Vaccine xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Rotavirus vaccine effectiveness in Hong Kong children

Karene Hoi Ting Yeung BSc [a], Jacqueline E. Tate PhD [b], Ching Ching Chan MBChB, FHKAM, FHKCPaed [a], Martin C.W. Chan PhD [c], Paul K.S. Chan MBBS, MSc, MD, FRCPath, FHKCPath, FHKAM [c], Kin Hung Poon MBBS, FHKAM, FHKCPaed [d], Sylvia Luen Yee Siu MBChB, FHKAM, FHKCPaed [d], Genevieve Po Gee Fung MBBChir, FHKAM, FHKCPaed [e], Kwok Leung Ng MBBS, FHKAM, FHKCPaed, FRCP [e], Iris Mei Ching Chan MBBS, FHKAM [f], Pui Tak Yu MBBS [f], Chi Hang Ng MBBS, FHKAM, FHKCPaed [g], Yu Lung Lau MBChB, MD, FRCPCH, FHKAM, FHKCPaed [h], E. Anthony S. Nelson MBChB, MD, FRCP, FRCPCH, FHKCPaed [a,*]

[a] Department of Paediatrics, The Chinese University of Hong Kong, Hong Kong Special Administrative Region
[b] Epidemiology Branch, Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, USA
[c] Department of Microbiology, The Chinese University of Hong Kong, Hong Kong Special Administrative Region
[d] Department of Paediatrics and Adolescent Medicine, Tuen Mun Hospital, Hong Kong Special Administrative Region
[e] Department of Paediatrics and Adolescent Medicine, United Christian Hospital, Hong Kong Special Administrative Region
[f] Department of Paediatrics, Kwong Wah Hospital, Hong Kong Special Administrative Region
[g] Department of Paediatrics, Queen Elizabeth Hospital, Hong Kong Special Administrative Region
[h] Department of Paediatrics and Adolescent Medicine, The University of Hong Kong, Hong Kong Special Administrative Region

ARTICLE INFO

Article history:
Received 30 May 2016
Received in revised form 15 August 2016
Accepted 16 August 2016
Available online xxxx

Keywords:
Rotavirus
Gastroenteritis
Rotavirus vaccine
Vaccine effectiveness

ABSTRACT

Background: Rotavirus is a common infectious cause of childhood hospitalisation in Hong Kong. Rotavirus vaccines have been used in the private sector since licensure in 2006 but have not been incorporated in the government's universal Childhood Immunisation Programme. This study aimed to evaluate rotavirus vaccine effectiveness against hospitalisation.

Methods: This case-control study was conducted in the 2014/2015 rotavirus season in six public hospitals. Hospitalised acute gastroenteritis patients meeting inclusion criteria were recruited and copies of their immunisation records were collected. Case-patients were defined as enrolled subjects with stool specimens obtained in the first 48 h of hospitalisation that tested positive for rotavirus, whereas control-patients were those with stool specimens obtained in the first 48 h of hospitalisation testing negative for rotavirus. Vaccine effectiveness for administration of at least one dose of either Rotarix® (GlaxoSmithKline Biologicals) or RotaTeq® (Merck Research Laboratories) was calculated as 1 minus the odds ratio for rotavirus vaccination history for case-patients versus control-patients.

Results: Among the 525 eligible subjects recruited, immunisation records were seen in 404 (77%) subjects. 31% (162/525 and 126/404) tested positive for rotavirus. In the 404 subjects assessed for vaccine effectiveness, 2.4% and 24% received at least 1 dose of either rotavirus vaccine in case- and control-patients respectively. The unmatched vaccine effectiveness against hospitalisation for administration of at least one dose of either rotavirus vaccines was 92% (95% confidence interval [CI]: 75%, 98%). The matched analyses by age only and both age and admission date showed 96% (95% CI: 72%, 100%) and 89% (95% CI: 51%, 97%) protection against rotavirus hospitalisation respectively.

Conclusions: Rotavirus vaccine is highly effective in preventing hospitalisation from rotavirus disease in young Hong Kong children.

1. Introduction

Although rotavirus causes no, or very low, mortality in Hong Kong, it does cause significant morbidity [1,2] and economic burden [3]. There are two oral rotavirus vaccines available in Hong Kong. Rotarix® (RV1, GlaxoSmithKline Biologicals) is a monovalent live-attenuated human rotavirus vaccine given with a two-dose

Abbreviations: AGE, acute gastroenteritis; CIP, Hong Kong's Childhood Immunisation Programme; NIP, National Immunisation Programme; RV1, Rotarix® (GlaxoSmithKline Biologicals); RV5, RotaTeq® (Merck Research Laboratories); VE, vaccine effectiveness.

* Corresponding author at: Department of Paediatrics, The Chinese University of Hong Kong, 6/F Lui Che Woo Clinical Sciences Building, Prince of Wales Hospital, Shatin, Hong Kong Special Administrative Region.

E-mail address: tony-nelson@cuhk.edu.hk (E. Anthony S. Nelson).

http://dx.doi.org/10.1016/j.vaccine.2016.08.047
0264-410X/

schedule usually at 2 and 4 months of age. RotaTeq® (RV5, Merck Research Laboratories) is a bovine-human reassortant pentavalent rotavirus vaccine given with a three-dose schedule usually at 2, 4 and 6 months of age. In 2006, these vaccines were reported to be safe and highly efficacious in the Americas and Europe [4,5], and subsequently were shown to have about 96% efficacy against severe acute rotavirus gastroenteritis through 2 and 3 years of age in Hong Kong, Singapore and Taiwan [6–8]. In 2013, the World Health Organization re-confirmed its 2009 recommendation that rotavirus vaccines be included in all National Immunisation Programs (NIP) [9]. An economic evaluation from the Hong Kong government's perspective showed that inclusion of the vaccine in the universal Childhood Immunisation Programme (CIP) would be likely cost-saving if the vaccine cost per course was less than USD 40–92 assuming a vaccine efficacy of 96% for preventing hospitalisations and 89.5% for preventing outpatient visits [10]. This analysis did not include societal or wider economic benefits such as herd protection [11], reduction of nosocomial infections [12] and reduction of seizures [13]. Since 2012 the Hong Kong CIP offers vaccines to all children at no cost to the families that protect against 11 infectious diseases (Bacillus Calmette–Guérin, hepatitis B, diphtheria, acellular pertussis, tetanus, inactivated polio, 13-valent conjugate pneumococcus, measles, mumps, rubella and varicella). Although both rotavirus vaccines have been licensed in Hong Kong since 2006, they have not been included in the CIP and have only been available in the private sector. This non-universal use of rotavirus vaccine has allowed us to evaluate rotavirus vaccine effectiveness in Hong Kong.

2. Methodology

2.1. Subjects

During the 2014/2015 rotavirus season, we conducted a case-control study to assess rotavirus vaccine effectiveness in acute gastroenteritis (AGE) patients admitted to public hospitals in Hong Kong. During this period Hong Kong's Hospital Authority managed 12 government funded public hospitals with general paediatric services. These 12 hospitals were officially grouped into seven clusters. This study was carried out in six public hospitals located from six clusters: Kwong Wah Hospital, Prince of Wales Hospital, Queen Elizabeth Hospital, Queen Mary Hospital, Tuen Mun Hospital and United Christian Hospital. An estimated 71% of all inpatient paediatric care in Hong Kong is provided by these public hospitals [14]. Although families from higher socioeconomic backgrounds are more likely to use the private sector, public hospitals provide care for all Hong Kong residents from all socioeconomic backgrounds.

AGE was defined as the occurrence of two or more episodes of vomiting and/or three or more episodes of diarrhoea (stools of a less formed character than usual) within a 24-h period. Families of children meeting the inclusion criteria were invited to participate in the study. Inclusion criteria for selection of subjects included: (1) admitted to one of the study hospitals for treatment of AGE during the study period; (2) aged from 30 days to below 5 years; (3) onset of diarrhoea or vomiting started less than or equal to 14 days before admission; (4) normally receive vaccination and/or medical care in Hong Kong; and (5) written informed consent obtained from parents or guardians. Patients with parents or guardians unable to speak Chinese (Cantonese or Mandarin) or English were excluded. Research staff identified the potential AGE patients by looking up the admission records of hospitalised children with AGE symptoms. However, since these records may not reflect the real diagnoses at recruitment, some recruited patients were subsequently shown not to have a diagnosis of AGE. Discharge summaries or case records were reviewed independently by two of the authors and non-AGE patients were excluded from the analysis. Subjects without stool specimens known to be collected and tested for rotavirus within the first 48 h of hospitalisation and subjects without copies of immunisation records were excluded from the final analyses.

Rotavirus testing was performed on routinely collected stool specimens from diarrhoea patients at five of the six study hospitals (except Kwong Wah Hospital). During the study period, stool specimens were collected from diarrhoea patients at Kwong Wah Hospital and transported on ice for rotavirus testing with enzyme immunoassay (EIA) at the Prince of Wales Hospital laboratory. Specimens from four of the study hospitals were tested for rotavirus by EIA and by reverse-transcriptase-polymerase chain reaction (RT-PCR) at the remaining two sites (Appendix). Case-patients were defined as AGE recruited subjects with stool specimens obtained during the first 48 h of hospitalisation that tested positive for rotavirus, whereas the control-patients were AGE recruited subjects with stool specimens obtained within the first 48 h of hospitalisation testing negative for rotavirus (i.e. test-negative controls). Analyses were done using three groups of controls: (1) matched with case-patients by date of birth (±30 days) and date of admission (±30 days); (2) matched by date of birth only; and (3) unmatched controls. The matched analyses allowed for up to 5 control-patients to be matched to each case-patient without replacement.

2.2. Data collection

Parents or guardians of recruited patients were interviewed at the study hospitals with a standardised questionnaire [15] modified for local use. Demographic information, birth and medical history were collected. Admission details, disease severity, final diagnoses and laboratory results were obtained from patients' medical records. Copies of subjects' immunisation records were obtained from their parents or guardians after interviews. If the immunisation records were not available during the hospital admission, verbal reports of vaccination history were collected and copies of immunisation records were requested to be sent by text message, e-mail, fax or post.

2.3. Statistical analyses

Characteristics of case-patients and control-patients were compared using chi-square tests and Wilcoxon rank-sum tests. Diarrhoea severity was examined by using the Vesikari score [16] and other markers such as length of hospital stay and the use of intravenous fluids. A dose of vaccine was considered relevant if it was administered at least 14 days before admission. Patients were regarded as fully vaccinated if they had received 2 doses of RV1 or 3 doses of RV5, whereas patients were regarded as partially vaccinated if they had received 1 dose of RV1 or 1–2 doses of RV5. For the unmatched analysis, we used unconditional logistic regression, adjusting for age on admission and month of admission, to obtain the adjusted odds ratios (ORs) for rotavirus vaccination rate (at least one dose and full series versus unvaccinated) among case-patients compared with control-patients. Conditional logistic regressions were used for matched analyses. We investigated rotavirus vaccine effectiveness using each of the control groups. Vaccine effectiveness was calculated as $(1 - OR) \times 100$, where the ORs were those obtained from the unconditional and conditional logistic regressions. All analyses were performed using statistical software R version 3.2.2 and SAS version 9.3 (SAS Institute, Cary, NC). A two-tailed p-value of <0.05 was considered statistically significant.

Please cite this article in press as: Yeung KHT et al. Rotavirus vaccine effectiveness in Hong Kong children. Vaccine (2016), http://dx.doi.org/10.1016/j.vaccine.2016.08.047