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Review

Rotavirus epidemiology: The Asian Rotavirus Surveillance Network[☆]E.A.S. Nelson^{a,*}, J.S. Bresee^b, U.D. Parashar^b, M.-A. Widdowson^b, R.I. Glass^c,the members of the Asian Rotavirus Surveillance Network^d^a Department of Paediatrics, The Chinese University of Hong Kong, Hong Kong SAR, China^b Centers for Disease Control and Prevention, Atlanta, GA, United States^c Fogarty International Center, National Institutes of Health, Bethesda, MD, United States^d Asian Rotavirus Surveillance Network Members—China: Zhao-Yin Fang, Bei Wang, Li-Jie Zhang, Li-Wei Sun, Zeng-Qing Du, Jing-Yu Tang, An-Cun Hou, Hui Shen, Xiao-Bo Song, Xuan-Yi Wang, Zhi-Yi Xu, Ying-Lin Zhang, Shou-Jun Zhao, Zhi-Yong Hao, Zhan-Chun Xing, Chang-Quan Han, Jing-Chen Ma, Ji-Chao Chen; Hong Kong, SAR: John S Tam, Paul.K.S. Chan, Ly-Mee Yu, Ying-Chu Ng, Kin-Hung Poon, Chi-Hang Ng, Kin-Sing Ip, Tai-Fai Fok; India: Rajiv Bahl, Pratima Ray, Swati Subodh, Prashant Shambharkar, Manju Saxena, M.K. Bhan, Gagandeep Kang, Shobhana D. Kelkar, Shoba D. Chitambar, Pratima Ray, Trailokyannath Naik. Indonesia: Yati Soenarto, Siswanto Agus Wilopo, Abu Tholib Aman, Mega, Rully, Bachryan Eljuta, Nenny Sri Mulyani; Japan: Toyoko Nakagomi, Osamu Nakagomi, Yoshihiro Takahashi, Masamichi Enoki, Takashi Suzuki; Korea: Jung S. Kim, Jung O. Kang, Soo C. Cho, Young T. Jang, Sae A. Min, Tae H. Park, Dae S. Jo, Paul E. Kilgore, Batmunkh Nyambat, Zhi Y. Xu, Lorenz von Seidlein, Oak Pil Han, John Clemens; Malaysia: Hasan bin Abdul Rahman, Swee Lan Wong, Lailanor H. J. Ibrahim, Ahmad Faudzi H. J. Yusoff, Lee Gaik Chan; Myanmar: Kyaw Moe, Win Mar Oo, Thandar Lwin, Tin Tin Htwe; Taiwan: Kow-Tong Chen, Po-Yen Chen, Ren-Bin Tang, Yung-Feng Huang, Ping-Ing Lee, Jyh-Yuan Yang, Hour-Young Chen; Thailand: Chuleeporn Jiraphongsa, Yaowapa Pongsuwanna, Pipat Kluabwang, Urai Poonawagul, Pramote Arpornitip, Manas Kanoksil, Nakorn Premisri, Utcharee Intusoma; Vietnam: Nguyen Van Man, Le Thi Luan, Dang Duc Trach, Nguyen Thi Hien Thanh, Phan Van Tu, Nguyen Thanh Long, Dang Duc Anh; United States: Erik Hummelman, Jon R. Gentsch, Thea K. Fischer, Vincent P. Hsu, Ashley R. Laird, Brittany Bielfelt, Dixie D. Griffin, Madhu Ramachandran, Vivek Jain, Baoming Jiang, Laura Jean Podewils, Lynn Antil, Richard Rheingans, T. Christopher Mast; World Health Organization and collaborating laboratories: Bernard Ivanoff, Duncan Steele, Carl D. Kirkwood, Krisztia Bañ nyai, Nigel A. Cunliffe

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ABSTRACT

Availability of new rotavirus vaccines has highlighted the need to collect local disease and economic burden data to aid decision makers at global, regional and country level. The World Health Organization and the GAVI Alliance recommended that generic protocols be used and that regional surveillance networks be established to collect these data, thereby helping to fast-track the introduction of these new vaccines into developing countries. Nine countries and regions participated in the first phase of the Asian Rotavirus Surveillance Network (ARSN), which collected data over a 2-year period during 2001–2003. Overall 45% of diarrhoea admissions in the region were positive for rotavirus, which was higher than had been anticipated. Significant rotavirus strain diversity was noted during the surveillance period. Data collection for a second phase of the ARSN commenced in 2004 and included a greater proportion of poorer countries that would in future be eligible for funding support for rotavirus immunization from GAVI. Limited economic evaluations in Asia have demonstrated the potential for new rotavirus vaccines to be cost-effective but more local analyses are required. Despite the ARSN's comprehensive data from a mix of developed and developing countries, Asia has lagged the Americas in terms of the introduction of rotavirus vaccines into National Immunization Programmes (NIPs). Lack of rotavirus vaccine efficacy data in Asia, particularly in poorer populations, will have contributed to this delay. Thus ensuring that all global regions are simultaneously involved in the evaluation of new vaccines from the beginning and also encouraging more regional collaborations of Ministry of Health representatives could help to accelerate the introduction of new vaccines into NIPs.

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Abbreviations: ARSN, Asian Rotavirus Surveillance Network; CDC, centers for disease control and prevention of the US; GAVI, GAVI Alliance; NIP, National Immunisation Programme; PATH, Program for Appropriate Health Technologies; US, United States of America; WHO, World Health Organization.

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1. Introduction

Rotashield[®], an oral tetravalent rotavirus vaccine, was first licensed by the United States of America's (US) Food and Drug Administration in 1998 and recommended by the Advisory Committee on Immunisation Practices for use in the routine immunisation schedule of all US infants at 2,4 and 6 months of age [1]. This development was greeted with much enthusiasm, as a number of international organisations including the World Health Organization (WHO), the Institutes of Medicine, the GAVI Alliance, and the Program for Appropriate Health Technologies (PATH) had identified rotavirus vaccine as a priority with the potential to significantly reduce child mortality and morbidity globally and helping reach the 2010 Millennium Development Goals. GAVI and others have increasingly highlighted the unacceptable long delays that have occurred between the licensing of a new vaccine in rich developed countries and the eventual introduction of the vaccine into poor developing countries. These delays in introduction are increasingly seen as morally indefensible, as the majority of disease burden and mortality preventable by these new vaccines are in poor developing countries.

2. Asian Rotavirus Surveillance Network (ARSN)

The Centers for Disease Control and Prevention of the US (CDC), WHO and industry partners convened a workshop in Bangkok in February 1999 to establish the ARSN. Invited participants included Ministry of Health officials and academics from a number of Asian countries who had published or participated in previous diarrhoeal disease burden studies in the region. The key message to participants was that, with a newly licensed rotavirus vaccine available, regional decision makers would first and foremost require updated rotavirus disease burden data to evaluate the vaccine's potential use in their locality. Although most doctors and policy makers recognise the importance of diarrhoeal diseases as a leading cause of mortality and morbidity, the majority do not appreciate the importance of rotavirus disease in clinical settings for a number of reasons. First, diarrhoea management guidelines have emphasised that the aetiology of the diarrhoeal disease usually does not alter the management, which should focus on treating and preventing dehydration [2]. Second, tests for rotavirus are costly and not routinely available. Lastly, many policy makers are wrongly of the opinion that all diarrhoeal disease can be prevented by improvements in hygiene and sanitation. Global estimates of rotavirus disease burden have emphasised that virtually all children in both developed and developing countries will be infected with rotavirus at a young age [3], which has helped highlight the fact that, in contrast to many other diarrhoeal diseases, rotavirus disease will not disappear with improving socio-economic conditions. To collect these disease burden data for policy makers, WHO and GAVI recommended that simple generic protocols be developed and that regional rotavirus surveillance networks be established. It was hoped that this method of data collection would speed up the process of introducing rotavirus vaccines into National Immunisation

Programmes (NIPs). GAVI has also provided funding to establish the Rotavirus Vaccine Program at PATH, which has been given the task to fast-tracking rotavirus vaccine development and introduction in developing countries [4]. The first regional network, the (ARSN), was established following the February 1999 workshop [5]. The ARSN workshop participants were provided with a draft generic surveillance protocol (subsequently published by WHO) to plan local surveillance in their countries and regions [6].

Less than 6 months after the 1st ARSN workshop, the routine administration of Rotashield[®] was suspended, and then the vaccine was withdrawn in the latter part of 1999 as a result of an association with intussusception [7–10]. This unexpected event was a major setback and there was initially uncertainty as to whether the ARSN surveillance activities would continue. However it subsequently became apparent that the withdrawal of Rotashield[®] had a number of positive effects, including renewed interest in developing other rotavirus vaccines (both by large pharmaceutical companies and a number of local producers in developing countries) and the recognition that that clinical trials for new rotavirus vaccines should be conducted simultaneously in both developed and developing countries [11]. Had Rotashield[®] been licensed in both developed and developing countries, it was possible that its use could have continued in developing countries where the risk-benefit ratio may have been assessed to be very different to that of the US. Although the initial estimate of the risk of intussusception due to the vaccine was 1 in 10,000, subsequent analyses suggested lower risk and risk was shown to rise with increasing age at vaccination [12,13]. A key question at that time was whether other rotavirus vaccine candidates would also be linked with intussusception. Reassuring was the fact that natural rotavirus infection did not appear to have a strong association with intussusception [14]. By early 2001, nine countries and regions (China, Hong Kong, Indonesia, Malaysia, Myanmar, South Korea, Taiwan, Thailand, and Vietnam) were collecting data for the ARSN using the framework of the WHO generic protocol. Three of these countries, China, Myanmar and Vietnam, were poorer "GAVI eligible" countries with <1000 US\$ Gross National Income per capita, whereas the remainder were richer middle and high income countries that would not be eligible to receive GAVI funding support for purchase of rotavirus vaccines.

3. Results of the ARSN surveillance activities

A 2nd ARSN was held in Bangkok in May 2002 to review the first year surveillance data. Results from eight of the nine participating regions and countries were subsequently published [5]. Participating centres had submitted monthly surveillance data to CDC for collation and for the period August 2001 to July 2002 there was information on 16,173 hospitalisations for diarrhoea from 33 participating centres. Seventy-one percent of the diarrhoea admissions had stool specimens tested for rotavirus and overall 45% of the tested specimens were shown to be positive. There was variation in the positive rate both within and between the participating countries and regions with the highest positive rate in Vietnam (59%) and the lowest in Hong Kong (28%) (Table 1). These data also demon-

Table 1
First year results from the ARSN [5]

| Site | No. of specimens tested | Rotavirus positive (%) | Range (%) |
|-----------|-------------------------|------------------------|-----------|
| China | 2,079 | 44 | 24–65 |
| Taiwan | 1,532 | 49 | 43–53 |
| Hong Kong | 2,986 | 28 | 18–35 |
| Vietnam | 1,570 | 59 | 47–67 |
| Myanmar | 388 | 53 | 53 |
| Thailand | 992 | 44 | 38–49 |
| Malaysia | 1,374 | 57 | 52–59 |
| Indonesia | 577 | 52 | 47–57 |
| Overall | 11,498 | 45 | 18–67 |

strated some differences in seasonality of rotavirus disease, with pronounced winter peaks in China, Hong Kong and Thailand, and relatively less seasonality in Malaysia and Indonesia. A 3rd Workshop of the ARSN was held in Hong Kong in March 2003 to look at economic issues related to rotavirus vaccines and a 4th Workshop in Manila, Philippines in October 2003. The latter event had two main objectives: first to review of the surveillance data for the full 2-year period of the first phase of the ARSN; and second to launch a second phase of the ARSN with a greater proportion of GAVI eligible countries. Surveillance activities for this second phase of the ARSN were largely supported by the Rotavirus Vaccine Program at PATH and conducted through partnership with CDC and WHO.

Results of disease and economic burden studies of the first phase of the ARSN, together with updates on various vaccine candidates in development were published as a journal supplement in the latter part of 2005 [15]. China reported data from six sentinel hospitals on 3149 diarrhoeal admissions with a rotavirus positive rate of 50% [16]. A separate outpatient study from rural China, showed that rotavirus was a leading cause of severe diarrhoea in children under 5 years with an estimated incidence of rotavirus infection of 151 cases/1000 children per year [17]. Hong Kong had the lowest rotavirus positive rate of 30% based on 7391 diarrhoea admissions [18]. Hong Kong's active rotavirus surveillance data were linked to passive computerised discharge surveillance data from all of the territory's government hospitals. This linkage showed the annual incidence of hospitalisation for rotavirus disease in the first 5 years of life was 8.8 per 1000 births (assuming that 90% of hospitalisations in Hong Kong are to government hospitals). This estimate was fourfold higher than a previous estimate based on the passive surveillance data alone. This equates to a cumulative risk of hospitalisation for rotavirus diarrhoea by age 5 years of 1 in 24—significantly higher than the global estimate of 1 in 50 [3]. South Korea reported data on 4106 children followed for a 2-year period [19]. Of the 94 children admitted to hospital during this period that had a stool specimen tested, 73% were positive for rotavirus, as were 18% of those with stool specimens tested from outpatient settings. The annual incidence of hospitalisation for rotavirus in the first 5 years of life was calculated as 11.6 per 1000. Malaysia reported Ministry of Health data on over 14,000 gastroenteritis admissions and showed that 50% were positive for rotavirus—equating to a cumulative risk of hospitalisation for rotavirus by age 5 years of 1 in 61 [20]. Myanmar, one of the GAVI eligible countries, reported that 18% of admissions ($n=1736$) to their single surveillance site were due to gastroenteritis and that 53% of the latter were due to rotavirus [21]. Taiwan reported data on 2600 diarrhoea admissions of which 43% were positive for rotavirus, 11% positive for a bacterial pathogen and 2.5% positive for adenovirus [22]. Dual infection with rotavirus and another pathogen was noted in 3.9%. Thailand noted that 43% of the 4057 diarrhoea admissions enrolled in their surveillance study were rotavirus positive [23]. A separate community study in Thailand noted that 12% of the diarrhoea cases of any severity assessed were

Table 2

Rotavirus strain surveillance from the 1st phase of the ARSN conducted during the 2-year period April 2001 to March 2003 showing the overall percentage of G serotypes identified

| Site | <i>n</i> | G1 (%) | G2 (%) | G3 (%) | G4 (%) | G9 (%) | M/O/U (%) |
|----------------|----------|--------|--------|--------|--------|--------|-----------|
| China [16] | 470 | 14 | 5 | 67 | <1 | 5 | 10 |
| Hong Kong [38] | 300 | 49 | 15 | 23 | 4 | 5 | 5 |
| Korea [39] | 203 | 25 | 13 | 19 | 2 | 39 | 2 |
| Taiwan [22] | 300 | 31 | 10 | 9 | 4 | 37 | 9 |
| Thailand [23] | 838 | 1 | 17 | <1 | 5 | 55 | 22 |
| Vietnam [24] | 499 | 47 | 15 | – | 10 | 22 | 6 |

M/O/U: mixed, other, untypeable.

due to rotavirus. Vietnam had the highest overall rate of rotavirus positivity (55%) in the 5809 diarrhoea admissions assessed [24]. A small study of 443 diarrhoea admissions from 3 sentinel hospitals in Japan showed that 58% were rotavirus positive, equating to an incidence of hospitalisation for rotavirus under 5 years of age of 15 per 1000, and a cumulative risk of hospitalisation for rotavirus by 5 years of 1 in 15 [25]. The key finding from this first phase of the ARSN data was that the rates of rotavirus positive diarrhoea were much higher than had been anticipated [15]. The peak age of onset of rotavirus diarrhoea was shown to vary significantly, with the higher income countries having a later age of onset than the poorer developing countries [15]. These data from ARSN contributed to the update of previous estimates of global rotavirus disease burden [26], with the revised estimates of annual morbidity and mortality being 114 million rotavirus infections, 24 million outpatient visits, 2.4 million hospital admissions and 610,000 deaths [3]. Some participating countries and regions also conducted rotavirus strain surveillance, showing differences in predominant strains during the surveillance period, i.e. G1 (Hong Kong, Vietnam), G3 (China) and G9 (Korea, Taiwan, Thailand) (Table 2). There are currently 42 strains of rotavirus with different P-G combinations and monitoring serotype diversity will be of particular importance now that new rotavirus vaccines have been licensed and are being introduced into NIPs [27].

The second phase of the ARSN includes 14 countries (with 37 centres): *Bangladesh* (2), *Cambodia* (1), *Kyrgyzstan* (2), *Laos PDR* (1), *Mongolia* (2), *Nepal* (1), *Pakistan* (2), *Philippines* (7), *Sri Lanka* (1), *Uzbekistan* (2), *China* (8), *Indonesia* (5), *Myanmar* (1), *Thailand* (2) (GAVI-eligible countries in italics). Preliminary data from these countries, presented at the 5th ARSN meeting in July 2006, showed rates of diarrhoea admissions positive for rotavirus were similar to those rates seen in countries participating in the first phase of the ARSN.

4. Economic burden and economic evaluation

Economic analyses are important to determine the cost of rotavirus diarrhoea to the country and the cost-effectiveness of universal rotavirus vaccination programmes, essential components to inform decision makers on introduction. The economic burden of rotavirus disease was reported for Hong Kong [28]. A sub-sample of 471 diarrhoea admissions participating in the main disease burden surveillance study were enrolled in a study to estimate all costs associated with the child's admission. The Hong Kong government hospital system is highly subsidised to families who are responsible for only a modest fixed fee for each day their child is an inpatient. Information was collected on the costs of hospitalisation from both the government and the family perspectives and in addition family out of pocket expenses and indirect costs were estimated. The total social cost of rotavirus disease in Hong Kong was estimated to be US\$ 4.3 M, of which the vast majority (US\$ 4 M) was direct medical costs. The cost to government for each rotavirus diarrhoea admis-

Table 3
Countries recommending rotavirus vaccine in their NIPs (as of May 2007)

| Country | Date of recommendation | Birth cohort (millions) |
|-------------------------|------------------------|-------------------------|
| United States | February 2006 | 4 |
| Panama | March 2006 | 0.07 |
| Brazil | March 2006 | 3.3 |
| Venezuela | April 2006 | 0.57 |
| Mexico | June 2006 | Phased introduction |
| Nicaragua | October 2006 | 0.15 |
| El Salvador | October 2006 | 0.17 |
| Australia ^a | May 2007 | 0.25 |
| Austria ^b | before April 2007 | |
| Belgium ^b | before April 2007 | |
| Luxembourg ^b | before April 2007 | |

Source: M.J Lewis, L Oliveira, Pan American Health Organization, presentation at World Health Organization, Initiative for Vaccine Research, Global Vaccine Research Forum, Bangkok Thailand, December 2006.

^a <http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/rotavirus-provider>.

^b <http://www.eurosurveillance.org/ViewArticle.aspx?PublicationType=W&Volume=12&Issue=17&OrderNumber=1>

sion was US\$ 1868 and the cost to the family was US\$ 120. Indirect costs appeared to be surprisingly small in contrast to reports from the US [29]. This was presumably due to fact that parents take little time off work during their child's illness as a result of readily available domestic help and well-established extended family networks. Data from Japan suggested that the direct medical cost a rotavirus admission was US\$ 1236, which was extrapolated to an estimated US\$ 96 M for the whole of Japan [25]. Based on the data from the 1st phase of the ARSN, projections were made about the potential cost-effectiveness of rotavirus vaccines for Asia [30]. Assuming all children in Asia could be immunised with a rotavirus vaccine, it was estimated that for a birth cohort followed for 5 years, it would be possible to avert 109,000 of 171,000 deaths, 1.4 M of 1.9 M hospitalisations and 7.7 M of 13.5 M outpatient visits. Universal immunisation in Asia could avoid US\$ 191 M of direct medical costs, but whether rotavirus vaccination would be cost-effective would depend particularly on the vaccine price and the income level of each country.

5. Prospects for early introduction of rotavirus vaccines into National Immunisation Programmes in Asia

Reliable information on local disease burden is considered an essential foundation on which policy makers will formulate rational decisions about the introduction of new vaccines into NIPs. As a result of the ARSN, Asia has very good regional rotavirus disease burden data from a range of developed and developing countries. Safe and effective rotavirus vaccines are now available [31,32], and more vaccines are in various stages of development [33–35]. However as of late 2006, no Asian country had introduced rotavirus vaccine into its NIP. In contrast, at least seven countries in the Americas had done so (Table 3), despite the later establishment of the Latin American Rotavirus Surveillance Network. A number of factors may explain this differential rate of introducing rotavirus vaccines into the NIPs of Latin America and Asia. In July 2004 at the 6th International Rotavirus Symposium in Mexico City, representatives of Ministries of Health of 14 countries (Argentina, Bolivia, Brazil, Ecuador, Guatemala, Honduras, Jamaica, Mexico, Nicaragua, Panama, Paraguay, Saint Vincent, Suriname, Trinidad & Tobago and Venezuela) made a declaration calling upon the Pan American Health Organization and its Revolving Fund for the acquisition of vaccines to work together with bilateral and multilateral agencies, GAVI and the manufacturers of vaccines to facilitate the introduction of rotavirus vaccine, as soon as it becomes available

at affordable prices for the countries of the region [36]. Asia has no similar mechanism to the Revolving Fund of PAHO, which is likely to foster greater regional collaboration of Ministries of Health with regards to issues related to vaccination. The currently licensed rotavirus vaccines were to a large extent initially evaluated in the Americas [31,32]. Although vaccine studies are ongoing in Asia, these are still to be completed and reported. WHO in a recent position paper on rotavirus vaccines noted that “clinical efficacy of rotavirus vaccines has been demonstrated mainly in the United States, Europe and Latin America and that WHO strongly recommends the inclusion of rotavirus vaccination into the (NIPs) of regions where vaccine efficacy data suggest a significant public health impact and where appropriate infrastructure and financing mechanisms are available” [37]. Lack of data on efficacy in Asian countries, particularly those with poor populations, has prevented WHO from making a universal recommendation. This experience suggests that even though up-to-date local disease burden data may be an important requirement of decision makers, it is by no means sufficient. To facilitate the rapid introduction of new vaccines into NIPs, vaccine efficacy data should be simultaneously collected at the earliest stage in all global regions, and particularly in poor populations. Regional initiatives involving Ministries of Health, together with more support from local opinion leaders, are likely to important additional requirements to fast-track the introduction process.

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