associated with AGE increased. To date, major viruses known to be associated with the disease are rotavirus, enteric adenovirus, norovirus, sapovirus, astrovirus, coronavirus, picobirnavirus, pestivirus and torovirus. Viral diarrhea can occur in two major epidemiological forms: endemic and epidemic disease [Glass et al., 2001:5-19]. Most commonly identified cause of endemic or sporadic AGE is group A rotavirus [Kapikian et al., 1976:965-972]. However, association of other viruses like enteric adenovirus, astrovirus, sapovirus is also known. Although, outbreaks caused due to group B and C rotaviruses and astroviruses are reported, the leading cause of epidemic AGE is noroviruses (NoVs) that accounts for ~50% of all-cause outbreaks worldwide [Fankhauser et al., 1998:1571-1578, Patel et al.2009:1-8]. These viruses are also known to cause sporadic infections of AGE with prevalence rates varying from 5.5 to 44% in different parts of the world [O'Ryan et al., 2000:1519-1522, Parashar et al., 2004:1088-1092; Kirkwood et al., 2005:96-101; Lindell et al., 2005:1086-1092; Nguyen et al., 2007:582-590].

NoVs are highly infectious and even a very low dose can cause serious outbreaks [Yuen et al., 2001:2690-2694; Lindell et al., 2005:1086-1092]. Virus transmission occurs through contaminated food and water, contact with contaminated surfaces by the fecal-oral route and also by airborne transmission [Lahti and Hiisvirta, 1995:33-36; Girish et al., 2002; Meakins et al., 2003:1-5]. The NoVs belong to the family *Caliciviridae* and possess a single-stranded RNA genome of 7.5-7.7kb. The genome consists of three open reading frames (ORF) 1, 2 and 3. Based on amino acid sequence diversities of the VP1 gene, classification of NoVs has been proposed into five major groups Genogroup I (GI) to Genogroup V (GV) [Zheng et al., 2006:312-323]. GI, GII and GIV infect primarily humans; GIII and GV infect bovine and murine species, respectively.

Molecular epidemiology data accumulated from different geographic regions have revealed that GII is the most common genogroup circulating with variants of GII.4 (genogroup II, genotype 4) as the major cause of outbreaks and sporadic
infections around the world [Noel et al., 1999:1334-1378; Castilho et al., 2006:3947-3953]. However, recombinant NoV GII.4 has emerged recently as the main causative agent of many outbreaks across Europe, Australia and Asia [Ambert-Balay et al., 2005:5179-5186; Bull et al., 2005:1079-1085; Phan et al., 2006:971-978; Phan et al., 2007:1388-1400].

The global prevalence and genetic diversity of NoVs and their association in epidemic and endemic acute gastroenteritis make them a constant challenge for health care professionals. Measures to control NoV infections rely on identification of the mode of transmission, control of contamination of food and water, maintenance of strict hygiene by food-handlers and reduction of secondary propagation of outbreaks through person-to-person spread [Patel et al., 2009:1-8].

Oral rehydration solutions providing essential electrolyte replacement plus sugar (glucose or sucrose) are administered as first-line therapy for the disease. Parenteral administration of fluids is necessary if severe vomiting or diarrhea occurs with symptoms of significant dehydration. Recent advances in understanding the genomic structure, individual viral proteins, RNA replication strategy and virus-host interaction of the NoVs have provided new strategies in the development of antinoroviral agents that could inhibit viral attachment to host cells through carbohydrate receptors, viral protease and polymerase functions and viral replication [Tan and Jiang, 2008:146-151].

A safe and effective vaccine could reduce the incidence of epidemic NoV infections. However, inability to grow NoV in cell culture system, incomplete understanding of the immune correlates of protection, lack of long-term and cross-protective immunity, the existence of multiple genetic and antigenic types and limited information on the genetic diversity of NoVs from different parts of the world are major obstacles in formulating strategies for immunization against NoVs.