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REVIEW

Rotavirus epidemiology and vaccine demand: considering Bangladesh chapter through the book of global disease burden

Abdullah Mahmud-Al-Rafat[1] · Abdul Muktadir[1] · Hasneen Muktadir[1] · Mahbubul Karim[1] · Arpan Maheshwari[1] · Mohammad Mainul Ahasan[1]

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Abstract
Background Rotavirus is the major cause of gastroenteritis in children throughout the world. Every year, a large number of children aged < 5 years die from rotavirus-related diarrhoeal diseases. Though these infections are vaccine-preventable, the vast majority of children in low-income countries suffer from the infection. The situation leads to severe economic loss and constitutes a major public health problem.
Methods We searched electronic databases including PubMed and Google scholar using the following words: "features of rotavirus," "epidemiology of rotavirus," "rotavirus serotypes," "rotavirus in Bangladesh," "disease burden of rotavirus," "rotavirus vaccine," "low efficacy of rotavirus vaccine," "inactivated rotavirus vaccine". Publications until July 2017 have been considered for this work.
Results and conclusion Currently, two live attenuated vaccines are available throughout the world. Many countries have included rotavirus vaccines in national immunization program to reduce the disease burden. However, due to low efficacy of the available vaccines, satisfactory outcome has not yet been achieved in developing countries such as Bangladesh. Poor economic, public health, treatment, and sanitation status of the low-income countries necessitate the need for the most effective rotavirus vaccines. Therefore, the present scenario demands the development of a highly effective rotavirus vaccine. In this regard, inactivated rotavirus vaccine concept holds much promise for reducing the current disease burden. Recent advancements in developing an inactivated rotavirus vaccine indicate a significant progress towards disease prophylaxis and control.

Keywords Rotavirus · Gastroenteritis · Environmental enteropathy · Live attenuated vaccine · Inactivated rotavirus vaccine · Rotarix™ · RotaTeq®

Introduction

Diarrhoeal diseases are one of the common causes of child death around the world, though rate of death is slightly lower in developed countries in comparison to developing ones. Majority of diarrhoeal incidences and deaths are attributed to rotavirus [1]. For many decades, rotavirus has been the greatest public health problem especially in developing countries such as Bangladesh [2]. Two WHO-prequalified vaccines (Rotarix™ and RotaTeq®) are commercially available worldwide for human use [3]. These vaccines are proven highly efficacious in clinical trials conducted in high-income countries (HIC) and upper middle-income countries (UMIC). However, the efficacy is poor in low–middle-income countries (LMIC) and low-income countries (LIC) [3]. Like other countries, oral rotavirus vaccines are available in Bangladesh market, but because of lower efficacy of available vaccines, achievements towards the prevention against rotavirus are still not remarkable [4]. Low efficacy of available live oral rotavirus vaccine is now a global concern and a new replacement of the available ones is under constant investigation. Inactivated vaccines are considered as best alternatives. Therefore, development of a safe inactivated rotavirus vaccine is always a matter of commercial interest. The scope of this review includes the features related to epidemiology and disease burden of rotavirus around the world with an emphasis on Bangladesh

✉ Mohammad Mainul Ahasan
mainulahasan@inceptavaccine.com; ahasanmm@gmail.com

[1] Research & Development Division, Incepta Vaccine Ltd, Zirabo, Savar, Dhaka 1341, Bangladesh

scenario as well as considers the available vaccine options, their limitations, and prospects of new vaccine candidates in future.

Virology and pathogenesis of rotavirus

Rotavirus, member of *Reoviridae* family, is a medium-sized (70–100 nm) non-enveloped virus. Rotavirus is further divided in seven groups (A–G) [5, 6]. Group A rotavirus is the most prevalent around the world since its discovery, while groups B and C were not found to be epidemiologically important outside China [7, 8]. A mature rotavirus particle consists of a triple-layered icosahedral capsid with outer, intermediate, and inner layers. The capsid surrounds 11 double-stranded RNA segments. The outer capsid is composed of two proteins (VP7 and VP4) and intermediate layer is of VP6, while inner layer is of VP2 enclosed with VP1 and VP3. Therefore, a complete virion is called triple-layered particle [5, 9, 10]. As VP7 is a glycoprotein, VP7 serotype is designated as G and VP4 being a protease-sensitive is designated as P. Ten G types (G1–G6, G8–G10, and G12) and nine P types (P1, P2A, P3, P4, P5A, P7, P8, P11, and P12) have been recovered from human [5]. Moreover, 88% of detected strain worldwide originates from conjugation between four common G types (G1, G2, G3, and G4) and P[8] or P[4]. Among these, P[8] G1 has been found to be the most widely distributed one [11–13].

Rotavirus infection can be asymptomatic or symptomatic [14]. However, diarrhoea is the main clinical manifestation of rotavirus, yet there is distinguishable hallmark that makes it remarkable from those of bacterial-induced diarrhoea. A little inflammation is observed in rotavirus-infected intestines, which is not common in bacterial-infected cases [15, 16]. Both viral and host factors influence rotavirus clinical outcomes. Viral factors could include the presence of specific alleles of VP4 associated with asymptomatic infection [17–20], host selectivity, and attenuated virus strain with limited replication ability, while host factors may include malnutrition, expression of intestinal mucins, and most importantly age [21–25]. Adults are usually less prone to rotavirus infection, but acute symptoms may result from uncommon virus strains or extreme viral load [14]. Pathophysiological changes during infection are commonly limited to intestine [16]. Infection progress is multifactorial and pathogenic outcome can limit from malabsorptive, diarrhoea to enterocyte destruction [15, 16]. Absorption of Na^+, water, and mucosal disaccharidases is shown to be reduced during infection [18, 26]. During malabsorption, osmotically active undigested monosaccharides, disaccharides, carbohydrates, fats, and proteins transport into colon. Colon cannot absorb sufficient water, which finally leads to osmotic diarrhoea [16, 27, 28]. Viral non-structural protein NSP4 or secretory component of NSP4 shows toxic effect by inducing diarrhoea in animal models [29–31].

Rotavirus around the world

Bishop et al. [32] first described acute non-bacterial gastroenteritis in children. That was the first report on human rotavirus just few years after discovery of animal rotavirus [33, 34]. Since then, rotavirus is causing a significant health and economic loss globally. In developing countries, it is now the third most common cause of death, while in developed countries, it is the second most common cause for doctor visits and hospitalizations [35, 36]. In the early 1980s, rotavirus was responsible for approximately 870,000 deaths annually [37], which dropped slightly in subsequent years with progress of improved health management and surveillance system. A recent study on rotavirus mortality ranging from 2000 to 2013 showed that mortality had reduced to 215,000 in 2013 which was 528,000 in 2000 [38]. Annual rotavirus detection rate also dropped from 42.5 to 37.3% in the year 2000–2013, respectively. In 2013, India alone covered 22% of all global deaths, while four countries (India, Nigeria, Pakistan, and Democratic Republic of Congo) covered almost half (49%). In 2013, Angola suffered from the highest rotavirus mortality rate. In addition, 90% of global deaths in the year were from 72 low-income and low–middle-income countries [38]. Based on recent surveillance, global rotavirus disease burden is 111 million cases requiring home care, 25 million hospital visits, 2 million hospitalizations, and 352,000–592,000 death for the children below 5 years of age in each year. In a narrower scale, by the age of 5, almost every child suffer from a case of rotavirus gastroenteritis among which 1 in 5 require clinic visit, 1 in 65 need hospitalization, and 1 in 293 face death [39, 40]. Data from Western Europe show that each year rotavirus is responsible for 50% of gastroenteritis cases as well as 230 deaths of children less than 5 years of age [41–43]. In US, 50% of children hospitalized for gastroenteritis had rotavirus infection [44]. More detailed studies suggest that, in US, 410,000 physician visits, 55,000–70,000 hospitalizations, and 20–60 deaths are caused by rotavirus [45, 46]. Nosocomial infection could also be responsible for rotavirus. Another study estimated that one nosocomial infection case emerged from every four children hospitalized for rotavirus infection [47]. Annual health and societal costs exceed one billion USD in US, whereas it is 45 million USD in India each year for rotavirus disease [32, 48]. According to Asian Rotavirus Surveillance Network (ARSN) report, among all diarrhoea cases-related children (< 5 years) hospitalization are at

an average of 45% due to rotavirus. Nonetheless, proportion of rotavirus-related hospitalizations in different Asian countries is such as Myanmar (56%), Hong Kong (30%), Vietnam (54%), China (46%), Taiwan (44%), Malaysia (49%), Thailand (43%), and Indonesia (54%) [49].

Rotavirus in Bangladesh

Among major public health concern and child hospitalization, diarrhoeal diseases are on top where rotavirus has contributed largely for the last 2 decades in Bangladesh [50, 51]. Rotavirus incidences have been reported during cold seasons in different regions of the world, whereas in Bangladesh, both winter and monsoon months are marked with maximum incidences [52, 53]. Unlike different high-income countries, available rotavirus vaccines failed to show enough efficacy (< 60%) in low-income countries including Bangladesh. Each year, rotavirus is accounted for 6000–14,000 children deaths (< 5 years of age) in Bangladesh [54]. A study showed that 18,544 children admitted to hospitals only in Dhaka, Bangladesh from 1993 to 2004 were 33% positive for rotavirus infection [54]. In 1994, it was estimated that rotavirus was responsible for 1 death per 111–203 children less than 5 years of age [55]. The mortality rate has slightly improved during 2001–2004. According to the study, there was one death per 275–642 children during this period [54, 56]. Nationwide flood in 1988 in Bangladesh had increased rotavirus-mixed infection from 8.1 to 22.7% in the year [55]. However, during 2002–2004, rotavirus was responsible for 42% of all diarrhoeal cases which was 22% during 1993–1995 [57]. Based on a study on diarrhoeal treatment center at Matlab in rural Bangladesh, during 2000–2006, 33% of 4519 children less than 5 years of age were detected as rotavirus infection positive, of which 56% were less than 1 year of age [58]. During the period of 2002–2005, G1 serotype was most prevalent, while in 2005–2006, G2 was predominant over G1. From another study, distribution of strains from 2001 to 2005 was G1P[8] (36.4%), G9P[8] (27.7%), G2P[4] (15.4%), and G12P[56] (3.1%), but later in 2005–2006, G2P[4] was 43.2% and G12P[6] also became more prevalent equaling as 11.1% [53, 58, 59]. During another study from 2006 to 2012 at Matlab, Bangladesh, among 9678 samples, 20.3% were rotavirus positive where G1P[8] strain was predominant (22.4%). The proportions for other strains were G9P[8] 20.8%, G2P[4] 16.9%, and G12P[8] 10.4% [60]. The period of 2011–2012 was remarkable for the emergence of unusual G9P[4] strain. This unusual strain was predominant in this period and believed to evolve from co-infection with G2P[4] and G9P[8] [11]. G3 and G4, both strains, are no longer detected in Bangladesh. G4 was most common from 1992 to 1997 but later decreased gradually and there had been no reports since 2006–2007, while no G3 was reported since 2001 [53]. Similar reports were also evident from other Southeast Asian countries, which indicated the same declining pattern of these two strains. However, they are still detected in other regions of the world [61–63].

As for monthly market distribution of rotavirus vaccines in Bangladesh, approximately 1500 vials of RotaTeq® and 6000 vials of RotarixTM are distributed in the market which evidently show a rise of demand for these vaccines in the Bangladeshi market (personal communication). However, high price (approximately 19–24 USD per dose) of these vaccines hinders the access of them to low-income or slum-dwelling people who need it most. The vaccines are usually considered as optional vaccines as neither of vaccines are a part or inclusive of national immunization program in Bangladesh. People who are well off and very conscious of the rotavirus infection usually choose the option for this vaccine. As a result, a vast majority of the population are neither aware of the vaccines nor can afford it as this is not part of regular immunization schedule. However, the recent approval from Global Alliance for Vaccines and Immunization to support the initiative of Bangladesh government to introduce rotavirus vaccine in its national immunization program could be paradigm shift towards the management of rotavirus infection. It is expected that the vaccine would be included in 2018 [64]. Therefore, a more effective rotavirus vaccine to meet the challenges in this region would be a good candidate for inclusion into national immunization program in Bangladesh.

Rotavirus vaccine: success and limitations seem to be the two sides of the same coin

The first proposition for the candidate oral rotavirus vaccine came in 1983–1984 by Vesikari and his team. They reported the first trial of candidate oral vaccine using a bovine rotavirus strain RIT 4237 [65]. This paved the first framework of oral vaccine development principles. Unlike other vaccines, the long history of rotavirus vaccine development has progressed through small steps, some missteps, extraordinary efforts and dedications, long desired triumph, as well as many disappointments. 15 years after the work by the team of Vesikari, Wyeth-Lederle, York, US, brought the first licensed rotavirus vaccine 'RotaShield' [66] into the market place. Kapikian, National Institute of Health holds the credit for the development of this tetravalent rhesus rotavirus vaccine [67]. Clinical trials of RotaShield took place in US, Finland, and Venezuela. According to clinical trial data, this vaccine was safe and highly effective in preventing more than 90 and 79% rotavirus-associated diarrhoea in US and Venezuela, respectively [68–71]. However, an unexpected complication 'intussusception' led to the

cessation of RotaShield in 1999. The complication related to the administration of the tetravalent rhesus vaccine caused the withdrawal of over 1.5-million-dose vaccine [72–75]. A recent study in Ghana showed the safety, immunogenicity, and cost-effectiveness of this vaccine, and suggested that targeting optimal schedule of vaccination could reduce intussusception risk [76].

Two more oral vaccines were available in the market after the fall of RotaShield. The first one is Rotarix™ developed by GlaxoSmithKline (GSK) and second one RotaTeq® by Merck [77–79]. Rotarix™ is a lyophilized vaccine developed from the strain RIX 4414 [78, 79]. GSK conducted the initial trials of Rotarix™ in Finland where it showed efficacy, immunogenicity, and safety [80, 81]. Later, they tested this vaccine in Latin American countries (i.e., Mexico, Brazil, and Venezuela) and Asia (Singapore). The vaccine showed no significant side effects with the comparison on rate of side effects in between both vaccine recipient and control groups [78]. Rotarix™ showed 70–85% efficacy against any rotavirus diarrhoeal disease [81, 82]. Based on the positive outcomes of the previous clinical trials, GSK conducted a large safety trial among 63,000 infants from 12 Latin American countries and Finland. The trial proved the inability of the vaccine to cause any intussusception [83, 84].

RotaTeq® vaccine from Merck utilized a bovine rotavirus strain WC3 [85]. This pentavalent vaccine contains reassortant of one gene for human serotype capsid protein (G1, G2, G3, G4, and P1A[8]) with bovine WC3 [77, 86]. Initial clinical trials took place in US, China, and Africa [87–89]. To check intussusception, a large trial considered 70,000 infants from US, Finland, and some countries from Central and South America, Europe, and Asia [55]. Results from this trial confirmed the absence of possible intussusception. Moreover, this vaccine showed 96% efficacy against rotaviral diarrhoea cases [55].

The licensing for Rotarix™ first took place in Mexico and Dominican Republic in 2004. Later, it received approval for use in 35 other countries and European Union [84]. The US Food and Drug Administration approved the license for RotaTeq® in 2006, and 2 weeks later, Centers for Disease Control recommended it for regular immunization schedule in the US [90]. These two vaccines received licensing approval over 100 countries by the end of 2006 [55, 83]. In 2009, World Health Organization (WHO) recommended the inclusion of these vaccines in national immunization program of all countries but most especially for those with high diarrhoea-related mortality [91].In the year 2014, over 70 countries introduced rotavirus vaccines in their national immunization program for children [38].

Despite of all success stories, both vaccines suffer from common limitations. Results from clinical trials proved that both vaccines are less effective in Latin America, Africa, and Asia where the demand of an effective rotavirus vaccine is always high [92]. Studies have revealed that immunogenicity of both Rotarix™ and RotaTeq® ranged from 60% in Latin America, 76% South Africa, and less than 50% in Bangladesh, Vietnam, and Malawi, while the value was above 90% in Europe [83, 91, 93–96]. A study in Bangladesh showed that oral rotavirus vaccines failed to give protection in 68.5% of cases [95]. The lower efficacy of available vaccines in low-income countries necessitates the development of an alternative vaccine with higher efficacy. A new alternative should not only confer sufficient protection but also should be easily affordable and free from potential risks. In 2010, porcine circovirus I (PCV-1) DNA had been found in Rotarix™. US Food and Drug Administration restricted the use of Rotarix™ temporarily. The restriction was also followed by some European countries. Though PCV-1 does not infect humans, but its presence in vaccine is still very much unlikely. Later, WHO recommended the use of Rotarix™. GSK did a background check to find the contamination source, and finally, master seed virus was found to be contaminated with PCV-1 DNA. PCV-1DNA-free vaccine will be available soon after revision of all steps in production process using PCV-1 DNA-free virus seed. RotaTeq® was also found to be contaminated with PCV-1 and PCV-2 DNA fragments in 2010. Trypsin used in production was found to be responsible for this contamination [97].

Besides the two WHO-prequalified commercially available vaccines, three other live, attenuated oral rotavirus vaccines are available locally in the country of manufacture [3]. The first one is ROTAVAC™ by Bharat Biotech International Ltd., India [98]. This vaccine is derived from a naturally occurring human reassortant strain G9P[11] isolated from an Indian child [99, 100]. The second one is an attenuated Lanzhou Lamb Rotavirus (LLR-85) vaccine developed by Lanzhou Institute of Biological Products, China [101]. This monovalent vaccine is derived from a lamb rotavirus strain G10P[12] isolated from calf kidney cell in 1984 [101]. The third one is Rotavin-M1 developed by Center for Research and Production of Vaccines and Biologicals, Vietnam [102]. Though initially three candidate strains (G1P[8], G1P[4], and G4P[6]) were isolated, after analysis, the KH0118-2003 strain (G1P[8]) was selected for the vaccine development [103]. Besides several other vaccines, candidates are now under clinical trials, e.g.,UK-BRV in India [104], trivalent lamb reassortant vaccine in China [3], RV3-BB in Australia, New Zealand, Indonesia [105], and sub-unit vaccine P2-VP8* in South Africa [3, 106].

Factors limiting oral rotavirus vaccine efficacy

The factors limiting the efficacy of live oral rotavirus vaccines could provide insight why oral vaccines are highly effective in developed countries but not in developing and

under-developed countries. Host or environmental factors, strain diversity, antigenic variations, and most importantly environmental enteropathy (EE) are the major contributing factors behind poor vaccine efficacy [107–110]. Bangladeshi G1 strain shows four amino acid position differences with G1 strains of RotaTeq® and Rotarix™, while Bangladeshi G2 strain shows six amino acid position differences with RotaTeq® G2 strain [60]. Oral vaccines delivered to gut can be affected by several host factors including maternal antibody, components of breast milk, acidic environment in stomach, and presence of gut microbiota [94]. Studies conducted in Bangladesh and South Africa indicate that high transplacental antibody from infant could neutralize vaccine antigen in gut and also reduce immune response against vaccine antigen [79, 94, 111]. Breastfeeding practice could also interfere with oral vaccine efficacy [112]. Breast milk contains high amount of IgA antibodies which can neutralize rotavirus vaccine antigen and receptor analogues [113]. Data suggest that, if vaccine recipient infant had breast milk in mouth or in stomach while vaccinated, then neutralizing antibody could diminish vaccine response [114, 115]. Another study suggests that vaccine antigen can reach to gut easily if infant does not receive breast milk recently [115]. Rotavirus vaccine antigen can be damaged by low pH in stomach [116]. It could be possible that highly acidic juice in stomach could damage vaccine epitopes, though quantity of stomach acid in infant from developing countries is not yet measured to check any difference with infant from the developed countries [116].

Recently, EE is identified as the main responsible factor for lowering the oral vaccine efficacy [117]. It can be defined as chronic intestinal inflammation and dysfunction as a result of frequent intestinal infection [118]. Villous blunting, chronic inflammation, and increased intestinal permeability are major characteristics of EE [118, 119]. In the developing countries, water and food are highly contaminated with a variety of microbes [120, 121]. Dweller from these regions has high oral intake of this type of contaminated food and water. This results in high microbiota load in intestine. It leads to chronic activation of mucosal immune system and altered intestinal immune system [121–123]. Under this circumstance, intestinal immune cells are constantly engaged in preventing infection by microbiota. For this reason, the preoccupied cells show less affinity to oral

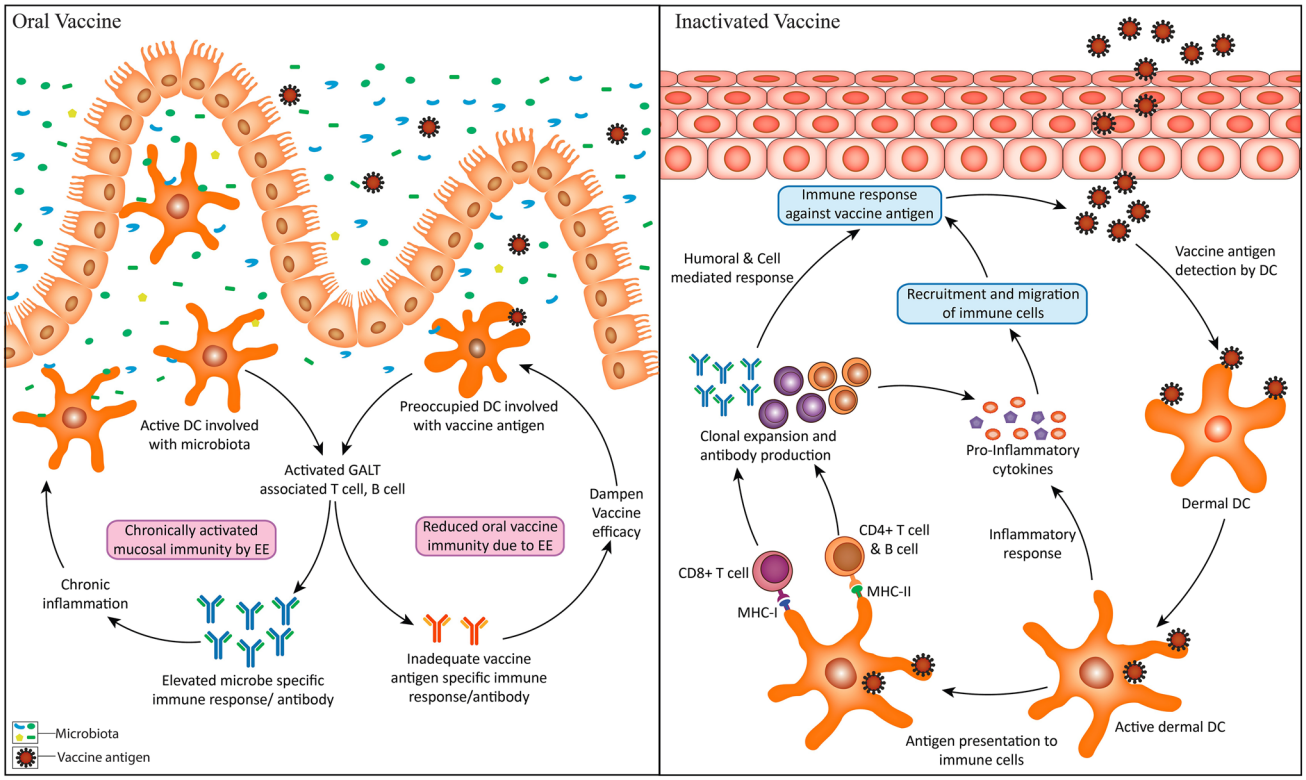

Fig. 1 Comparison between effectiveness of oral vaccine and inactivated vaccine. Oral vaccine: due to environmental enteropathy dendritic cells in gut-associated lymphoid tissue is chronically activated against microbiota population in gut. Elevated antibody response is initiated towards microbiota, while less affinity to oral vaccine antigens. Consequently, oral vaccine induces lower immunity against rotavirus. Inactivated vaccine: the absence of microbiota and dense network of immune cells in dermis make it more suitable for vaccine administration. Figure shows how vaccine antigen is detected and subsequent elevated immune response is created in response of vaccine antigen

vaccine antigens and thereby dampen the immunity (Fig. 1) [117]. Figure 1 illustrates a generalized mechanism how oral vaccine response is diminished by EE and how inactivated vaccine can overcome this hindrance (will be discussed in later section). This mechanism could also be acceptable for rotavirus vaccine as hypothesized by Valdez et al. [117]. From different studies, it is now evident that EE is linked with poverty and poor living conditions that is most common in developing countries [118]. Thus, it relates itself as the main culprit to lower oral rotavirus vaccine performance in developing countries where it requires utmost attention. In Bangladesh, more than 80% infants have EE, which clearly explains the low efficacy of rotavirus vaccine in Bangladesh [95].

Inactivated rotavirus vaccine, best alternative to present solution: why and how?

The limitations of currently available vaccines led to the development of a better alternative and the scientists are in the pursuit of an ideal vaccine that would provide proper efficacy and safety. Withdrawal of RotaShield for intussusceptions seriously affects other oral vaccine candidates. All other oral vaccine candidates including existing two must have to go through extended trials and testing for intussusceptions which delays their licensure as well as increase cost. To ensure safety, there is no other way to avoid this in case of live oral vaccines but which can be negligible in case of non-living candidates [124]. In this context, inactivated vaccines could provide the best alternatives to oral vaccines [125]. Research towards the development of an effective inactivated rotavirus vaccine is underway around the world [126]. Based on the scientific evidences, inactivated vaccines have advantages over oral vaccines, and therefore, it is now more rational to introduce an inactivated rotavirus vaccine [92, 127]. Inactivated vaccine is free from risk factors such as breastfeeding, gastric acid, microbiota in gut, as well as EE, and will not cause any intussusception [92, 126]. Inactivated vaccine can also overcome the problem associated with lower efficacy of the existing rotavirus vaccine. Inactivated vaccine could be administered through intradermal route [128, 129]. Due to the presence of dense network of antigen presenting cell in skin, intradermal route of vaccine administration ensures greater efficacy of inactivated rotavirus vaccine (Fig. 1). Vaccine antigen administrated through intradermal route will be free from competition with microbiota. Thus, inactivated vaccine ensures production of greater immunity [125, 130, 131]. Moreover, lower production cost of inactivated rotavirus vaccine will also ensure greater accessibility and affordability to common people [92]. Several research groups are already trying to develop new technologies to produce an effective inactivated rotavirus vaccine [132, 133]. Conventionally, rotavirus inactivation takes place by formalin, though it has some disputes [134, 135]. Scientists from Centers for Disease Control and Prevention and Sanofi Pasteur have developed a new technology to inactivate rotavirus by heat treatment [136]. This thermal inactivation technology is also safe, rapid, cost-effective, and would put a stop of using conventional controversial chemicals such as formalin and beta-propiolactone [134–138]. Animal trials have confirmed that heat-inactivated rotavirus vaccine is enough immunogenic to protect from rotavirus infection [136, 139, 140]. However, data from human studies are not available yet.

Concluding remarks

Rotavirus-associated diarrhoea is believed to be a vaccine-preventable disease. It is anticipated that a new generation vaccine will soon be available that would be highly effective, free from present limitations, easily affordable to poor community and available globally. Inactivated rotavirus vaccines offer themselves as the best candidate in this regard. However, scientists are giving their immense efforts to develop an inactivated rotavirus vaccine. Bringing an effective solution requires high time, patience, and investment. A newly developed vaccine demands the attribute of possessing high immunogenicity, most importantly in developing countries where the currently available vaccines are less immunogenic.

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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