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Rotavirus incidence in hospitalised Hong Kong children: 1 July 1997 to 31 March 2011

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ABSTRACT

Sentinel laboratory surveillance from one hospital and passive discharge diagnosis (Clinical Management System, CMS) data from all public Hospital Authority (HA) hospitals were used to estimate disease burden and incidence of rotavirus in hospitalised Hong Kong children over 14 rotavirus seasons (1 July 1997 to 31 March 2011). A primary diagnosis of a gastroenteritis-related disorder was noted in 9.8% of children aged below 5 years, and a primary or secondary diagnosis in 11.8%. Any CMS diagnosis of rotavirus (ICD 008.61) was initially used to derive incidence estimates of rotavirus by age group. Rotavirus was recorded as any primary or any secondary diagnosis in 1.6% of children below 5 years of age. The unadjusted incidence rates per 100,000 person-years based on any CMS diagnosis of rotavirus were: 249 (0 to <1m); 612 (1 to <2m); 1066 (2 to <6m); 1383 (6 to <11m); 959 (1 to <2y); 406 (2 to <3y); 233 (3 to <4y); 124 (4 to <5y). Overall the rotavirus incidence was 1071 in children below 2 years and 542 in children below 5 years, and a primary diagnosis of a gastroenteritis-related disorder was noted in 9.8% of children aged below 5 years, and a primary or secondary diagnosis in 11.8%. Any CMS diagnosis of rotavirus (ICD 008.61) was initially used to derive incidence estimates of rotavirus by age group. Rotavirus was recorded as any primary or any secondary diagnosis in 1.6% of children below 5 years of age. The unadjusted incidence rates per 100,000 person-years based on any CMS diagnosis of rotavirus were: 249 (0 to <1m); 612 (1 to <2m); 1066 (2 to <6m); 1383 (6 to <11m); 959 (1 to <2y); 406 (2 to <3y); 233 (3 to <4y); 124 (4 to <5y). Overall the rotavirus incidence was 1071 in children below 2 years and 542 in children below 5 years of age, with the incidence rates trending up during the time period (p=0.001). A similar but less marked upward trend (p=0.046) was noted for the incidence of all-cause gastroenteritis. Laboratory results from a single surveillance hospital (1 July 2000 to 31 March 2011) were then linked to these CMS codes to derive adjustment factors for possible over- and under-diagnosis of rotavirus based on CMS codes alone. This analysis suggested that a CMS diagnosis of rotavirus alone likely under-reported true incidence by a factor of between 1.59 and 2.02 in children below 5 years of age. Despite the availability of rotavirus vaccines in the private sector since 2006, no reduction in the incidence of hospitalisation for either rotavirus or all-cause gastroenteritis was noted in Hong Kong children below 5 years of age over 14 rotavirus seasons (1997–2011).

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1. Introduction

In 2013, the World Health Organization (WHO) confirmed its previous 2009 recommendation that rotavirus vaccines should be used in all countries [1]. Country-specific rotavirus disease burden data are important for informing decisions regarding rotavirus vaccine introduction into National Immunisation Programmes. However use of passive surveillance data alone has been shown to underestimate rotavirus disease burden in Hong Kong [2], highlighting the need for active rotavirus surveillance [3]. The first phase of the Asian Rotavirus Surveillance Network (ARSN) used a WHO surveillance protocol and was conducted in China, Hong Kong, Indonesia, Malaysia, Myanmar, South Korea, Taiwan, Thailand and Vietnam between 2001 and 2003 [3,4]. Overall 30–55% of hospitalizations for diarrhoea in children aged less than 5 years were due to rotavirus [4], with Hong Kong reporting the lowest percentage (30%) [3]. These Hong Kong rotavirus admissions were associated with significant health care and societal costs [5], and an economic evaluation using a Markov model and 2002 cost assumptions estimated that the introduction of routine rotavirus vaccination at a cost of US$40–92 per course could be potentially cost-saving from a government perspective alone [6].

Countries that introduced universal rotavirus vaccination have witnessed a fall in rotavirus-associated hospitalisation rates in
children under two years of age of around 70% in both developed countries (Australia [7,8]; Austria [9], Belgium [10,11], United States [12]) and developing countries (Brazil [13,14], El Salvador [15,16], Mexico [17], Nicaragua [18], Panama [19]). Corresponding reductions in all-cause gastroenteritis admissions have been in the region of 35% [20]. Universal rotavirus vaccination may also reduce nosocomial infections [21], and provide indirect protection to unvaccinated older children and adults [22]. Although rotavirus vaccines were licensed in Hong Kong in 2006, they have not been included in the territory’s universal childhood immunisation programme. The proportion of Hong Kong children that receive rotavirus vaccine through the private sector is unknown.

Discharge data has been collected routinely through the Hospital Authority’s (Hong Kong’s public hospital system, HA) central computerised database (Clinical Management System, CMS) since 1996 [3]. These CMS data are now analysed and combined with sentinel laboratory surveillance from the Prince of Wales Hospital (PWH) to make estimates of disease burden and incidence of rotavirus infection in hospitalised Hong Kong children over 14 rotavirus seasons from 1 July 1997 to 31 March 2011.

2. Methodology

2.1. CMS data

CMS information collected includes patient identifiers, date of birth, sex, a maximum of 15 diagnoses and 15 procedures (classified by International Classification of Diseases ICD9-CM codes), and admission and discharge dates [3]. The CMS was rolled out from 1 July 1997 to 31 March 2011. These CMS data are now analysed and combined with sentinel laboratory surveillance from the Prince of Wales Hospital (PWH) to make estimates of disease burden and incidence of rotavirus infection in hospitalised Hong Kong children over 14 rotavirus seasons from 1 July 1997 to 31 March 2011.

2.2. Laboratory methods at Prince of Wales Hospital

All stool specimens collected from patients with symptoms of acute gastroenteritis admitted to the PWH were tested for rotavirus (ProSpecT Rotavirus, formerly known as IDEIA Rotavirus), DAKO (sensitivity of 100% and specificity of 99.2%) and cultured for bacteria.

2.3. Linking of CMS with laboratory data for Prince of Wales Hospital

Laboratory data for all paediatric admissions from the PWH were matched on the unique hospital number with the CMS data for the period 1 July 2000 to 31 March 2011. There were 100,330 separate admissions of patients below the age of 18 years in the CMS database and 8705 of these had unique hospital numbers (inducing unique admissions) in the laboratory database of stool specimens. All the analyses were based on the CMS calculated dayage (date of admission minus date of birth in days + 1) and monthage (dayage divided by 30.475). If there was more than one stool specimen for the same hospital admission (same hospital number) in the laboratory dataset, then only the first positive (if any) result was retained for analysis.

2.4. Calculation of rotavirus hospitalisation incidence rates by age group from CMS discharge diagnosis

Incidence rates of hospitalisation for rotavirus for all HA hospitals in Hong Kong were first estimated from the total number of children with any CMS diagnosis of rotavirus (ICD-CM 008.61) (CMS rotavirus+). These initial unadjusted CMS rotavirus incidence rates for each year were calculated:

\[
x/y \times 100,000
\]

where

- \(x\) = number of admissions by age with any CMS rotavirus diagnosis (ICD-CM 008.61).
- \(y\) = admissions to public HA hospitals as a percentage of total admissions by age (Appendix 1).

These proportions were weighted by the number of admissions when incidence estimates were calculated for different age groups:

\[
\frac{\sum_j (\text{Admissions}_j \times P_j)}{\sum_j \text{Admissions}_j}
\]

where Admissions\(_j\) is the number of admissions in the \(j\)th age group, and \(P_j\) is the proportion of admissions to HA hospitals in the \(j\)th age group.

\(z\) = estimated resident population by age (Appendix 2)

Incidence rates were calculated by monthly age groups prior to the application of adjustment factors (see below). These monthly age group estimates were then re-grouped according to the following age ranges: 0d to <1m; 1m to <2m; 2m to <6m; 6m to <12m; 1y to <2y; 2y to <3y; 3y to <4y; 4y to <5y; 5y to <10y; 10y to <14y; 14y to <18y.

2.5. Calculation of adjustment factors

Since a CMS rotavirus diagnosis may reflect both under- and over-diagnosis [2,3], we then applied adjustment factors to this CMS rotavirus incidence estimate. These factors were derived by linking the PWH laboratory surveillance data (LAB rotavirus + or –) with the PWH CMS data (CMS rotavirus + or –) (Table 1, Appendix 3). The first factor was derived to adjust for potential under-reporting of rotavirus infection by the CMS system. The second factor was derived to reflect the potential under-estimation of a PWH laboratory diagnosis of rotavirus by accounting for the fact that not all admissions with a primary gastroenteritis-associated diagnosis had a stool specimen sent to the laboratory for testing. The third adjustment factor was the proportion of all admissions to PWH by age group that had a laboratory confirmed diagnosis of rotavirus.

2.6. Incidence trends

Linear regression analysis was undertaken to determine whether there was a significant increase in incidence of CMS rotavirus, adjusted rotavirus and all-cause gastroenteritis admissions over the 14 seasons.

3. Results

During the study period 1 July 1997 to 31 March 2011, there were 1,312,424 admissions to the paediatric medical wards of Hong Kong’s HA hospitals. Three had no gender specified and 118 had missing age data and were excluded. Of the 1,312,303 admissions...
Table 1

| Age (years) | No. (%) of admission | No. (%) with rotavirus diagnosis (CMS) | No. (%) with CMS gastroenteritis diagnosis (ICD = 008.61) | No. (%) stool specimen sent to lab | No. (%) with GE and stool specimen NOT sent to lab | No. (%) with GE and stool specimen sent to lab |
|------------|----------------------|---------------------------------------|---------------------------------------------------------|----------------------------------|-----------------------------------------------|-----------------------------------------------|
| <6m        | 0.0%                 | 0.0%                                  | 0.0%                                                    | 0.0%                             | 0.0%                                          | 0.0%                                          |
| 6-11m      | 1.2%                 | 1.2%                                  | 1.2%                                                    | 1.2%                             | 1.2%                                          | 1.2%                                          |
| 1-2y       | 3.8%                 | 3.8%                                  | 3.8%                                                    | 3.8%                             | 3.8%                                          | 3.8%                                          |
| 2-3y       | 5.6%                 | 5.6%                                  | 5.6%                                                    | 5.6%                             | 5.6%                                          | 5.6%                                          |
| 3-4y       | 7.4%                 | 7.4%                                  | 7.4%                                                    | 7.4%                             | 7.4%                                          | 7.4%                                          |
| 4-5y       | 8.2%                 | 8.2%                                  | 8.2%                                                    | 8.2%                             | 8.2%                                          | 8.2%                                          |
| 5-6y       | 8.9%                 | 8.9%                                  | 8.9%                                                    | 8.9%                             | 8.9%                                          | 8.9%                                          |
| 6-7y       | 9.6%                 | 9.6%                                  | 9.6%                                                    | 9.6%                             | 9.6%                                          | 9.6%                                          |
| 7-11y      | 11.4%                | 11.4%                                 | 11.4%                                                   | 11.4%                            | 11.4%                                         | 11.4%                                         |
| 12-17y     | 12.2%                | 12.2%                                 | 12.2%                                                   | 12.2%                            | 12.2%                                         | 12.2%                                         |
| 18y+       | 12.9%                | 12.9%                                 | 12.9%                                                   | 12.9%                            | 12.9%                                         | 12.9%                                         |

Diarrhoea-associated hospitalizations by reported diagnosis (primary diagnosis only) from Clinical Management System (CMS) among 100,330 children aged 0 to <18 years admitted to the Prince of Wales Hospital, Hong Kong were from November to March as previously noted [3], and the 2008/9 rotavirus season had the greatest total number of CMS rotavirus positive admissions (Appendix 7).

Adjustment factor 1 was not age related (Appendix 3) and a mean value of 1.59 was used for all age groups below 5 years of age. However adjustment factor 2 and adjustment factor 3 varied with age so a smoothed value was used for each age group below 5 years of age (Appendix 3). 1.7% of all admissions below 5 years of age had a CMS rotavirus diagnosis. Applying adjustment factor 1 (1.59) would increase this proportion to 2.7%. The proportion of all admissions at PWH due to rotavirus (adjustment factor 3) peaked between about 12–18 months (Appendix 3). Overall 2.4% of admissions to PWH below 2 years and 2.6% below 5 years had laboratory confirmation of rotavirus (Table 1 and Appendix 8). The proportion of all admissions that had laboratory confirmed rotavirus also varied by year of admission (Appendix 8).

The incidence rates of hospitalisation for rotavirus per 100,000 person-years were lowest in the first two months of life, then peaked between 7 and 8 months, and then declined from about 18 to 24 months (Fig. 1). Similar patterns were observed over all 14 rotavirus seasons of the study. The unadjusted incidence rates per 100,000 person-years based on any CMS rotavirus diagnosis (ICD = 008.61) were: 249 (0 to <1m); 612 (1 to <2m); 1066 (2 to <6m); 1383 (6 to <11m); 959 (1 to <2y); 406 (2 to <3y); 233 (3 to <4y); 124 (4 to <5y) (Table 2). Overall the incidence was 1071 in children below 2 years old and 542 in children below 5 years of age. Adjusted incidence rates were generally higher than the unadjusted rates (Table 2, Fig. 1). In the older age groups the effect of adjustment factor 3 was less i.e. this factor assumes that the proportion of rotavirus positive admissions as a proportion of all admissions by age group were the same in all HA hospitals as they were in PWH. Incidence rates of both unadjusted CMS rotavirus diagnosis (p = 0.001, standardised coefficient = 0.778) and adjusted rotavirus diagnosis (adjustment factor 1, p = 0.001, standardised coefficient = 0.778; adjustment factor 2, p = 0.001, standardised coefficient = 0.778; adjustment factor 3, p < 0.0001, standardised coefficient = 0.959) trended up over the 14 rotavirus seasons (Fig. 2).
Although there was a similar upward trend for the incidence of all-cause gastroenteritis based on primary CMS diagnosis alone \( (p = 0.046, \text{standardised coefficient} = 0.540) \), this was less marked than that seen for rotavirus (Fig. 2).

The length of stay (LOS, date of discharge minus date of admission plus one) is one measure of severity of illness. The median LOS for rotavirus diarrhoea (4 days) was longer than that of other viral gastroenteritis (3 days) for children aged both below 5 years and below 18 years of age (Appendix 9). The LOS in rotavirus was similar to that of bacterial and parasitic gastroenteritis. In PWH, there were two deaths in children below 18 years old during the period July 2000 to March 2011. Both children were over 5 years old and were coded respectively as gastroenteritis of presumed infectious and non-infectious diarrhoea and vomiting and gastritis. No patient coded as rotavirus gastroenteritis died. Most of the patients were discharged without follow up, and 13.5% of the patients coded as rotavirus gastroenteritis below 5 years of age had a follow-up visit scheduled after discharge. This proportion was similar to that of patients with other viral and non-specific gastroenteritis but less than that for patients with bacterial and parasitic gastroenteritis (Appendix 9). Similar patterns were seen for all patients admitted to other HA hospitals, although the proportions of patients with follow-up was greater. There were 5 deaths in all HA hospitals coded as a gastroenteritis-related illness, and three of these were below 5 years of age.

### 4. Discussion

The unadjusted incidence rates per 100,000 person-years based on any CMS diagnosis of rotavirus hospitalisation were 542 for

Table 2

| Estimates based on | Estimates based on ANY CMS diagnosis of rotavirus (ICD9-CM 008.61) with adjustment for under- and over-CMS RV diagnosis based on data from Prince of Wales Hospital (adjustment factor 1)\(^a\) | Estimates based on ANY CMS diagnosis of rotavirus (ICD9-CM 008.61) with adjustment for under- and over-CMS RV diagnosis and failure to send stool on all gastroenteritis-related admissions based on data from Prince of Wales Hospital (smoothed adjustment factor 2 omitting first month of life)\(^b\) | Estimates based on assumption that laboratory confirmed rotavirus admissions as a proportion of all admissions by age group identified in Prince of Wales Hospital (laboratory confirmation) is the same proportion of all admissions to all HA hospitals (smoothed adjustment factor 3 with unsmoothed value for first month of life)\(^c\) | Estimates based on primary ICD diagnosis of gastroenteritis | Estimates based on ANY primary or secondary ICD diagnosis of gastroenteritis |
|-------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| <24m              | 1071                                             | 1093                                             | 1029                                             | 1093                                             | 1029                                             |
| <60m              | 542                                              | 863                                              | 1093                                             | 1093                                             | 1029                                             |
| Total             | 117                                              | 117                                              | 117                                              | 117                                              | 117                                              |

\(^a\) See Appendix 3 for description of adjustment factors 1, 2, and 3.
children below 5 years of age. However after applying adjustment factors 1, 2 and 3 (derived from laboratory data from one hospital) these estimates increased to 863, 1093 and 1029 respectively, indicating the potential magnitude of under-coding and/or under-testing. Stool specimens were actively collected at four hospitals during the two-year period 2001–2003 as part of the Asian Rotavirus Surveillance Network (ARSN) [4]. We previously reported for children below 5 years of age rotavirus incidence rates per 100,000 of 810–880 during this two-year active surveillance period [3]. The corresponding CMS rotavirus diagnosis incidence during this same two-year period was 300 per 100,000. Although our current analysis includes data from the ARSN study period, our results suggest that the adjusted rotavirus incidence estimates were similar during the same period but trended up during the subsequent rotavirus seasons (Fig. 2). The current analysis suggests that between 1.7% (unadjusted CMS diagnosis of rotavirus...
at one hospital), 2.6% (laboratory confirmed rotavirus confirmed at one hospital), and 3.4% (1.7% \times 2.02) (CMS diagnosis adjusted for under-diagnosis and under-testing with adjustment factor 2) of hospital admissions below 5 years of age were due to rotavirus infection. The ARSN surveillance data estimated a cumulative risk of admission by five years of age of 4.2% (1 in 24 children) [3]. Estimates of cumulative risk of admission by five years of age from the current analysis ranged from 1.4% (1 in 69 children) to 4.5% (1 in 22 children) during the 11 year period from 1 April 2000 to 31 March 2011 (Fig. 3). The cumulative risk of admission by five years of age was higher in 2008/9 peak of rotavirus admissions (Fig. 3, Appendix 7). The possible reasons for the 2008/9 peak are unknown.

Our current analysis shows the potential of combining passive discharge diagnostic coding surveillance with sentinel laboratory surveillance to monitor disease burden of pathogens that are vaccine-preventable or potentially vaccine-preventable [2,3,23]. However even though all children admitted with gastroenteritis to PWH were anticipated to have stool specimens sent for rotavirus testing, this did not happen. In our analysis we have made estimates of possible increased disease burden that all children had specimens taken.

A number of assumptions have been made that should be considered when interpreting our results. First our incidence estimates assumed the proportion of admissions to public HA hospitals and the resident Hong Kong population was constant over the entire study period. In our previous analyses it was assumed that public hospitals catered for 90% of paediatric admissions and that all Hong Kong births utilised the Hong Kong health system [3]. However in recent years there have been two significant changes that challenge these assumptions. With improvements in the economy since the 1997 economic downturn, there has been an increased use of private hospital facilities (Appendix 1). Second there has been a significant increase in the number of cross-border births and these have accounted for up to 50% of all Hong Kong births in recent years. All children born in Hong Kong are eligible to obtain a Hong Kong identity card and access to Hong Kong medical care. There is limited data on the subsequent residence and health care utilisation of these cross border births i.e. some live with parent(s)/relatives in Hong Kong and others return to live in the Mainland, but still potentially seeking medical care in Hong Kong. PWH is in close proximity to the Hong Kong-Mainland border and likely caters for a greater proportion of children moving frequently to-and-fro for medical care, than do other distant HA hospitals. These limitations mean that our incidence estimates (Table 2) are likely under-estimates rather than over-estimates since they exclude rotavirus admissions to hospitals in mainland China. However countering this is the fact that this analysis did not determine the proportion of children readmitted for the same diarrheal episode and those with nosocomial rotavirus infection, factors that could result in an overestimation of incidence. Also our adjustment for under-testing (adjustment factor 2) assumed that the rotavirus positive rate in untested stools was equal to that in tested stools and could therefore over-estimate true incidence since it is possible that children who are not tested have more mild disease and lower likelihood of rotavirus infection. Population census data were mid-year estimates (January to December), whereas the rotavirus admission data was calculated by rotavirus season (July to the following June). We have also assumed that the adjustment factors derived from one institution, PWH, can be applied uniformly across all the HA hospitals, and that these factors are stable over time. This may not be a valid assumption. Although PWH is one of the largest HA hospitals and one of the two university teaching hospitals in Hong Kong, it accounts for only about 10% of all the public hospital paediatric admissions. It is possible that there may be differences in clinical practices, admission policies and laboratory services between PWH and other HA hospitals and also over time. During the period 2001 to 2003 PWH was one of four HA hospitals to participate in active rotavirus surveillance as part of the ARSN, and it is likely that testing for rotavirus is more frequent at PWH than at some of the other HA hospitals. Ideally having laboratory data from other sentinel surveillance hospitals, that have a policy of routine testing for rotavirus, could strengthen our incidence estimates in future studies.

Despite the availability of rotavirus vaccines in Hong Kong since 2006, an upward trend of incidence rate of both rotavirus gastroenteritis and all-cause gastroenteritis is observed. Possible reasons for this could include the limited use of vaccine within the private sector. Increased awareness of rotavirus following the ARSN active surveillance period (2001–2003) and increased surveillance and infection control measures for respiratory and diarrhoeal diseases following the outbreak of severe acute respiratory syndrome in 2003, could have contributed to the increased testing for rotavirus during the latter part of the study period and improved accuracy of CMS coding. More permissive admission policies could be another explanation for the increased trends in incidence of rotavirus and all-cause gastroenteritis observed.

5. Conclusion

Estimates of the incidence of rotavirus that requires hospital admission were highest in children aged 6 months to below 2 years. After adjustment for likely under-coding and under-testing our overall estimates of incidence of rotavirus hospitalisation over 14 rotavirus seasons are similar to our previous estimates made during the active surveillance period 2001–2003 but trended up over the study period. Our data suggest that estimates of rotavirus disease burden and incidence can be derived from passive discharge data combined with data from laboratory surveillance but should ideally include data from more than one sentinel hospital.

Conflict of interest

EASN has received funding and support from Merck and Pfizer for diarrhoeal and respiratory disease surveillance studies, has participated in vaccine studies funded by Baxter, GlaxoSmithKline, MedImmune and Wyeth, and has received lecture fees and travel support from GlaxoSmithKline, Merck, Intercell and Pfizer. MI has received funding and support from Pfizer for respiratory disease surveillance studies. PKSC has participated in vaccine studies funded by Baxter, GlaxoSmithKline, MedImmune and Wyeth, and has received lecture fees and travel support from GlaxoSmithKline, Merck and Roche.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2014.01.065.
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