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Norovirus, the Next Target for Vaccine Development in China

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ABSTRACT

Enteric virus-induced disease, even death, greatly affects the life quality of children <5 years of age in China, and imposes a heavy sociometric burden on family and government. The infectious diarrhea diseases and hand-foot-mouth disease (HFMD) have been enrolled in the list of notifiable infectious diseases in China. Fortunately, the highly valued rotavirus-induced diarrhea and enterovirus 71-induced HFMD can be prevented by the commercial vaccines. However, the underrated norovirus vaccine is still in progress, even norovirus was considered as the leading cause of acute gastroenteritis in children <5 years of age in the world, partially due to the inability to cultivate norovirus. Besides, the broad genetic and serotypic diversity of norovirus also complicates selection of candidate vaccine strain(s). Therefore, the primary objective of this article is to review norovirus epidemics in China recur to the data published in recent five years.

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Key Words: Enteric virus; Rotavirus; Hand-foot-mouth disease; Norovirus; Vaccine;China; Gastroenteritis; Epidemiology

Abbreviations: HFMD, Hand-foot-mouth disease; EV71, Enterovirus 71; NoV, Norovirus; GII.4, NoV genogroup II genotype 4; VLP, Virus-like particles

Introduction

Enteric virus-induced disease is the leading cause of hospitalization and death in children <5 years of age in China, including rotavirus induced diarrhea, enterovirus 71 and coxsackievirus A16/A6/A10 induced hand-foot-mouth disease (HFMD), norovirus (NoV) induced gastroenteritis, and so on. Rotavirus has been considered as the chief culprit in the late 1990s,

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which is the most common cause of severe vomiting and diarrhoea among infants and young children [1]. Nearly every child in the world has been infected with rotavirus at least once by the age of five [2]. Rotavirus vaccines have been proved to be effective in preventing rotavirus-induced diarrhea, especially reducing the mortality resulted from severe diarrhea. With the license of rotavirus vaccine LLR from 2000 in China, rotavirus disease burden decreased, but no detailed number was calculated owing to the huge population number living in China. Hopefully, the novel domestic trivalent LLR based vaccine and the imported vaccines (RotaTeq and RotaRix) have been already completed the phase III clinical trials in China. Furthermore, several domestic vaccines are being under R&D. Predictably it will bring great benefit for further reducing the disease burden of rotavirus induced diarrhea in China.

Another enteric virus-induced illness, the hand-foot-mouth disease (HFMD) has been under the spotlight arises from three death cases with clinically severe pneumonia in Fuyang city Anhui province in March 2008 [3]. Subsequently, domestic scientists focused on the epidemiology investigation of HFMD-inducing viruses, followed by the R&D of HFMD vaccines [4]. Undergoing several years study, EV71 and several CVs (CVA16/CVA6/CVA10) were confirmed to be the major causes of HFMD, and the severe HFMD cases preferred to be caused by EV71, not CVA16. Up to date, two of the three EV71 candidate vaccines have been licensed in China [4], which is the first EV71 vaccine in the world. However, CVA16 or CVA6 vaccines should be paid more attention, owing to the potential predominant epidemic of CVA6 [5] or other EVs [6] as the causative agent of HFMD cases in different areas.

NoV-induced gastroenteritis, while generally regarded as mild infections in otherwise healthy individuals, has been estimated to result in almost 200,000 deaths in developing countries among young children per year [7]. It was considered as the leading cause of acute gastroenteritis in children <5 years of age in the world [8], but has been left in the basket in low-income countries, owing to the lack of rapid, sensitive, and high cost-effective clinical diagnostic techniques [7, 9]. NoV, as estimated, has lead to similar risk to the health of human beings as rotavirus and influenza [10], especially in high-risk populations like children and elders. However, only a few NoV vaccine candidates are still placed in the start stage [11-14]. In addition the broad genetic and serotypic diversity of NoVs complicates selection of candidate vaccine strain(s). Therefore, understanding the epidemiology of NoV genotypes is important given the development of vaccines.

For this purpose, the articles, which

published in the recent five years in pubmed (http://www.ncbi.nlm.nih.gov/pubmed/), have been searched by using the keywords “norovirus” and “China”.

Totally, 212 articles were extracted, and among them 127 articles introduced theNoV infection in different areas. Key studies that investigated human NoV infection in China in the past five years were listed in table.

Table: Key Studies that Investigated Human NoV Infection in China in the past five years

Authors	Genotypes founded	Regions	Years	Published in
Yu Y [16]	GII.4, GII.12, GII.3	China	1999-2011	Biomed Res Int
Yu J [17,18]	GII (89.8%), GI (10.2%)	27 provinces	2009-2013	Chin J Epidemiol & J Infect
Xue L [34]	GII.6	Guangdong	2010	Infect Genet Evol
Ao YY [35]	GIV.1	Hebei	2011	J ClinVirol
Mai H [19]	GII.4 Sydney	Beijing	2012-2013	PLoS One
Luo LF [33]	GII.6	Shanghai	2013	World J Gastroenterol
Chan MC [15]	GII.17	Hongkong	2014	Nat Commun
Sun XM [36]	GII.4, GII.3, GII.17, GII.12	Hebei	2014-2015	Biomed Environ Sci
Zhang XF [20]	GII.17	Guangdong	2014	Sci Rep
Qin M [21]	GII.17	Hebei	2014	Food Environ Virol
Shi C [22]	GII.17	Jiangsu	2014	Int J Infect Dis
Chen H [23]	GII.17	Shanghai	2014-2015	Emerg Microbes Infect
Xue L [24,25]	GII.17	Guangdong	2014-2015	Infect Genet Evol & J Appl Microbiol
Wang HB [26]	GII.17	Guangdong	2015	Infect Genet Evol
Gao Z [27]	GII.17	Beijing	2014-2015	BMC Infect Dis
Chan MC [28]	GII.Pe_GII.17	Hongkong	2015	Genome Announc
Han J [29]	GII.17	Huzhou	2014-2015	Virol J
Lee CC [30]	GII.17	Taiwan	2015	Clin Infect Dis
Fu J [31]	GII.17	Jiangsu	2014-2015	Euro Surveill
Lu J [32]	GII.17	Guangdong	2014-2015	Emerg Infect Dis

NoV genogroup II genotype 4 (GII.4) has been the predominant cause of viral gastroenteritis since 1996 [15]. In China, all NoV sequences partial or complete, obtained from 1999 to 2011 (n=983) were downloaded from GenBank and analyzed. The results indicated that approximately 90% of NoV sequences were obtained from the coastal regions of China, and most of the NoV sequences from distinct geographical regions appeared to be closely related. GII.4 was the most prevalent genotype, accounting for 64.4% of all genotypes, followed by GII.12 (13.9%) and GII.3 (7.0%). Over that decade, the GII.4 variants were dominated by successive circulation of GII.4/2002, GII.4/2004, GII.4/2006b, and GII.4/2008, with GII.4/2006b continuing to 2011 [16].

Surveillance data collected from 213 hospitals between 2009 and 2013 showed that NoV accounted for 11.8% of all diarrhea following rotavirus (29.7%), among children under the age five [17]. Age group of 6-23 month-old children and that of people over 45 years old were found with the highest positive percentage, 13.7% and 12.4% respectively. The most prevalent genotypes detected were still norovirus GII, accounting for 89.9% of identified strains [18].

During 2012-2013, when the global epidemic associated with the emergence of GII.4 Sydney, one study conducted in Beijing in the winter of 2012-2013 indicated that twenty-six (15.2%, 26/171) outpatients with diarrhea were infected with NoV. Twenty-two of the 26 (84.6%) identified NoV strains clustered into GII.4 Sydney [19], which causes severe fever, abdominal pain and higher diarrhea frequency clinically compared to other NoV infections, following its global emer--gency.

During the winter of 2014-2015, NoVGII.17, which was sporadic in previous outbreaks, predominated over GII.4 Syndey as the course of outbreaks in China[15,20-32]. It attacked Beijing, Guang--dong, Hebei, Jiangsu, Zhejiang, Taiwan and Hongkong [20-32]. Besides, other rare prevalent genotypes were also confirmed, including GII.6 [33,34] and GIV.1 [35].

As evidenced, NoV recognizes human histo-blood group antigens as cell attach--ment factors [36]. Genotyping of the sym--ptomatic patients in Guangdong showed that individuals with a secretory positive status, including those with A, B, and O secretors and Lewis positive blood types, were sensitive to the virus, while the non-secretors and the Lewis negative individual were not. Accordingly, the recombinant capsid P protein of the GII.17 isolate showed a wide binding spectrum to saliva samples of all A, B, and O secretors. Thus, the broad binding spectrum of the new GII.17 variant could explain its widely spread nature in China and surrounding areas in the past two years [20].

Since their emergence, these novel GII.17 viruses have replaced the previously dominant GII.4 genotype Sydney 2012 variant in some areas in Asia but were only detected in a limited number of cases on other continents. For example, the same GII.17 strain was also present in the United States during the 2014-15 NoV season (winter) [37] and it remains to be seen if the currently dominant NoV strain GII.4 Sydney 2012 will be replaced in other parts of the world [38]. It is crucial for the vaccine development and evaluation, because current candidate vaccines have targeted the most common NoV genotypes, and it remains to be seen if vaccine immunity is cross-reactive with GII.17 viruses.

Since multiple genotypes of NoV co-circulate in humans changing the genotype composition and escaping from the host immunity, it is desirable to develop a polyvalent vaccine against norovirus, in which the genotypes of vaccine strains are matched to those of major strains in circulation in the target season. Possibly the change in the genotype composition in circulating strains can be predicted by using the fitness model as in the study of influenza A virus [39].

Referred to NoV vaccine, due to the inability to cultivate NoV, current NoV vaccine development relies on bioenginee--ring technologies to produce virus-like particles (VLPs) and other subviral particles of NoV as subunit vaccines [40]. The first VLP vaccine has reached phase II clinical trials and several others are under development in pre-clinical research. Several subviral complexes made from the protruding (P) domains of NoV capsid share common features of easy production, high stability and high immunogenicity and thus are candidates for low cost vaccines. These P domain complexes can also be used as vaccine platforms to present foreign antigens for potential dual vaccines against NoV and other pathogens [41-43].

In conclusion, although the VLPs and subviral particles have a favourable prospect as NoV vaccine and/or multivalent vaccines towards NoV and other pathogens, the cross-reactivity to emerging genotypes/serotypes should be considered seriously. Perhaps, culture of NoV, finding of consensus sequence, and prediction of genotype composition in circulating strains, should be emphasized during the R&D of NoV vaccine.

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