

WORLD HEALTH ORGANIZATION

External Review of Burden of Disease Attributable to Rotavirus

30 November to 1 December 2005

**World Health Organization
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1. Introduction

Credible estimates of the national, regional, and global burden attributable to rotavirus infection are needed to understand its absolute and relative public health importance as well as the potential impact of controlling rotavirus disease through public health interventions such as vaccination. Estimates of the number of episodes, their relative severity and the mortality associated with rotavirus infection are important factors in estimating the social and economic cost of the virus and serve as a central component in the analysis of the costs and benefits of different interventions. Estimates contribute to strong advocacy for national and international investment in rotavirus control. And finally, in conjunction with other data, they support analysis on the impact of vaccination.

Ideally, the mortality and morbidity attributable to rotavirus infection would be measured using reliable surveillance and vital registration systems with the ability to confirm rotavirus infection by biological markers. Given, however, that such systems are either nonexistent or do not currently provide reliable and timely information in most countries, rotavirus burden has been estimated using models incorporating data from several sources using different methods in a variety of locations and years. Since the burden of rotavirus has been estimated rather than measured directly it is important that the uncertainty in the estimates be ascertained and described.

WHO has established standards and a process to be followed when making estimates of disease burden; an independent review of the methods and the estimates is one important part of this "good practice". An independent panel of experts, WHO resource persons and secretariat, partners from the industry and international agencies, and the group of investigators that developed and applied the model to estimate the rotavirus disease burden met in Geneva on 30 November and 1 December 2005 to review the proposed model and the model-based estimates of rotavirus disease burden. The proceedings of this meeting and the recommendations of the panel are summarised in this report

2. Objectives of the review

- 2.1 To assess the need for rotavirus disease burden estimates as well as the essential and desirable characteristics of the estimates.
- 2.2 To assess the robustness of the assumptions underlying the proposed model to estimate the rotavirus disease burden.
- 2.3 To assess the validity and generalisability of the model parameter values.
- 2.4 To suggest appropriate methods for estimating uncertainty in the estimates of rotavirus mortality burden.
- 2.5 To suggest further methodological work needed to improve the robustness of rotavirus disease burden estimates.

3. Conclusions and recommendations

3.1.1 Need for rotavirus disease burden estimates The panel agreed that rotavirus disease burden estimates are needed: (1) To facilitate evidence-based country decision making on rotavirus vaccine introduction; (2) To prepare an investment case for the introduction of available rotavirus vaccines; (3) To prioritize resource allocation; (4) To monitor and evaluate vaccination impact; (5) To forecast demand for vaccine and to plan vaccine production/distribution; (6) To design appropriate trials (e.g. estimates of endpoints); (7) to help international partners in planning, monitoring and evaluation of rotavirus disease control.

3.1.2 Characteristics of the estimates needed

Because estimates of rotavirus burden should meet programmatic needs as well as be robust and scientifically sound it is necessary to make the best use of available data despite the fact that they are often incomplete and/or imperfect. The panel reached the following conclusions on the characteristics of the estimates:

- (a) The number of rotavirus deaths in children less than 5 years of age is the most essential estimate particularly in countries/regions with high under five mortality rates. It would be desirable to further disaggregate rotavirus mortality deaths by 0-2, 3-11, 12-23, and 24-59 month age groups, if sufficient data are available for such disaggregation. This disaggregation would be helpful in deciding on appropriate vaccination schedules and monitoring the effect of vaccination on the transmission dynamics.
- (b) The rotavirus deaths should be disaggregated by country to be most useful to Member States and to facilitate reaggregation by various regional groupings (e.g. WHO, UNICEF, Millennium Development Goals and World Bank regional groups).
- (c) Although rotavirus morbidity estimates are desirable, the existing data were considered too sparse and inconclusive to support the available method of case estimation. Only three studies in developing countries estimate the burden due to rotavirus of all of the following: hospitalisation, outpatient care and home care^{1 2 3}. As health care seeking behaviour varies significantly between sites,

¹ Ferreccio C, Prado V, Ojeda A, Cayyazon M, Abrego , Guers L, et al. Epidemiologic patterns of acute diarrhea and endemic Shigella infection in children in a poor periurban setting in Santiago, Chile. Am J Epidemiol 1991; 134:614-27.

the panel was reluctant to base global mortality estimates on such limited data. Because rotavirus mortality reduction alone may not justify the costs of vaccination in middle and high income countries, however, the panel recognized the need for morbidity estimates in these countries. Decisions for incorporating the vaccine into national immunization programs in these countries will be dependent, in large part, on the morbidity burden. Data on morbidity can be used for advocacy, planning, economic evaluation, and monitoring purposes. Methods of morbidity estimation and costing should be developed by WHO to meet the needs of these countries.

3.2. Robustness of the model assumptions

3.2.1. Proportion of diarrhoea deaths attributable to rotavirus

The following model is proposed to assess the rotavirus mortality burden in <5 year old children:

$$\text{rotadeaths} < 5 \text{ years} = (\text{totaldeaths} < 5 \text{ years})(\text{proportiondiarrhoea})(\text{proportionrota})$$

As no data are available on proportion of diarrhoea deaths attributable to rotavirus, the model proposed uses the proportion of hospitalized diarrhoea cases attributable to rotavirus as a proxy for the proportion of diarrhoea deaths attributable to rotavirus.

3.2.2. Proportion of deaths attributable to diarrhoea

The proportion of deaths attributable to diarrhoea are derived primarily based on verbal autopsy methods. Verbal autopsy is an indirect method of deriving causes of death from information on symptoms, signs and circumstances that led to death, and is prone to misclassification error. The verbal autopsy method tends to be more sensitive to diseases that have easily recognisable and distinctive symptoms, and may over or under-estimate diarrhoea deaths depending on the prevalence of other conditions.

3.2.3. Proportion of diarrhoea deaths attributable to rotavirus

Using the proportion of hospitalized diarrhoea cases in which rotavirus was detected as a proxy for the proportion of rotavirus deaths in all diarrhoea deaths is based on the following assumptions that: (1) in the absence of treatment the hospitalised severe diarrhoea cases would not have survived; (2) the treatment effect on survival of severe diarrhoea is equal for rotavirus diarrhoea and non rotavirus diarrhoea; (3) the rotavirus attributable fraction of severe diarrhoea observed in sentinel hospitals are generalisable to the general population within each stratum of countries. Several panel members questioned the validity of these assumptions. Since treatment practices

² Jiraphongsa C, Bresee J, Pongsuwanna Y, Klubwang P, Poonawagul U, Arporntip P, et al. Epidemiology and burden of rotavirus diarrhea in Thailand: results of sentinel surveillance. *JID*; 2005;192 (Suppl 1). S87

³ Fang ZY, Zhang LJ, Tang JY, Zhang Q, Hu HK, Xie HP, et al. Rotavirus Diarrhea Among Children in Lulong County, Hebei Province, China, 1999-2003. *Chinese Journal of Virology*. 2005; 21(1):21-26. (Chinese)

and effectiveness may vary within counties (rural/urban variation) the proportion of severe diarrhoea attributable to rotavirus derived from tertiary/specialist units may not be generalisable to entire countries and /or regions. However, the panel recognised the fact that there are no reliable data on the direct measurement of the proportion of diarrhoea deaths that are attributable to rotavirus. Therefore, the panel supported use of available data on the rotavirus attributable fraction of severe diarrhoea (i.e., hospitalized diarrhoea) as a proxy for the rotavirus attributable fraction of diarrhoea deaths.

Studies done since 1990 showed an increasing trend in the proportion of severe diarrhoea attributable to rotavirus compared to earlier studies. The median proportion of severe diarrhoea attributable to rotavirus derived from studies since 1990 was 30%. If the study period is restricted to 1995 onwards the median proportion of severe diarrhoea attributable to rotavirus increased to 33%. The panel agreed to include studies since 1990 for the following reasons: (1) to maximize power (75 studies if 1990 is the start year compared to 54 studies if 1995 is the start year) and thereby minimize the size of the uncertainty bounds around the point estimate; (2) the difference in the point estimate between the two starting points is very small (30 vs 33%).

The potential sources of bias that would under or overestimate the rotavirus mortality burden are shown in Figure 1. The following factors would underestimate the fraction of severe diarrhoea attributable to rotavirus in sentinel surveillance sites: (1). Use of rectal swabs. Rectal swab samples decrease the sensitivity for detecting rotavirus by up to 50%; (2). PAGE and latex assays to detect rotavirus. Such assays can be less sensitive than EIAs (3). Delayed collection of faecal specimens; (4) Misclassification of mild diarrhoea as severe diarrhoea (typically lower proportions of rotavirus are detected among children with mild diarrhoea); (5). Age misclassification of cases (collection from children older than 5 years who have lower rates of rotavirus infection due to acquired immunity); and (6). Data collection restricted to low rotavirus transmission season.

The following factors would overestimate the fraction of diarrhoea attributable to rotavirus: (1) Mixed infections where rotavirus is coincidental and is not contributing to the illness (2). Data collection restricted to rotavirus transmission season (winter months).

3.2.4 Grouping of countries

For estimating cause-specific mortality, WHO groups countries into five strata (A, B, C, D and E) based on levels of <5 years of age and adult mortality. The estimates of diarrhoea mortality per stratum are adjusted for inter-country variability in cause-specific mortality due to factors such prevalence of HIV and malaria. The panel considered the option of estimating rotavirus mortality for India (stratum D) and China (stratum B) separately since they have very large populations, but then recommended keeping them in their respective stratum for the following reasons: (1) the median proportion of severe diarrhoea cases attributable to rotavirus derived from studies conducted in India and China were not significantly different from their

respective stratum-specific rotavirus attributable fraction of severe diarrhoea; (2) Removing the studies from India and China from their respective strata will reduce the sample size and increase the uncertainty bounds of the stratum-specific estimates. Since the variation in the diarrhoea mortality and the proportion of severe diarrhoea attributable to rotavirus was not significantly different between stratum B and C, and D and E, the panel suggested the number of strata should be reduced from 5 to 3 (strata A, B+C and D+E). The panel discussed the limitations of generalising results of hospital-based studies done in Asia to Africa. As there are substantial differences in population characteristics (population density, socio-economic factors, access and health care utilisation, etc) and it is theoretically possible that the virus strain characteristics and the host-agent interaction could differ between Asia and Africa, the panel agreed to subdivide the stratum D+E into Asia D+E and Africa D+E for estimating national, regional and global estimates of rotavirus mortality burden.

3.4 Uncertainty bounds

Using the inter-quartile range (IQR) may not be the best way to estimate uncertainty around the median; IQRs are not based on a sensitive measure of variance and are difficult to interpret. The panel discussed two alternative options (1) excluding outliers and re-calculating a mean and standard error and (2) random effects meta-analysis model for estimating the central value and Monte Carlo estimation for propagating uncertainty around the central value. The panel did not agree to exclude outliers because these studies may be of good quality and provide meaningful results. Although it was difficult to judge the quality of studies, there was general agreement to make use of data available from the existing studies judged to be of good quality. Furthermore the random effects meta-analysis model is used for estimating burden of other common causes of childhood diseases e.g., pneumonia. Thus the panel opted to use a random effects meta-analysis model for estimating the central value and Monte Carlo methods for estimating the uncertainty bounds.

3.5 Further work to improve the robustness of rotavirus disease burden estimates

- 3.5.1 **Frequency of updating rotavirus mortality estimates:** WHO/EIP will produce estimates of diarrhoea mortality every 2 to 3 years. The panel suggested synchronizing the update of rotavirus disease burden with updates in diarrhoea mortality estimates. However if more reliable data on the key model parameter i.e. the proportion of diarrhoea deaths attributable to rotavirus become available, a more frequent update of the rotavirus mortality burden should be considered.
- 3.5.2 **Target year data points for trend analysis:** Since there is no national rotavirus vaccination programme in existence as of 2005 (with the exception of the short-lived Rotashield[®] experience in the US), vaccination can not play any role in influencing rotavirus mortality prior to 2005. Hence the panel recommended the most recent year (2004) for which EIP has produced diarrhoea mortality as the pre-vaccination baseline mortality levels. The rotavirus estimates can be

updated based on programmatic needs when vaccination becomes more widespread and/or more reliable data on model parameters become available.

- 3.5.3 **Updating model parameter values:** The panel recommended active solicitation of data from ongoing and recently completed studies. It was suggested to search local language literature for additional published data and to consider assessing the quality of unpublished data for their possible use for updating model parameters values.
- 3.5.4 **Age-specific rotavirus mortality estimates:** Most demographic surveillance and sample registration systems that monitor diarrhoea mortality also allow for age disaggregation by month. Attempts should be made to collect rotavirus surveillance data by monthly age groupings to allow for rotavirus mortality estimates by 0-2 month, 3-11 month, 12-23 month, 24-59 month age groupings.
- 3.5.5 **Proportion of child mortality attributable to rotavirus:** Using the fraction of severe diarrhoea attributable to rotavirus as a proxy for mortality attributable to rotavirus has several limitations. The panel recommended the following exploratory analyses to better understand (and possibly overcome) the potential limitations: (1) Disaggregate diarrhoea deaths into acute diarrhoea, chronic persistent diarrhoea and dysentery; then assess the proportion of severe acute diarrhoea cases attributable to rotavirus from the hospital-based surveillance systems. This would refine the model inputs by restricting the proportion of deaths due to acute diarrhoea and proportion of acute diarrhoea attributable to rotavirus. (2) Estimate the proportion of diarrhoea mortality and proportion of severe diarrhoea attributable to rotavirus in urban and rural settings separately. (3) Use the data from vaccine probe studies as they become available to estimate directly the proportion of deaths attributable to rotavirus. (3) Assess rotavirus endpoints using serology and autopsies in addition to faecal assays. (4)
- 3.5.6 **Rotavirus mortality:** Estimating the number of deaths attributable to rotavirus using age-specific rotavirus mortality rates may be a more robust method of estimating rotavirus mortality. The panel recommended an increased emphasis on surveillance sites with known catchment populations to generate more data on rates of rotavirus mortality and morbidity
- 3.5.7 **Estimating rotavirus morbidity, economic and social burden:** Develop a generic protocol for measuring rotavirus morbidity, economic and social burden and to assess cost-effectiveness of national rotavirus vaccine programmes.
- 3.5.8 **Assessing quality of studies:** Develop objective and measurable criteria for evaluating quality of studies used for estimating the proportion of severe diarrhoea cases attributable to rotavirus.

3.5.9 **Impact of co-infections on rotavirus mortality estimates:** Conduct sensitivity analysis to assess impact of co-infection on rotavirus mortality estimates.

3.5.10 **Monitoring and evaluating the impact of national rotavirus vaccine programmes:**

The impact of vaccine programmes on mortality attributable to rotavirus will be difficult to measure. In poor countries with relatively high rotavirus mortality the vital registration systems are incomplete and inaccurate and the verbal autopsy method to assess cause of death cannot reliably determine deaths attributable to rotavirus. In low mortality countries, very large sample sizes and complete vital registration systems are needed. In addition to measurement difficulties, the relationship between vaccination coverage levels and mortality reduction may be blurred for several reasons. Vaccination may not be targeted to the populations most at risk of mortality. For example, high levels of coverage achieved in populations served by the private sector where the risk of mortality is low may not lead to high levels of mortality reduction. Alternatively, attributing diarrhoea mortality reductions to vaccination will be difficult in the presence of other diarrhoea control programs such as improved case management, hand-washing, improved water and sanitation etc. Considering these complexities, the panel suggested the following methods/approaches to monitor the impact of vaccine.

- (a) A case-control study design is a feasible and appropriate method to estimate effectiveness of the vaccine during the early periods of vaccine introduction.
- (b) If the vaccine is introduced in countries with good vital registration systems the impact of vaccine on mortality should be monitored over time.
- (c) In countries with good data on hospitalizations for diarrhoea the impact the vaccine has on the incidence of severe diarrhoea could be monitored
- (d) Stratify the population by income level as a proxy for diarrhoea mortality risk and monitor the immunization coverage levels and mortality by strata.

3.5.11 **Research issues:**

(a) Surveillance: Introduction of national level rotavirus vaccination may alter the epidemiology of the disease including selection of strains either not included in the vaccine or against which the vaccine may be less effective; rotavirus strain surveillance may therefore be an additional way of monitoring the impact of rotavirus vaccination. The panel recommended strengthening the existing surveillance networks to include rotavirus, and the establishment of additional sites to characterise rotavirus strains and monitor strain variations over time.

(b) Modelling: Introduction of vaccines would change the rotavirus infection dynamics. The panel recommended the development and testing of rotavirus

infection dynamic models using time series data available from surveillance sites.

(c) Interaction between rotavirus infection and nutritional status: Poor nutrition could be a risk factor for severe rotavirus infection, and rotavirus diarrhoea could lead to malnutrition. The panel recommended studies to examine the interaction between nutritional status and rotavirus disease.

(d) Vaccine dose schedule: Maternal antibodies give protection against rotavirus disease from 0-2 months of age, but also tend to negatively affect the immunogenicity of vaccine in this age group. Nevertheless, vaccination coverage levels would probably be higher if a dose of rotavirus vaccine could be offered during the first contact for EPI vaccines. Thus the protective efficacy of rotavirus vaccine given to neonates and/or at 6-8 weeks of age needs to be further evaluated.

4. Background presentations and documents:

4.1. Context and objectives of the review:

M.Birmingham (WHO)

Dr Birmingham explained the objectives and the expected outcomes of the review meeting (see annex 1). She highlighted the following issues: Rotavirus disease burden is unacceptably high particularly in the developing world and reducing this burden is a public health priority. Evaluating the estimates of rotavirus disease burden is of particular relevance at this point in time because of the new vaccines that are becoming available to combat it. Having estimates that are robust and independently reviewed will help advance public health interventions to reduce the burden of rotavirus. WHO has established standards of good practice in estimating disease burden; this independent review is one important part of this "good practice". The technical working group from CDC, CHERG, and WHO (CAH, MHI, IVB) has developed a model and has assembled all available data on model parameters for estimating the disease burden. She believes that the independent expert panel which will be making the recommendations, resource people/observers (including critical partners from Path, CDC, industry) and the WHO secretariat provides the best mix of expertise and experience in the world to grapple with these estimates - in terms of epidemiology, programmatic activities, quantitative methods, and general issues of mortality estimation in developing countries. By the end of the meeting, the expert panel will need to make a collective judgement on the acceptability of the estimates. She highlighted the challenge in bringing together science, imperfect information and programmatic needs in making this collective judgment.

4.2. Perspectives on characteristics of burden estimates by partners
M.Goveia/C.Mast (Merck, USA)

Merck has recently begun phase III trials for a rotavirus vaccine, enrolling 72 000 children. The vaccine is tolerated well, safe (not associated with intussusception), and has a 74% efficacy for illness caused by G1 - G4 strains and 98% efficacy against severe disease. Merck is working with the Programme for Appropriate Technology for Health to make sure the vaccine is available in the developing world and is planning trials in the developing world beginning next year. The vaccine has been approved by the Mexican regulatory authorities and has been submitted to the United States Food and Drug Authorities and the European Union Drug Regulatory Authority. Approval is expected by June 2006.

Rotavirus disease burden estimates help national authorities and programmes in deciding whether to introduce a vaccine, serve as a baseline for demonstrating impact, and facilitate trial design in other settings. They also help in identifying the appropriate end points for vaccine trials. Estimates also provide manufacturers with information for demand forecasting and help international partners arrive at a common stance for vaccine introduction. In addition to mortality estimates, estimates on hospitalization rates, outpatient care and low health care access (home care) are useful. Country-specific estimates of burden are important inputs in considerations for differential pricing.

4.3. Perspectives on characteristics of burden estimates by partners
R Beillik (Path, Europe for the Rota ADIP)

In 2003, PATH was awarded a grant by GAVI to undertake the Rotavirus Accelerated Development and Introduction Program (ADIP), with strategic partners CDC and WHO. One of the primary tasks of the ADIP is to build a comprehensive evidence base to guide technical officers and political leaders through the process of country decision-making regarding the value of introducing rotavirus vaccine into the national infant immunization schedule. This evidence base may be roughly divided into the following sets of issues⁴:

- Policy issues:
 - Public health priority of rotavirus disease:
 - Disease burden
 - Economic burden
 - Vaccine cost-effectiveness
 - Vaccine quality, safety and efficacy
 - Vaccine cost, financing options, sustainability
- Operational issues:
 - Vaccine presentation, vial size, cold chain requirements
 - Guaranteed vaccine supply
 - Overall programme capacity to introduce a new vaccine.

It is clear that estimating the burden of rotavirus disease is a critical step in developing evidence for national consideration. For this reason, the Rotavirus ADIP has provided financial support to develop new rotavirus surveillance networks or

⁴ Adapted from publication WHO/IVB/05.18, figure 1

sustain those already in place in 2003. PATH is supporting rotavirus surveillance systems in 3 regions and has plans to expand in the eastern Mediterranean region, and in PAHO. PATH has planned to set up new surveillance systems in Africa and in Europe. Dr Beillik pointed out that ADIP funding for supporting surveillance systems will end in 2007 and the need to look for more resources to continue this important activity

The Rotavirus ADIP has also developed a web-based resource library of documents covering all the topics listed above, which countries will be encouraged to access free-of-charge to compile the information that policy-makers will eventually call upon. (www.rotavirusvaccine.com). Furthermore, the Rotavirus ADIP has developed an Advanced Immunization Management (AIM) module for electronic learning, from a CD-ROM or direct from the web, which presents all the topic areas listed above in an interactive training format, with exercises. Both components of the programme will be launched in Q2 2006.

4.4. Review of rotavirus epidemiology ***R Glass (United States Centers for Disease Control)***

The incubation period of rotavirus ranges from 18 to 36 hours. The infective dose is low (e.g. 10 virus particles may be sufficient). The duration of disease linked to enteric villous re-growth is usually one week. Among normal children with severe acute rotavirus diarrhoea, approximately 70% will have rotavirus antigen in their blood. This finding suggests that rotavirus disease can probably be diagnosed by a post-mortem blood test.

Dr Glass presented the data from one post-mortem case study which showed overwhelming replication of rotavirus in the gut and raised the question – what pathophysiological mechanism leads to death in rotavirus disease, dehydration or fulminant viral infection?

A study in Mexico showed that shedding of rotavirus was high only for the first infection (74%) and very low for the third (18%) and intermediate for the second infection (35%). Antibody responses were measured in about 70% of children after each infection. Protection against subsequent infections was greater among those whose first infection was symptomatic compared to those with asymptomatic first infections. These data also showed that humoral antibodies are indicative of an immune response, necessary for protection against infection in children.

Seasonality (high transmission during winter) is more marked in the temperate climates. Probably transmission via the faecal-oral route leads to year-round transmission, while respiratory droplet infection causes seasonal peaks. Mixed infections with rotavirus (more than one strain) is common in developing countries but rare in the US.

The following factors would under-estimate rotavirus burden in surveillance systems:

- Use of rectal swab (versus collection of fresh stool)
- Studies on mild diarrhoeal disease
- Enrollment of patients during the low season only,
- Low sensitivity assays (e.g. PAGE or latex assays).

- Certain case definitions (e.g. inclusion of bloody diarrhoea)

Vaccine probe studies are showing that the benefit of vaccine is greater than what would have been predicted based on measurement of rotavirus infections. This suggests that some of the diarrhoea episodes in which rotavirus was not detected were probably due to rotavirus and highlights potential insensitivity of rotavirus diagnostics

Adults working as day care attendants and travellers are at a higher risk of rotavirus infection. Among 7 rotavirus adult outbreaks known to Dr. Glass, all have been associated with G2. (Outbreaks associated with G1, G2, G4 and G9 rotavirus have been reported⁵).

Roger alluded to new reassortants which have been frequently isolated in some studies but are not clearly associated with outbreaks or disease in adults who are probably not immune to these new strains.

Serotype G2 is a unique strain and not similar to the G1, G3 or G4 strains. The GSK vaccine has showed a reduced vaccine efficacy against G2 strains, which may increase the risk of G2 outbreaks in those countries which use the GSK vaccine.

A study in Vietnam involving 7 hospitals in 4 cities showed that 56% of diarrhoea admissions were due to rotavirus. Recent data from the Asian network, showed the >50% of hospital admissions for diarrhoea were attributable to rotavirus.

In closing, Dr. Glass recommended the following:

- Additional studies on children dying with diarrhoea, to further characterize the cause of death.
- A reassessment of the potential sources of biases that affect rotavirus surveillance sensitivity (e.g. the use of rectal swabs rather than fresh stools, diagnostics tools, etc).
- Additional surveillance studies using the WHO generic protocol on rotavirus surveillance.
- Further epidemiologic assessment of the indirect effect of vaccine, the impact on disease burden of improved sanitation, the age patterns of severe disease, seasonality of rotavirus, and mixed infections.
- Vaccine probe studies to assess the preventable rotavirus disease burden.
- Studies which assess the impact of rotavirus vaccine on overall mortality. (e.g. Honduras, with nationwide introduction, would be able to measure impact on overall mortality).

4.5. Estimates of diarrhoea mortality

C Boschi-Pinto (WHO)

The purpose of Dr. Boschi-Pinto's presentation was to: (1) describe how WHO estimates causes of death among children under-five; (2) present the

⁵ Marshall, et.al., Rotavirus detection and characterization in outbreaks of gastroenteritis in age-care facilities. Journal of Clinical Virology. 28: 331-338, 2003

CHERG/WHO/UNICEF estimation methods, with especial focus on diarrhoea proportional mortality; (3) provide some background on how rotavirus estimation fits into this process.

It was highlighted that the starting point for cause-specific mortality distribution is the total number of deaths among children under age five - the mortality "envelope". The second step is the distribution of causes within this "envelope". These two steps assure that the sum of the number of deaths from each cause does not exceed the total expected number of deaths.

The presentation followed with the description of the general strategy and estimation methods used by the Child Health Epidemiology Reference Group (CHERG).

A more detailed explanation on the estimates of the proportional mortality due to diarrhoea described the two main methodological approaches from the CHERG: the single- and multi-cause models. For each model, the following was presented:

- literature review and inclusion criteria;
- input data for both the dependent and independent variables included in the models;
- data summary and description;
- methodological issues;
- the triangulation process of comparing all available estimates with respective input data and methods;
- final results;
- advantages; and
- limitations.

This presentation allowed the participants of the review panel to better understand the starting point of the rotavirus estimation and how it should also fit into the "envelope" of all deaths due to diarrhoea.

4.6. Global burden of rotavirus disease

C. Lanata (CHERG, Instituto de Investigación Nutricional)

The Child Health Epidemiology Reference Group (CHERG) is in the process of developing etiology-specific (including rotavirus) estimates of mortality and morbidity of childhood diarrhoea. Approximately 4500 studies published between 1990 and 2002 related to child diarrhoea, its mortality and morbidity, epidemiology, and burden were identified. Studies describing any type of diarrhoea (including dysentery) were included if they met the following conditions: (1) the duration of study was at least one full calendar year or multiples of full years, (2) had at least one contact per week, and (3) had stool examination. Studies describing outbreaks, studies in special populations (nursing homes, day care centers, AIDS patients, nosocomial infections, etc) or with inadequate methods descriptions were excluded. The analysis below is based on 239 articles describing 266 studies which included 61 community studies, 98 outpatient studies, and 107 inpatient studies.

The proportion of diarrhoeal morbidity and mortality for children 0-4 years of age was estimated for 11 etiological agents: salmonella, shigella sp., campylobacter, vibrio cholera, ETEC, EPEC, giardia, cryptosporidium, entamoeba, and rotavirus. Estimates for co-infections and unknown agents were also made.

Study setting	% rotovirus	% co-infection	% unknown
Community	8.0%	10.8%	25.4%
Outpatient	18.0%	12.0%	23.0%
Inpatient	25.4	12.1%	15.1%

The etiological proportion of diarrhoea in inpatients was used as a proxy for the proportion of etiology-specific diarrhoea mortality proportions. This proportion (25.4%) was applied to the estimated global number of diarrhoea deaths (1.8 million) resulting in a global estimate of 457 000 rotavirus deaths in 2000.

4.7 Global and national estimate, 2003 ***U Parashar (US CDC)***

This presentation describes the work published in Global burden of rotavirus disease in children, Parashar U, Hummelman E, Bresee J, Miller M, Glass R, Emerging Infectious Diseases, 2003.

In 1985 the United States Institute of Medicine published an estimate of 873 000 annual deaths attributable to rotavirus infection; no update has been made in the last fifteen years. Previous work shows a decline in childhood diarrhoea mortality from an estimate of 4.6 million deaths in 1982 to a 1.3 million death estimate in the WHO World Health Report, 2000. This study reviewed the literature of causes of childhood deaths published between 1986-2000 for the proportion of deaths attributable to diarrhoea, supplemented with vital registration data where appropriate, and estimated the number of diarrhoea deaths by gross national product (GNP).

Income group	% childhood deaths to diarrhoea	IQR
Low	21%	17-30%
Lower middle	17%	11-23%
Upper middle	9%	5-17%
High	1%	NA

These proportions of deaths attributable to diarrhoea were applied to the country-specific estimates of total childhood deaths (UNICEF, State of the World's Children, 2001) for an estimated global total of 2 112 000 childhood deaths attributable to diarrhoea.

Seven hundred and fifty two studies, published between 1986 and 2000 were reviewed and laboratory based studies were excluded. The final analysis was conducted on 245 studies of inpatient diarrhoea cases having at least one full calendar year of data, at least 100 diarrhoea cases and a reliable rotavirus detection assay.

Income group	% childhood diarrhoea deaths	
	attributable to rotavirus	IQR
Low	19%	15-26%
Lower middle	25%	20-33%
Upper middle	31%	25-42%
High	31%	26-38%

These proportions of diarrhoea attributable to rotavirus were then applied to the country-specific estimates of under five diarrhoea deaths (above) for an estimated global total of 440 000 childhood deaths attributable to rotavirus.

This paper also estimated 1 395 000000 total episodes of diarrhoea of which approximately 150 000 000 were attributed to rotavirus.

4.8 Global estimates, update (U. Parashar, CDC)

This presentation describes the work published on the increasing role of rotavirus in the etiology of severe childhood diarrhea. Parashar U, Gibson C, Bresee J, Glass R,⁶

Recent data from the Asian rotavirus surveillance network suggest that 45% (range 29% - 60%) of severe diarrhoea leading to hospitalisation is attributable to rotavirus, significantly higher than the previous global estimate of 25%.

Studies of inpatient diarrhoea cases conducted from 1994 onward, published after 2000 having at least one full calendar year of data and at least 100 diarrhoea cases were reviewed and the median rotavirus detection rate by income group (gross national product) was compared with earlier studies.

Income group	Median rotavirus detection rate (%)	
	1986-1999	2000-2004
Low	20%	39%
Lower middle	25%	40%
Upper middle	31%	38%
High	34%	44%
Total	22%	39%

Applying the updated proportion of diarrhoea attributable to rotavirus (39%) to the previously published CHERG estimate of 1.56 million childhood diarrhoea deaths would result in an estimate of 608 000 childhood rotavirus deaths.

4.9. Process and characteristics of WHO estimates of rotavirus burden T Burton (WHO)

⁶ Parashar UD, Gibson CJ, Bresee JS, Glass RI. Rotavirus and severe childhood diarrhea. *Emerg Infect Dis* [serial on the Internet]. 2006 Feb [31 March 2006]. Available from <http://www.cdc.gov/ncidod/EID/vol12no02/05-0006.htm>

This review is the second step in the process followed by WHO's Department of Immunization, Vaccines and Biologicals in establishing estimates of Vaccine-Preventable Disease burden. The process is as follows:

- Establish a model and identify input data and model parameters, search the literature (including the grey literature, country reports, etc) for data to estimate model parameters, make parameter estimates (sometimes based on other models), use the model and input data to generate estimates, check the estimates for consistency and, if necessary, revise the model and parameter estimates.
- Subject the estimates to an external review. The review panel should consist of individuals of recognized experience representing their own views and not that of an agency or institution. The panel should include those knowledgeable in the natural history and epidemiology of the condition being estimated; those with local experience to provide an understanding of the geographic and social diversity of the condition, and finally those with experience in formal methods such as demography, statistics, and quantitative epidemiology to critique the process of quantification..
- Send estimates to national authorities for their comments and review. Note that we do not seek - although we appreciate - national approval. In many cases national authorities have relevant data or information not previously available which serves to improve the accuracy of the estimates. If necessary the estimates, model or parameters are modified based on results of the country review.
- Submit the estimates to WHO's Evidence and Information for Policy Cluster for their review. EIP has the mandate to review and approve quantitative claims of disease burden, risk factor distribution, and service delivery coverage and effectiveness made in the name of the World Health Organization. Upon approval by EIP the estimates become WHO estimates and may be disseminated and used as such.
- Disseminate the estimates through a variety of mechanisms such as WHO publications, the peer reviewed literature, WEB sites, and conferences.
- When necessary, update and improve the estimates. The estimates should be associated with a target year or period. In this instance the target year for the estimate is 2000. WHO has made estimates of diarrhoeal deaths for the year 2000. As of yet there is no intervention that causes rapid (within a year or so) changes in rotavirus mortality; therefore, these estimates should be reasonably accurate for 2-4 years or until rotavirus vaccine uptake is significant.

WHO/IVB prefers, to make country-specific estimates. Disaggregation of the estimates to the country level facilitates use of these data by countries and allows for internally consistent estimates for different country groupings - e.g., WHO regions, MDG regions, World Bank development status regions, etc.

As appropriate WHO/IVB also disaggregates estimates by important demographic, social, economic, or epidemiologically important characteristics. The most common disaggregations are by age and sex. The rotavirus estimates under review are only for children under age five, but other conditions may warrant further disaggregation.

When at all possible we attempt to develop and update time-series of estimates to analyze trends related to the epidemiology of the condition and the impact of interventions. For rotavirus estimates, such trends will be particularly important to assess the impact of rotavirus vaccination.

We attempt to incorporate quantitative estimates of the uncertainty in our estimates by providing a range for each of the components. The estimates presented incorporate such a range.

We strive to make the estimates, the methods, and the underlying data widely available so that others may extend our work and also improve the empirical and methodological foundations of the estimates. We intend to have these estimates - should they pass review - published, described in the peer reviewed literature, and the estimates themselves, the methods, and the underlying data available for public download on the WEB.

The process and characteristics are seen as part of a continuous process in providing reliable, accurate, valid and useful estimates of disease burden grounded in empirical data augmented with expertise, rigor, and robust methods.

4.10. Proposed WHO estimates of deaths and cases of rotavirus U. Parashar, CDC

The proposed WHO estimates of country-specific rotavirus deaths for the year 2000 is based on the assumption that the proportion of severe (inpatient) diarrhoea in which rotavirus can be detected is approximately equal to the proportion of all diarrhoea deaths attributable to rotavirus infection. Four modifications to the methods/inputs used by Parashar et al. were made.

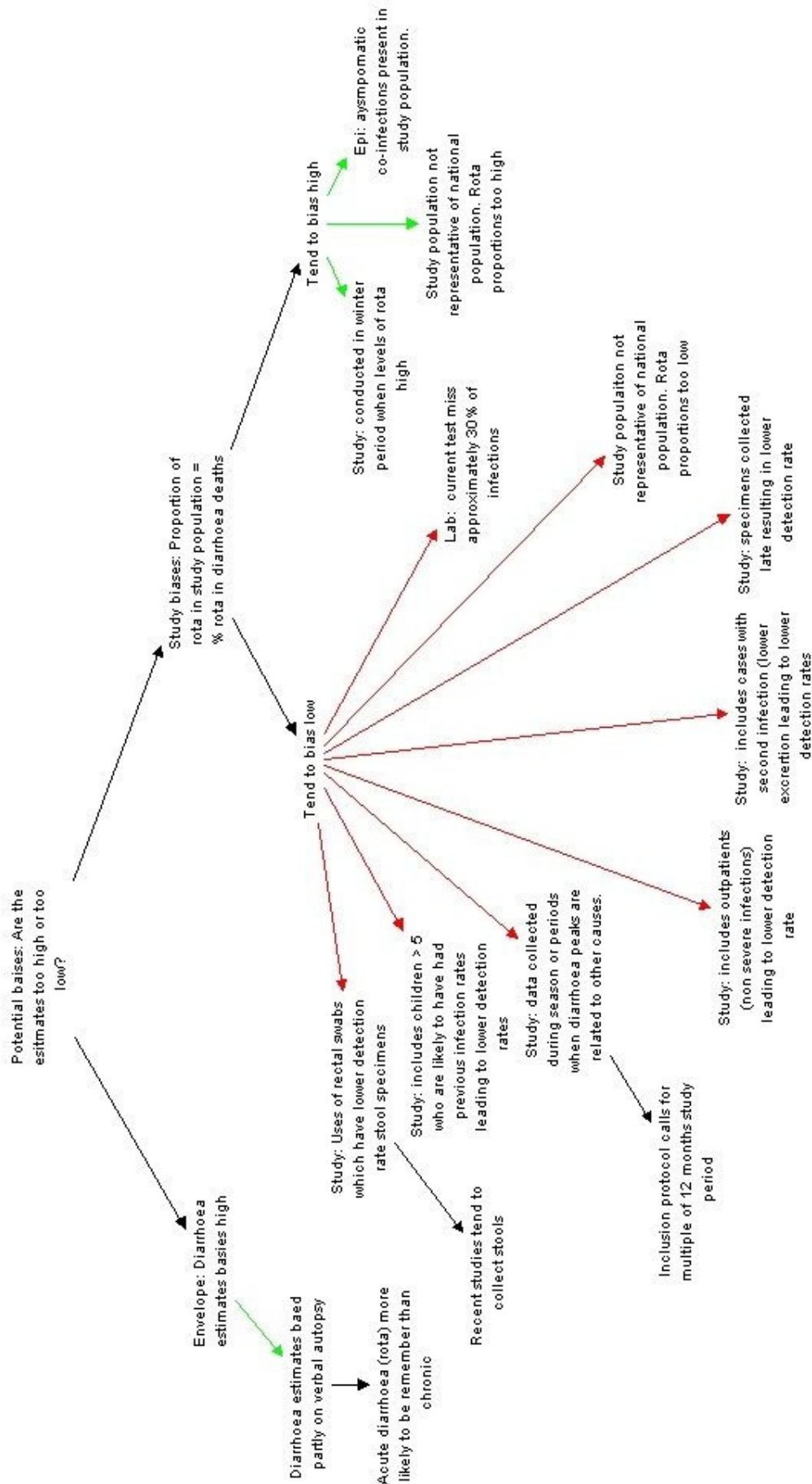
1. replace the country-specific estimates of total childhood deaths (UNICEF, State of the World's Children, 2001) with the WHO estimates of child diarrhoea deaths for the year 2000 (the diarrhoea "envelope").
2. use WHO child mortality strata to group countries instead of income (GNP)
3. change the inclusion criterion of studies from the year of publication to the mid-point of the study period (data collection)
4. include studies with the midpoint of study period from 1990 onward.

Analyses show that studies conducted from 2000 to 2004 had a higher rotavirus detection rate than those conducted from 1986 to 1999, suggesting an increasing temporal change in the proportion of severe diarrhoea (hospitalised) attributable to rotavirus. This relationship appears to hold across all mortality strata except mortality stratum E where the few studies show no change between 1980 and 2004. This analysis suggests that including studies from earlier periods may lead to an underestimate of the proportion of diarrhoea hospitalizations due to rotavirus and by extension, an underestimate of the proportion of diarrhoea deaths attributable to rotavirus.

The relationship between infant mortality rates and proportion of rotavirus detection among hospitalized cases with diarrhoea was reviewed with estimates based on more recent data again resulting in a higher estimate of rotavirus deaths. Estimates based on studies with a study period from 1990 onwards were compared with estimates based on studies from 1995 onward.

	1990 onward	1995 onward
Number of studies	75	41
% Rotavirus detection(weighted)	30%	33%
Rotavirus deaths	560 191	618 624

Application of the modified method and inputs (using inclusion criteria of studies with a study period of 1995 onward) results in a global estimate of 619 000 (inter-quartile range: 476 000 - 725 000) rotavirus deaths to children under five years of age for the year 2000.



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14:15 - 14:30 Clarification
14:30 - 14:45 Global estimates, update U Parashar
14:45 - 15:00 Discussion

15:00 - 15:30 Coffee

Session 5 - Proposed WHO estimates of rotavirus cases and deaths under age five

15:30 - 16:00 WHO estimates
Process and characteristics of WHO estimates
T.Burton
16:00 - 18:00 Proposed WHO estimates of deaths and cases of rotavirus
(methods, data, assumptions, and results)
Discussion

1 December 2005 (Morning Thursday)

Session 6 - Recommendations

9:00 - 10:00 Discussions

10:30 - 11:00 Coffee

11:00 - 12:00 drafting and presentation of the recommendations

Closure of the meeting