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Rotavirus gastroenteritis in India, 2011–2013: Revised estimates of disease burden and potential impact of vaccines

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A B S T R A C T

While improvements in oral rehydration use and access to healthcare have contributed to impressive gains in child survival, diarrheal diseases remain the second most important cause of child mortality in India. Pathogen specific disease rates, while key to deciding on the utility of specific public health interventions such as vaccines, are extremely difficult to obtain in developing country settings with less than optimal health access, diagnostic services and information systems.

This study combined disease burden within five cohorts of infants followed up for diarrheal morbidity with data from the nationally representative Indian Rotavirus Surveillance Network and applies rates of rotavirus related events to UNICEF birth and mortality estimates for India. These estimates, while limited by the lack of data from nationally representative population based studies, use methods consistent with those employed by the World Health Organization Child Health Epidemiology Reference Group.

We estimate that 11.37 million episodes of rotavirus gastroenteritis occur each year in India, requiring 3.27 million outpatient visits and 872,000 inpatient admissions when health access is unconstrained, resulting in a need for Rs. 10.37 billion each year in direct costs. An estimated 78,000 rotavirus-associated deaths occur annually of which 59,000 occur in the first 2 years of life. Introduction of a rotavirus vaccine of similar efficacy to the Rotavac in the national immunization program would result in 686,277 fewer outpatient visits, 291,756 fewer hospitalizations and 26,985 fewer deaths each year in India, assuming no indirect effects for the vaccine.

1. Introduction

With concerted effort toward the Millennium Development Goals (MDG) there are now 14,000 fewer child deaths each day across the world as compared to 1990 [1,2]. Improvements in oral rehydration solution (ORS) use and access to healthcare have contributed to impressive gains in diarrheal mortality [3]. Decline in pneumonia and diarrheal mortality have been instrumental in global decline of under five mortality from 88 to 56 per 1000 live births by contributing over 40% of this decline [4,5]. Notwithstanding the gains achieved in the past decade, over 700,000 children die each year of preventable diarrheal diseases in the developing world [2]. Developing countries such as India, where much of the gains in mortality reduction of the past decade have accrued, lack direct estimates of the extent, distribution and determinants of this decline resulting in uncertainty regarding disease specific estimates required for prioritizing public health strategies.

Acute gastroenteritis remains a leading cause of post-neonatal under-five mortality in India contributing about 13% of under-five mortality [5,6]. Rotavirus is the most important cause for severe gastroenteritis in this age group [2,7,8]. Studies in the last decade estimate the annual mortality due to rotavirus in India to be between 90,000 and 153,000 [4,9,10]. Debates on the public health utility of rotavirus specific interventions are, in part, fueled by the heterogeneity of mortality estimates and lack of data on the extent of morbidity associated with the disease. Morbidity, an important component of overall disease burden in developing countries, is under-recognized especially in high mortality settings where morbidity data is not readily available. Even where morbidity data is available, they underestimate true healthcare need, as socio-economic conditions, out of pocket spending and limited health infrastructure are overwhelming determinants of health access [11]. In situations with the highest burden of disease, health information and laboratory systems are inadequately equipped to detect and record etiology specific information.

A newer, more affordable rotavirus vaccine developed through an innovative social partnership may soon be available. Availability of affordable, efficacious vaccines holds promise but challenges policy makers to assess critically the burden of disease and the

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anticipated impact in the local conditions. We review the mortality, morbidity and economic burden of rotavirus diarrhea in India in the context of improving child survival and health access, and present estimates of morbidity associated with rotavirus diarrhea from the follow up of five observational cohorts that were offered access to healthcare without fees. This, we believe, represents morbidity not confounded by financial and access to care-related issues and therefore a more accurate measurement of the underlying burden of disease.

2. Methods

2.1. Data sources

We combined data from the Indian Rotavirus Strain Surveillance Network (IRSSN), the Million Death Study (MDS) [13] and statistics compiled by the World Health Organization (WHO) and UNICEF with data from five community-based cohorts to arrive at conservative estimates of the burden of rotavirus diarrhea across the disease spectrum and the economic costs related to the disease.

The IRSSN is a geographically representative, hospital based diarrheal surveillance system that used standardized protocols for enrolment and diagnostic evaluation at eight sites across India during 2005–2009 [12]. This surveillance system sampled diarrheal hospitalization in the sentinel hospitals and provides the proportion of hospitalized diarrhea that was related to rotavirus.

The Million Death Study (MDS), being conducted between 1998 and 2014 by the Registrar General of India and collaborators to determine causes of death in India derives its data from a nationally representative sample of 14 million people in 2.4 million households within the Sample Registration System, a large, routine demographic survey performed by the Registrar General of India. All deaths in the surveyed families have a cause of death assigned according to the International Classification of Diseases Revision 10 and are characterized by age, gender and region [13].

Incidence of diarrhea, diarrheal outpatient visits and hospitalization was obtained from five community-based cohorts that were intensively followed up for enteric diseases till at least two years of age. Three of these cohorts were in Vellore while the fourth was located in an urban slum in Delhi. Four of these cohorts also involved rotavirus testing of diarrheal samples, while a fifth cohort (also based in Vellore) had fortnightly follow-up and healthcare access data but not rotavirus testing of diarrheal samples. The details of the five cohorts are presented in Table 1. The overall rates of gastroenteritis, outpatient visits and hospitalizations due to rotavirus in the first two years of life were obtained as a weighted average from the cohorts. The 95% confidence intervals (95% CI) were calculated using the Byar's approximation of the exact interval for the Poisson distribution [17].

2.2. Rotavirus related diarrheal mortality

The <5 diarrheal mortality rate (defined as the number of diarrheal deaths in children under five per 1000 live births) was obtained by the product of <5 mortality rate of 61 per 1000 live births for India [18] and the proportion of all <5 deaths attributed to diarrhea in the Million Death Study (MDS) [10]

The rotavirus mortality rate was then estimated by applying to the <5 diarrheal mortality rate the proportion rotavirus positive in the IRSSN using methods and assumptions similar to those adopted by the WHO Child Health Epidemiology Reference Group (CHERG) [19,20]. The number of annual rotavirus deaths in India was determined by applying the rotavirus mortality rate to the 2011 birth cohort from UNICEF statistics. These numbers are compared with estimates published previously [9,10].

2.3. Rotavirus related diarrheal morbidity

The data from the five birth cohorts (Table 1) combined provide rotavirus hospitalization rates for children under-two years of age. Applying this rate to the entire under-five population would overestimate the burden, as the risk of rotavirus infection is greatest in the first two years. The proportion of diarrheal hospitalization in the IRSSN that was over three years of age was used as a correction factor to obtain a more conservative 3–5 year and a cumulative <5 year rotavirus hospitalization rate. The number of hospitalizations attributable to rotavirus was obtained by the product of the rotavirus hospitalization rate and the number of children in the 2011 Indian birth cohort.

The ratio of outpatient rotavirus gastroenteritis visits to rotavirus gastroenteritis admission in a phase III clinical trial population was 3.75. Applying this ratio to the number of hospitalized rotavirus gastroenteritis episodes we arrive at the number of rotavirus gastroenteritis outpatient visits. This ratio of ambulatory to hospitalized rotavirus was consistent with unpublished data from CHAD Hospital; a 120 bedded community hospital in Vellore that provides discounted care to a population of about 100,000 within its rural demographic surveillance system.

2.4. Potential impact of rotavirus vaccines

The vaccine efficacy (VE) of three doses of Rotavac®, an oral human-bovine natural reassortant vaccine obtained from a large multicenter phase III trial in India was extrapolated to the risk of rotavirus mortality, hospitalization and outpatient visits to determine the number of deaths, hospitalizations and outpatient visits potentially averted. Vaccine efficacy against severe rotavirus gastroenteritis, rotavirus hospitalization and all rotavirus gastroenteritis were used to calculate impact against rotavirus mortality, rotavirus hospitalization and rotavirus outpatient visits respectively. Risk (defined as the probability of event between 4 months and 5 years) is estimated by the expression cumulative risk = $(1 - \exp^{(-\sum \text{rate}^* \Delta t)})$, where 'rate' refers to event rate and 'Δt' the time interval. For estimating the absolute risk of rotavirus related events in the 4 month to 5 year period, we first estimated the event rate for the first two years of life as a weighted average from the cohort and applied this to the four months to two year period to obtain risk estimates for the corresponding period. We then obtained the 3–5-year incidence rate by applying to the 0–2 year incidence rate the relative proportion of cases that were 3–5 year old in the IRSSN study. Cumulating the incidence risk in the 4 months to 2 years with that in the 3–5 years provided the 4 months to 5 years risk of rotavirus related events. The number needed to vaccinate (NNV), under assumptions of no indirect effect, is provided by the inverse of the product of vaccine efficacy and absolute risk in the unvaccinated. We assumed national immunization coverage to be 74% and no herd protection while projecting the events averted.

2.5. Healthcare costs due to rotavirus infection

The data for estimation of healthcare costs of rotavirus disease was obtained from two published studies [21,22], conducted in 2006 and 2009 respectively, that used the WHO generic protocol [23] to estimate the economic burden of diarrhea including direct medical and non-medical (e.g., travel costs to and from the hospital) costs through review of patient charts, healthcare facility records, pharmacy records, and patient family interviews.

Healthcare costs, both hospitalizations and outpatient visits, were divided into three levels – primary, secondary, and tertiary. Secondary and tertiary level outpatient visits were further divided