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Pediatric acute gastroenteritis due to adenovirus 40/41 in low- and middle-income countries

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Abstract

Purpose of review: To review the roles of enteric adenovirus types 40 and 41 and non-enteric adenoviruses in the global burden of pediatric diarrhea.

Recent findings: Large studies using highly sensitive, type-specific molecular diagnostics have demonstrated a substantial and previously under-estimated burden of pediatric diarrheal disease due to enteric infections with adenovirus types 40/41. However, the true epidemiology of adenovirus 40/41 remains incompletely understood. Similarly, additional adenovirus types may also be implicated as agents of community-acquired pediatric gastroenteritis, but current data are too limited to elucidate their epidemiological role(s), if any.

Summary: Efforts at global diarrhea control in low- and middle-income countries will require combating pediatric gastroenteritis due to enteric adenovirus infections. Future research in these settings using type-specific molecular diagnostics or strain genotyping to fully characterize the epidemiology of adenovirus 40/41 infections, identify non-40/41 adenoviruses significantly associated with gastroenteritis, and develop vaccines effective at preventing adenovirus diarrhea is warranted.

Keywords

Acute gastroenteritis; diarrhea; adenovirus; pediatric

Introduction

Diarrheal disease is a leading cause of death and disability worldwide. Infants and young children are particularly vulnerable in regions with poor access to healthcare, where repeated episodes of moderate-to-severe diarrhea (MSD) and high rates of infection with enteric pathogens may be associated with growth faltering, impaired neurocognitive development, and increased mortality [1–3]. Accordingly, reducing pediatric diarrheal disease and enteric

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infections in resource-limited settings is critical to prevent early death and disability, maximize cognitive potential, and accelerate development out of poverty. Using molecular detection, recent studies in low- and middle-income countries (LMIC) have demonstrated a surprisingly high burden of diarrheal disease due to enteric adenoviruses among young children. Here, we will review the current understanding of enteric human adenovirus infections and the burden of community-acquired enteric adenovirus among children in LMICs, as determined using molecular diagnostics. This review will not discuss adenovirus infections that are healthcare-associated, non-enteric, or occur in adults or immunocompromised individuals, except as otherwise stated.

Background

Human adenoviruses are non-enveloped, double-stranded DNA viruses in the family Adenoviridae, genus Mastadenovirus. Over 100 types, many with well-characterized tropisms for specific tissues, have been identified and divided across seven species, A–G [4]. Types 40/41 (species F) have long been established as agents of pediatric gastroenteritis, characterized by fever, vomiting, and diarrhea [5–7]. Adenovirus 40/41 gastroenteritis can cause severe disease and is a frequent cause of hospitalization [8*,9**,10**]. Little distinguishes the presentation of acute gastroenteritis due to adenovirus 40/41 from that due to other pathogens. The epidemiology of adenovirus 40/41 infections has been difficult to describe due to large heterogeneity in study design, case definition, and methods of detection. However, some consistent features have emerged. The greatest burden of disease occurs in young children less than two, particularly infants less than twelve months [7,11,12**,13*]. Type 41 appears to be more common than 40 [8*,14*,15,16,17*]. Early studies found no apparent seasonal distribution [5, 6], while others have suggested summer-autumn peaks, particularly with type 41 [7,18,19]. Marked variation in yearly prevalence has been demonstrated, ranging from 0.7% to 6.5% and 8.5% to 18.9% in long-term studies from Australia and Ireland, respectively [7,20]. Others have documented local outbreaks, resulting in large variability in prevalence across regions or time [17*,19]. Together, the data suggest that adenovirus 40/41 typically follows a variable endemic pattern of disease subject to infrequent outbreaks, meaning that cross-sectional, case-control, or cohort studies of short duration may be at significant risk of mischaracterizing local incidence estimates.

Burden of enteric adenovirus disease in LMIC

We surveyed the literature to investigate recent trends in adenovirus 40/41 infections in LMIC, as determined using polymerase chain reaction (PCR) detection. Most studies were significantly limited by study design, scope, and scale, precluding generalizability. For example, the reported prevalence of adenovirus 40/41 infections in children with diarrhea was 1.5% in Brazil [21], 5.1% in Nigeria [22], and 13% in Guatemala [23]. The best data are derived from the re-analysis of two comprehensive studies of diarrheal etiology in LMIC: GEMS (Global Enteric Multicenter Study) and MAL-ED (Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development study). These two studies have convincingly demonstrated the under-appreciated burden of disease cause by adenovirus 40/41 in LMICs.

The GEMS study was a case-control study to determine the etiology of MSD in children <5 years of age in seven LMIC (Bangladesh, India, Pakistan, The Gambia, Kenya, Mali, Mozambique) [1]. Original study design used pan-adenovirus stool enzyme immunoassay (EIA) followed by type 40/41-specific stool EIA on positive specimens for diagnosis of adenovirus 40/41 infection in 9439 pediatric cases and 13219 matched controls from 2007 to 2011. Subsequent re-analysis using a custom TaqMan Array Card (TAC, Thermo Fisher), which included quantitative PCR (qPCR) detection of adenovirus 40/41, demonstrated a five-fold increase in attributable incidence (AI) compared to EIA [24]. Among infants, adenovirus 40/41 was revealed to have the second-highest AI of MSD (3.9 episodes per 100 child-years, 95% confidence interval (CI) 2.4–5.4). Surprisingly, about ten percent of cases of bloody diarrhea were attributable to adenovirus 40/41, even after controlling for other pathogens, including *Shigella*. Since many etiological studies of viral gastroenteritis specifically exclude bloody diarrhea, the burden of diarrhea due to adenovirus 40/41 in LMIC may be substantially under-reported [25]. Finally, the re-analysis also included pan-adenovirus detection, which was not associated with diarrhea after controlling for types 40/41, consistent with the expectation that non-40/41 adenovirus types are not typical agents of gastroenteritis.

MAL-ED was a birth cohort study performed among 2145 children <24 months across eight LMIC (Bangladesh, India, Nepal, Pakistan, Brazil, Peru, South Africa, and Tanzania) between 2009 and 2014 [26]. Active diarrheal surveillance was performed by twice-weekly home visit to calculate pathogen-specific diarrhea burden in the community. Adenovirus detection was performed using non-specific pan-adenovirus stool EIA. Reanalysis of these data using TAC for specific detection of types 40/41 increased the AI substantially in all age groups. Similar to GEMS, adenovirus 40/41 had the second-highest AI (20.9, 95% CI 17.4–25.8) among infants, following rotavirus [12**].

These data underscore the superiority of qPCR methods for adenovirus 40/41 detection. In addition to the increased sensitivity of PCR in general, this difference may also be due in part to false-negative EIA results, as type 40/41-specific EIA can fail to detect clinically important type 41 isolates, possibly due to antigenic drift within the targeted neutralization epitopes [27,28].

Similar findings have been demonstrated in other recent studies. A case-control study of diarrheal etiology following rotavirus vaccine introduction was conducted in Blantyre, Malawi from 2012 to 2015 [9**]. Diarrheal pathogens were detected by TAC among 684 hospitalized children <5 years of age and 527 matched community controls. Adenovirus 40/41 was detected in 29.1% of cases compared to 2.7% of controls with an adjusted attributable fraction (AF) of 27.7% (95% CI, 24.5–31.4), second-highest following rotavirus. In a phase 3, randomized, controlled rotavirus vaccine trial (Rotavac, Bharat Biotech) conducted between 2012 and 2014 in India, children underwent prospective, active community diarrheal surveillance from 6–8 weeks until 2 years of life [10**]. Diarrheal pathogens were detected by TAC in 1507 specimens from 1169 children. Once again, adenovirus 40/41 had the second-highest AF among all diarrheal pathogens, second only to rotavirus, irrespective of vaccination status.

These studies demonstrate that the burden of diarrheal disease due to adenovirus 40/41 infection among infants and young children in LMIC is substantial. Indeed, using mathematical modeling, the Global Burden of Diseases study estimated that in 2016, enteric adenovirus infections caused 75 million episodes of diarrhea globally among children <5 years of age, with an associated AF for mortality of 11.78% (95% uncertainty interval, 8.19–16.13), behind only rotavirus and *Shigella* [29**]. South Asia in particular appears to represent an important hotspot, as sites in India and Bangladesh have consistently reported the highest burdens of adenovirus 40/41-associated diarrhea relative to other pathogens; In MAL-ED, for example, adenovirus 40/41 had the highest AI of all pathogens tested at the Bangladesh site [10**,12**, 24]. These data suggest that in these settings, adenovirus 40/41 is poised to become the leading cause of pediatric gastroenteritis after rotavirus vaccine introduction, rather than norovirus, as was seen in western countries [17*].

Non-enteric adenoviruses as potential etiologies of gastroenteritis: Challenges in attribution of diarrheal etiology

A significant limitation in the approach to attribution of diarrheal etiology to human adenoviruses is use of detection methods that are not specific to adenovirus 40/41, which have been clearly identified as agents of diarrhea. All adenovirus types can be detected in stool specimens: in recent studies from LMIC, prevalence of any detectable adenovirus in the diarrheal specimens ranged from 1.6% to 34.2% [8*,30–35]. However, whether detection of these types is relevant for etiologic studies of diarrhea remains unclear [24,35–38]. In studies that performed definitive strain genotyping, a variety of strains were seen. In Ethiopia, 32% of stools from children with acute gastroenteritis were adenovirus positive, of which 21.5% were types 40/41 [39]. In China, 28.9% of children with diarrhea had adenovirus detected in stool, of which 56.9% were types 40/41 [14*]. In Thailand, 7.2% of pediatric gastroenteritis stool specimens were adenovirus positive, of which 28.5% were types 40/41 [16]. In Iran, 4.3% of children with gastroenteritis were positive for adenovirus, of which 62.5% were type 41 [40]. And finally, a different study from China found 3.9% of diarrheal specimens positive for adenovirus, of which 29.6% were types 40/41 [41]. Furthermore, interpretation of the literature is often hindered by lack of specificity regarding the term “enteric adenoviruses,” which in some studies refers to all adenoviruses detected in the stool, irrespective of type, and by a lack of methodological detail regarding pan-adenovirus vs type 40/41-specific detection.

Among non-type 40/41 adenoviruses, species B, type 3 (B/3), C/2, and A/31 adenoviruses are among the more frequent to be shed in the stool [14*,15,16,21,39,41,42]. However, their role as potential agents of community-acquired gastroenteritis in immunocompetent children remains controversial. These species are associated with high rates of respiratory disease with lower viral antigen loads in the stool [43], suggesting a greater role as agents of respiratory tract infection or generalized viral syndromes rather than gastrointestinal infection per se, unlike types 40/41, which only rarely can be recovered from the respiratory tract [44,45]. The duration of fecal shedding following primary adenovirus infection can be very prolonged, up to 3 months for C/2 in healthy infants [46]. In addition, an important feature of adenoviruses is the ability to establish latency, with lymphoid tissues of the gastrointestinal tract serving as a reservoir for multiple species, particularly C [47]. The gut

is the likely source of invasive infection in children following reactivation due to profound immunosuppression, such as with hematopoietic stem cell transplant [48].

A significant proportion of non-type 40/41 adenovirus stool detection is likely due to shedding of reactivated latent virus during illness caused by other pathogens, persistent shedding following remote primary infection [17*], or stool shedding incidental to primary infections in which gastrointestinal infection is not the primary disease process. Therefore, studies using pan-adenovirus detection for community-acquired gastroenteritis in children may yield misleading data regarding pathogen prevalence, disease incidence, and important epidemiological features, such as seasonality or age-adjusted risk. On the other hand, current inability to accurately estimate the contribution of non-type 40/41 types to pediatric gastroenteritis may lead to underestimates of true diarrheal disease burden due to adenovirus gastrointestinal infections.

A related challenge is the high frequency of coinfections with other enteric pathogens [8*,11]. In the reanalysis of both GEMS and MAL-ED, adenovirus 40/41 infection was most often associated with coinfections with other diarrhea-causing pathogens, but independently remained strongly associated with diarrhea. This means that the increased detection using more sensitive qPCR methods was not simply increased detection of clinically insignificant asymptomatic infection or shedding. The statistical power enabling these analyses were a key factor in this assessment, as multiple studies have previously noted that adenovirus 40/41 infections frequently occur as mixed infections with other pathogens but were likely underpowered to detect significant associations with diarrhea. This suggests a more complicated picture of diarrheal etiology compared to the traditional approach of identifying a single disease-associated pathogen. Instead, in environments with a high burden of enteropathogen carriage, diarrhea may result from the complex interplay of multiple organisms leading to emergence of symptomatic disease.

Treatment and prevention

The treatment of acute viral gastroenteritis for young children in LMIC, as endorsed by the World Health Organization, consists of oral or intravenous rehydration, zinc supplementation, and ensuring adequate nutritional intake; agents for symptom control or antiviral treatment are not recommended [49]. Mortality is chiefly due to acute dehydration; as uptake of ORT, the most basic intervention for acute gastroenteritis, still remains low in high-burden regions [50], we believe priority should be given towards disease prevention and improving access to ORT over development of targeted antiviral therapies.

Most enteric pathogens are presumed to cause infection via the fecal-oral route. Therefore, interventions to improve water quality, sanitation, and hygiene (WASH) at the household level in LMIC to prevent enteropathogen infections have recently been subjected to well-designed, large field trials [51*]. Unfortunately, no significant impact on enteric viral infections, including adenovirus 40/41, could be demonstrated [52*]. Adenovirus 40/41 infections are also recognized as an important cause of childhood diarrhea in high-income settings [38]. Similar to rotavirus, improved hygiene and sanitation alone, even at the community level, may be insufficient to adequately control adenovirus 40/41 disease.

In this context, given their importance as agents of gastroenteritis in LMIC, adenovirus 40/41 is an appealing target for vaccine development. Efficacious oral vaccines against respiratory adenovirus types 4 and 7 have been developed and are approved for use among military recruits in the United States [53], suggesting potential for other type-specific adenovirus vaccines. Vaccines against diarrheal pathogens may have the additional benefit of reducing antibiotic consumption and antimicrobial resistance, since an alarmingly high proportion of acute diarrheal episodes of diarrhea in LMIC ultimately receive unnecessary antimicrobial treatment [54]. Adenovirus gastroenteritis was also associated with decreased follow-up height for age among infected children in Bangladesh and with high average medical costs per episode, suggesting additional potential secondary benefits of enhanced disease control [13*]. However, there is currently not an active adenovirus 40/41 vaccine pipeline. Antigenic drift may occur within the neutralizing epitopes of type 41, particularly within the hypervariable regions of the hexon protein [27]. This might explain the presence of adenovirus 41 outbreaks and the regional yearly variations in adenovirus 41 prevalence. If adenovirus 41 does demonstrate antigenic drift, vaccine development may need to consider targets other than the hexon hypervariable regions. Potential options include development of live-attenuated vaccines, which suffer from reduced efficacy in LMIC [55**] but would most closely simulate natural infection and engage multiple branches of immune response, or development of formulations that would ensure generation of redundant humoral responses targeting multiple and/or alternate epitopes.

Summary and future directions

Enteric adenovirus types 40/41 are important agents of pediatric gastroenteritis, with a high burden of disease among young children in LMIC. In these regions, adenovirus 40/41 is one of the leading causes of childhood diarrheal disease and has the potential to become the leading cause of pediatric gastroenteritis as rotavirus vaccine coverage continues to improve. However, multiple challenges and unknowns remain. Due to the endemic pattern of disease with yearly variation in prevalence and the requirement for molecular diagnostics to reliably detect infection, the epidemiology and burden of adenovirus 40/41 in LMIC remains inadequately characterized. Future long-term, prospective studies using molecular detection are needed to more accurately assess the true impact of adenovirus 40/41 gastroenteritis. We suggest that qPCR detection of adenovirus 40/41 should be included in any future studies of diarrheal etiology in LMIC, and that EIA detection or pan-adenovirus stool detection in the absence of strain typing should be avoided, due to poor sensitivity of EIA and uncertainties regarding the etiologic contribution of non-40/41 strains to diarrhea. However, there is clearly a need for more research to elucidate the role(s), if any, for non-40/41 types in diarrheal disease burden. Despite these limitations, sufficient evidence exists to support the development of vaccines against adenovirus 40/41 to reduce the burden of pediatric diarrheal disease in LMIC. Vaccine development should take into consideration the known challenges related to the underperformance of oral vaccines in LMIC and previous observations regarding possible antigenic drift within neutralizing epitopes of adenovirus type 41.

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settings: a reanalysis of the MAL-ED cohort study. The Lancet Global health. 2018;6(12):e1309–e18. [PubMed: 30287127] This is perhaps the most comprehensive study yet undertaken to define the etiology of acute diarrhea among children at the community level in LMIC. Along with the GEMS re-analysis, MAL-ED has been instrumental in identifying priorities for intervention in the global prevention of pediatric diarrheal disease, and like GEMS has incontrovertibly demonstrated the burden of adenovirus 40/41 gastroenteritis in these settings and the requirement for type-specific molecular detection to reliably identify these infections.

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KEY POINTS

- Gastroenteritis due to adenovirus types 40/41 causes a substantial and under-appreciated burden of pediatric diarrheal disease in low- and middle-income countries, particularly in south Asia.
- The epidemiology of adenovirus 40/41 gastroenteritis in these settings remains poorly characterized due to the need for long-term prospective studies using type-specific molecular detection.
- The role of other non-40/41 adenovirus types as etiologic agents of pediatric gastroenteritis remains unclear and requires further investigation to determine the true burden of adenovirus infections on global diarrheal disease.
- Vaccines targeting adenovirus 40/41 should be developed to further combat pediatric diarrheal disease in low- and middle-income countries.