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BURDEN OF ROTAVIRUS AND OTHER DIARRHOEAL DISEASES IN CHILDREN- THE WORLD'S UNFINISHED PROJECT

Pediatrics

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ABSTRACT

This paper discusses the importance of rotavirus and other diarrhoeal diseases in global health. While noting the progress made overtime, it strongly draws attention to the outstanding issues, as well as research areas that remain to be addressed by the global community so as to bring childhood diarrhoeal morbidity and mortality to the barest minimum.

Introduction

Diarrhoeal diseases in general as well as rotavirus disease in particular are major contributors to under-five morbidity and mortality. Diarrhoea is the second commonest cause of under-five mortality[1]. Although significant progress has been made through various interventions resulting in decrease in its mortality and morbidity, diarrhea is still responsible for about 760,000 under five deaths annually. Nearly 80% of these deaths occur in the Africa and South-East Asia[2,3]. Although diarrhea deaths dropped significantly over the past few decades, incidence has relatively remained stable, see table 1[4]. While diarrhoea mortality dropped from 4.6 million in 1980 to1.5 million in 2000[5]; the incidence only dropped from 3.4 episodes/child year in 1990 to 2.9 episodes/child year in 2010, that is a drop of about 1.9 billion episodes of childhood diarrhea in 1990 and about 1.7 billion episodes in 2010[6].

Table 1: Diarrheal estimates in children of developing countries[4]

Author(s) (Publication Year)	Period	Deaths per Year (millions)	Deaths per 1000 per Year	Episodes per Child per Year	Methods
Snyder & Merson (1982) 4	1954-79	4.6	13.6	2.2	Long. Cohorts and active surveillance
Bern et al.(1992) 2	1980-90	3.3	7.6	2.6	Long. Cohorts and active surveillance
Kosek et al (2003) 1	1990-2000	2.5	4.6	3.2	Data from surveys using WHO methods

According to WHO, diarrhoea is defined as the passage of three or more loose or liquid stools per day (or more frequent passage than is normal for the individual)[2].

Studies show that ORS, one of the major interventions so far, has tremendously reduced diarrhea-related mortality and has been described as the most significant medical advance of the 20th century[7].

Major causes of diarrhea are viral and bacterial. These are acquired through the oro-faecal route. This implies that water, sanitation and hygiene are key factors in addressing the incidence. In most developing countries, these are persistent issues that require multi-sectional approach. Before the introduction of rotavirus vaccine in developed countries diarrhea incidence had been shown to drop over years with improved sanitation and hygiene, though only up to a level because studies have shown that improved environmental hygiene does not significantly affect the incidence of rotavirus diarrhea[8].

Rotavirus is the singular commonest cause of under-five diarrhea globally, being responsible for more than 40% of cases[9,10]. In the pre-rotavirus vaccine era, rotavirus accounted for about 450,000 deaths[11]. Most deaths occur in developing countries, although there are near-equal incidences in both developing and developed countries[12].

Progress so far

Tremendous progress has been made in the control of diarrhea diseases in children through the implementation of simple, low-cost, high-impact evidence-based interventions:

Oral rehydration solution: following results of studies showing that use of simple ORS prevented deaths from severe dehydration and electrolyte imbalance, WHO in 1970s[5,13,14] recommended the use of ORS for the treatment of diarrhoea. The solution basically consists of glucose, sodium, potassium, lactose and water. Ever since its introduction and use globally from the 1970s, ORS has been estimated to save up to 50 million lives[15]. Further studies showed better outcome if the osmolarity was reduced from 311 to 245mOsm/L by reducing the, glucose and sodium concentrations. Incidence of hypernatremia was reduced, as well as diarrheal duration, stool frequency and number of unscheduled intravenous fluids[4]. A systematic review on the effect of low osmolar ORS on diarrhea mortality showed that 93% relative reduction in diarrhoeal mortality would be expected with 100% coverage, given: 69% (95% CI: 51-80%) relative reduction in diarrhea mortality in communities in which ORS was promoted compared with comparison areas; and a mean coverage of 74% (52-96%).[16]

WHO therefore in 2004[13] recommended the use of low osmolar ORS in all cases of acute gastroenteritis irrespective of the aetiology[17].

Zinc: similarly, clinical trials also demonstrated that administration of zinc at 20mg daily for 10-14days (10mg for infants <6months) had beneficial effects in diarrhea patients.

Zinc was demonstrated to reduce stool frequency and volume, as well as diarrhoeal duration. It also prevented subsequent episodes of diarrhea. It has therefore become part of standard case management of acute gastroenteritis to administer low osmolar ORS and Zinc[18,19].

Breastfeeding: although the practice of breastfeeding had been abandoned by majority in preference for artificial formula, breastfeeding, in addition to numerous benefits is known to protect children during episodes of diarrhoea[20] and helps to ensure on-going feeding to prevent hypoglycemia, hypovoleamia/dehydration and malnutrition. It also protects against frequent episodes of diarrhea and has therefore been part of the standard case management to continue breastfeeding[21,22].

***Portable water, hygiene and sanitation*:** these have been shown to reduce diarrhea incidence from causes other than rotavirus. The reason is straight forward; most diarrhoeal diseases are transmitted by the faeco-oral route.

Awareness: Substantial progress has been made in terms of awareness of diarrhoeal disease, management options and preventive measures. This has no doubt contributed to the reduction in morbidity and mortality.

Vaccination: Vaccination against diarrhea includes the measles vaccine and the rotavirus vaccines. Over the years, measles-associated diarrhea morbidity and mortality have been averted by widespread measles immunization. Measles immunization coverage has increased from 72% in 2000 to 85% in 2010, although this progress has stalled as coverage has remained unchanged in the last four years[23].

Recently, another major progress against diarrhoeal diseases is the introduction of rotavirus vaccine in developed and developing countries. A rotavirus vaccine, Rotashield, was first introduced in 1998. While the current rotavirus vaccines were introduced in US in 2006 (RotaTeq) and 2008 (Rotarix)[24], introduction in developing countries was not until several years later. However, the interval is shorter than previous intervals between vaccine introduction in developed countries and time of introduction in developing countries. This is partly attributed to concerted global partnership efforts by various organizations including the WHO, Gavi alliance and the industry to ensure that this time-interval is shortened. These global efforts focused mainly on local disease burden data generation, advocacy and vaccine financing.

As at January 2016 up to 80 countries have introduced rotavirus vaccines, including 65 LMICs countries, 37 Gavi-eligible countries and 32 African countries. Many countries (including Nigeria) are planning to introduce in the next few years. Rotavirus vaccines are available in over 100 countries in the private market[25,26]. Countries where the vaccine has been introduced have consistently shown significant decline in rotavirus morbidity and mortality, all-cause diarrhea morbidity and mortality; as well as decline in diarrhoeal disease burden among unimmunized older children and adults.[27,28].

Case management: Active case management of moderate to severe diarrhea in health facilities by intravenous fluids and rational use of antibiotics when indicated has also impacted positively on diarrhea disease burden. Although significant proportion of children still do not have access to specialized care, active case management has improved over the years though sub-optimally[29].

What remains to be done

Challenges

Low ORS utilization rate - although ORS is one of the most cost-effective interventions in the history of diarrhea management, data show a decline in its use over the past few years[30,31]. Besides the decline, the utilization rate is yet to reach the target, as many still do not use in-spite of being aware of it[31,32]. For many in remote communities, awareness and accessibility to the low osmolar ORS is still a challenge as shown in figure 1[33]. The world community therefore needs to address these and other challenges like wrong reconstitution that results in hypernatremic or hyponatremic dehydration.

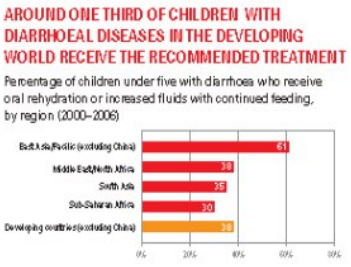


Figure 1

Low Zinc awareness and usage - until recently, the awareness of use of zinc in management of diarrhea had been very low[34] despite its recommendation by WHO since 2004[35]. Even now, its awareness is still not optimal among both care-givers and health care providers[36,37]. While some are not aware at all, others seem to forget while managing a case. Care givers often mix the zinc with the ORS and in some cases, child is unable to take all the ORS leading to zinc under-dosage. It therefore requires that strategies be put in place to enhance coverage in usage of zinc in the management of diarrhea in children. This includes training of HCWs and public awareness programmes in the mass media and during health talks in health facilities.

Low exclusive breastfeeding rates - again this scientifically proven profoundly beneficial practice has recorded very low rates across the globe and therefore has failed to reach acceptable rate of 90% over the years and has also be shown to be stagnant or even declining[38-41]. The health benefits of breastfeeding are enormous, especially its role in the control, prevention and management of diarrhea. It has become a globally huge task to raise the EBF rates to set targets and this task therefore remains outstanding for the international community to achieve and requires renewed vigor and efforts from all stakeholders.

Poor access to standard case management - especially in severe diarrhoea with moderate to severe dehydration and electrolyte imbalance, access to a health facility with hospitalisation facilities is not within the reach of many children in developing countries. Even where such facilities exist, there are still the issues of skilled / trained health workers to administer appropriate intravenous fluids and electrolytes in right quantities and concentrations; as well as financial access to these services when available. In many developing countries out-of-pocket expenses for care of children is still high[42]. With high poverty rates which according to World Bank[43], increases the need for health care while reducing the capacity to finance it, many children with diarrhoea lack access to services especially in the world's most unreached communities. This increases diarrhoea disease burden. Low-income countries share 56% of the global disease burden but account for only 2% of global health spending.

Inadequate access to portable water and sanitation - water and environmental sanitation remain to be achieved at a universal level. There is need for a simple and cheap means of universal provision of portable water in the remote and excluded communities in developing countries. Even urban cities record recurrent shortages of portable water and poor sewage disposal. These require more research based approaches. The other issue that must be on-going and sustained universally is basic education and health education on hygiene and sanitation. It is alarming how the ignorant population unwittingly creates potentials for transmission of disease especially by the oro-faecal route on a continuous basis.

Malnutrition - this increases the prevalence of diarrhoea diseases and vice versa. Diarrhoea is therefore a cause and effect of malnutrition[4,44,45].

The burden of malnutrition though improved over the years, is still a major global issue and is increasing in some countries and communities especially with rising level of conflicts and number of displaced families.

It therefore remains to be further strongly addressed together with its associated factors. These include illiteracy, poverty and conflicts. The increasing level of conflicts is becoming a global threat to children's health with the potential of reversing some gains made in the past years. Internally displaced and refugee camps are very good breeding grounds for infectious disease especially diarrheal disease since such camps frequently lack basic sanitation facilities and portable drinking water. The global community must work towards reversing the conflict trends in order to achieve better child health.

Hand hygiene- although this is receiving renewed global attention, it does not suffice for attention to wax and wane. A sustainability mechanism must be put in place as population renewal is also a

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continuous process.

Progressive decline in diarrhoea –related research – it has been documented by some authors that diarrhea-related research is on the decline[46]. This portends stagnation in process or even decline in addressing diarrhoea disease burden. Interest must be renewed, encouraged and funded to ensure improvement in diarrheal disease management, prevention, control and elimination.

Rrotavirus-related research

Rotavirus impact studies-with the growing widespread acceptance and country introduction of the rotavirus vaccine, it is expected that the commonest cause of diarrhoea (rotavirus) will be reduced drastically. Although the vaccine has been shown to reduce rotavirus- specific and all-cause diarrhoea hospitalisation and mortality, there is need for more impact studies especially in the African and Asian regions of the world, where introduction is currently taking place or will soon take place in the next few years.

Rotavirus safety studies- in addition to Rotavirus impact studies, there is an even greater need to conduct, post-marketing safety studies. It is already documented that previous rotavirus vaccine Rotashield was associated with relatively increased risk of intussusception especially in older infants[47–49]. The World Health Organisation has therefore recommended on-going post-marketing monitoring/surveillance of new rotavirus vaccines to continually demonstrate no increased risk for intussusceptions[50-52]. While earlier studies did not show increased risk, recent studies in Mexico, Brazil, and Australia suggest possibility of increased risk in some populations possibly in association with other factors like co-administered oral vaccines[53-55]. Now that there are progressively increasing number of developing countries in Africa and Asia introducing or planning to introduce rotavirus vaccine into their national routine immunization programmes, it has become increasingly more important to monitor the safety of rotavirus vaccines in field use.

Countries should therefore specifically plan vaccine safety monitoring together with vaccine introduction.

Other research areas include new and cheaper rotavirus vaccines, non-oral vaccines, needle-free and thermostable rotavirus vaccines; use of the old rotavirus vaccine, Rota shield, in neonates, barriers to ORS utilisation and breast-feeding practice[56].

The Way forward

Improving Current Intervention

There is an urgent need to increase the coverages of current interventions like ORS, Zinc and breastfeeding, others are hand hygiene, environmental, personal and food hygiene, portable water, sewage disposal, literacy level and awareness. There is need to not only reverse the downward trend in the coverage of interventions, but also upscale them. The gap between awareness of interventions and actual practice needs to be closed through research based approaches, strategies and policies.

Case Management

Home and facility based case management of diarrhoea requires a boost as well as universal availability. Increasing the use of ORS can avert up to 14% of child deaths[4]. The low osmolar ORS, Zinc and other interventions can drastically reduce child mortality. Community awareness should focus on increasing understanding of preventing, recognizing, and prompt and appropriate management of diarrhoea[33]. Accessibility to hospitalization and intravenous fluid and electrolyte therapy requires larger governmental role and therefore political commitment. This can be achieved through international advocacy and partnership measures.

Use of Rotavirus Vaccines

There is need to sustain the current global efforts towards widespread introduction of rotavirus vaccines especially in terms of advocacy, technical support and funding. The tempo must not wane. Also funding should target research into new rotavirus vaccines and formulations.

Prioritization of research

It has been noted that research in the area of diarrheal disease is declining. This trend needs to be reversed and governments and international development partners as well as non-governmental organizations have a larger role to play. Priority should be given to research questions that focus on increasing, not just awareness, but also uptake of current interventions to ensure high coverage and effectiveness in reducing morbidity and mortality. WHO recommends that priority research should be targeted at more understanding of barriers to implementation, effectiveness and optimization of use of available interventions like ORS, Zinc, exclusive breastfeeding and integrated management of childhood illnesses (IMCI)[57].

Operational, social and anthropological researches are therefore priority. These require donor support and such researches often do not attract donors.

Other causes of diarrhoea like the norovirus require attention. So also is the issue of access to portable water. The global community needs to find new ways of ensuring universal availability of portable water. When this is combined with improved literacy level and disease awareness, significant progress can be achieved in the fight to reduce diarrhoea disease burden.

Multiple interventions

The basic approach here recommended is an integrated, multi-interventional approach to achieve the greatest results.

Conclusion

Although tremendous efforts have been made in the past decades with significant results achieved, a lot still remains to be done and millions of children still die from diarrhoea, especially rotavirus diarrhoea. There is need to coordinate and harmonize global efforts close inter-regional gaps to bring about equity in global disease burden distribution. So the basic unfinished work is reduction in disease burden to the barest minimum with reasonable equity in diarrhoea disease burden distribution. This is the world's unfinished diarrheal project.

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