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Impact of rotavirus vaccination on the burden of acute gastroenteritis in Nagoya city, Japan

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ABSTRACT

Background: In Nagoya city, Japan, rotavirus (RV) vaccination has been available since 2011 with estimated coverage reaching 92% by 2015 after the introduction of a public subsidy in 2012. This study assessed the impact of vaccination on the RV gastroenteritis (RVGE) burden in children aged <5 years old (y) by comparing RVGE hospitalizations and outpatient visits during pre-vaccination (2007–2011), transition (2011–2012) and subsidization (2012–2016) periods.

Methods: All hospitalizations and outpatient visits in children aged <5 y from 2 administrative districts of Nagoya city were identified from the hospital-based electronic databases of 4 hospitals. RVGE cases were identified by diagnostic code and/or positive results of diagnostic kits.

Results: Compared to the pre-vaccination period, there was a decrease in RVGE hospitalizations for children <5 y from 5.59 per 1000 person-year (kPY) to 3.65/kPY in the subsidization period (i.e. 34.69%). In children <1 y, the incidence of RVGE hospitalizations decreased continuously from 6.62/kPY in the pre-vaccination period to 1.84/kPY in the subsidization period (i.e. 72.19%). The highest decrease was observed in the subsidization season i.e. when high coverage was reached: 69% and 75.57% in the 2013/2014 season for 2–3 y and 3–4 y, and 74.03% in the 2014/2015 season for 4–5 y, respectively. Proportion of RVGE outpatient visits decreased by 87.44% for children <1 y and 57.05% for <5 y from the pre-vaccination to the subsidization period. This decrease started the first year of subsidization for children <1 y, 1–2 y and 2–3 y (78.89%, 18.86% and 5.80%) and the second year (2013/2014 season) for children 3–4 y and 4–5 y (87.73% and 51.78%).

Conclusions: Although yearly fluctuations have been observed, the introduction of vaccination significantly decreased pediatric RVGE hospitalizations and outpatient visits, especially in the age group eligible for vaccination. During the second and third year of subsidization, we observed a herd protection effect on other age groups <5 y who were not eligible for vaccination.

Conclusions: Clinicaltrial.gov.registered#:NCT01733862.

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Abbreviations: AGE, acute gastroenteritis; CI, confidence interval; ICD, International Classification of Diseases and Related Health Problems diagnostic code; kPY, 1000 person-years; RV, rotavirus; RVGE, rotavirus gastroenteritis; SAS, statistical analysis software; y, years old.

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1. Introduction

Rotavirus (RV) is the leading cause of acute gastroenteritis (AGE) worldwide, and it is estimated that, by 5 years of age, almost all children will have experienced an episode of rotavirus gastroenteritis (RVGE) [1,2]. In Japan, RV infection causes considerable morbidity in children due to AGE with an incidence rate of 255 per 1000 person-years (/kPY) in children <3 years old (y) [3,4].

The estimated incidence of hospitalizations and outpatient visits due to RVGE is 5.3–17.6 and 110/kPY, respectively [2,5], with the highest incidence observed in infants. Approximately 25% of children with RVGE require 8–14 days for recovery, 28% need intravenous hydration, 70% medical intervention > 2 times and 32% medical intervention > 3 times [3]. The RV-infection mortality rate in Japan is not high but as recently as 2008, 19 children (0.5 per 100,000 children per year) have died [6], considered to have been caused by encephalopathy/encephalitis and sudden unexpected death based on a nationwide questionnaire survey [7]. Due to this significant disease burden and in the absence of vaccination, RVGE costs are expected to be over 20 billion yen including over 13 billion yen in direct medical costs, of which 53.1% are attributable to hospitalization costs [8,9].

Currently, two live oral RV vaccines are widely available and approved in more than 100 countries: *Rotarix* (GSK) and *Rotateq* (Merck & Co). Both vaccines have been shown to have acceptable safety profiles and to reduce morbidity and mortality due to RVGE in children [10,11]. RV vaccination has been available in Japan since November 2011 but has not yet been included in the universal routine vaccination program. Nationwide coverage was estimated at 51% by 2013 with coverage as low as 30% in some regions [12]. In Nagoya city, the coverage reached a level of 84–92% by 2015 after the local government introduced a public subsidy covering half of the vaccine costs in October 2012 [13,14].

Although remarkable reductions in the RVGE burden after introduction of universal RV vaccination have been demonstrated in several countries [15], in Japan the impact of RV vaccination on the reduction of RV disease burden needs to be documented further.

The present study was conducted to estimate the impact of RV vaccination on RVGE hospitalizations and outpatient visits for children <5 y in 2 districts of Nagoya city.

2. Material and methods

2.1. Study design and population

This retrospective observational study (NCT01733862) was conducted in Nagoya city in Japan at 4 hospitals admitting children with acute infectious diseases. The investigational sites were selected according to the following criteria: 1) located in areas with high coverage of RV vaccination after introduction of the vaccine subsidy, 2) large birth cohorts (over 2000) to achieve a sufficient sample size, 3) cover all hospitalizations of the children who live in the districts, 4) fully equipped with electronic diagnosis and laboratory record databases and 5) unchanged hospitalization environment and standards of laboratory testing during the study period.

The selected hospitals covered almost all pediatric hospitalizations of children within the 2 selected districts, Minami-ku and Tempaku-ku, where more than 12,000 children <5 y resided (Fig. 1) [16]. One of the hospitals, the Japanese Red Cross Nagoya Daini Hospital, was located in an adjacent district, Showa-ku, but some of the children residing in the study districts were admitted to this hospital. The extraction of recorded data was restricted to children residing in these 2 districts at the time of hospital admission or outpatient visit. Records of outpatient visits for children in 2 of the hospitals who routinely confirmed RVGE in outpatient practice by the RV rapid test (immunochromatography test kit [Eiken Chemical Co Ltd.: Dipstick Eiken Rota] and Sekisui Medical Co Ltd. [RapidTesta Rota Adeno]) were also examined to assess mild and moderate RVGE occurrences.

Three periods were distinguished: pre-vaccination (November 2007 to October 2011); transition, the first year after introduction

of RV vaccination (November 2011 to October 2012); and subsidization (November 2012 to October 2016). Vaccination coverage was estimated by the number of manufacturer shipments and subsidy records, which reported the number of vaccination doses actually subsidized by Nagoya city relative to the size of the birth cohorts within both districts [13,14].

2.2. Data collection and case definitions

The hospitals' electronic databases were used to identify hospitalizations and outpatient visits for children <5 y diagnosed with AGE or RVGE either by the International Classification of Diseases and Related Health Problems (ICD10) diagnostic code (A00–A09 for intestinal infectious diseases for AGE and A08.0 for RVGE) or who tested RV-positive with a rapid RV diagnosis kit. The RV diagnosis kits differed between sites, but each site used the same kit throughout the study period. All RVGE cases were reviewed by the investigators and defined as either having a positive lab test or were clinically coded as ICD10 A08.0 to assess the accuracy of the diagnosis. RVGE cases were confirmed by laboratory tests or by direct review of the consultation records (e.g., the patient was referred from a clinic or hospital where (s)he had been diagnosed with RVGE by an RV antigen test). Each new hospitalization or outpatient visit for the same child was considered as a separate case, for instance, if a child was readmitted this was recorded as two independent cases, not one.

2.3. Statistical analyses

Data was analyzed using statistical analysis software (SAS). The incidence of RVGE and AGE hospitalizations (/kPY) were calculated with Poisson exact 95% confidence intervals (CI) based on the number of RVGE and AGE hospitalizations and the size of the target population in the hospitals' uptake areas [16]. The average annual number of RVGE and AGE outpatient visits was calculated for 2 of the participating hospitals. The initial and incremental proportions of RVGE and AGE hospitalizations and outpatient visits among children <5 y were estimated and tested for statistical significance by an asymptotic score test.

2.4. Ethics

The study was conducted in accordance with the Ethical Guidelines for Epidemiological Research and the Ethical Guidelines for Medical and Health Research Involving Human Subjects, subject privacy requirements and the guiding principles of the Declaration of Helsinki and was approved by the ethics committee of each hospital. The databases used for the study were fully anonymized. In Japan, informed consent is not required for observational epidemiological studies that do not use human biological specimens.

3. Results

3.1. AGE and RVGE incidence

Over the study period, the total number of hospitalizations and outpatient visits recorded for children <5 y were 12,748 and 84,905; of these children, 55.21% and 55.89% were males, respectively. Throughout the study period, the annual number of hospitalizations remained stable at approximately 1400 (1305–1554), but the mean annual number of outpatient visits varied from 8335 (6274–10,209) in the pre-vaccination period, to 11,710 in the transition period and 9964 (8481–11,500) in the subsidization period. The seasonality of RVGE and AGE hospitalizations was similar from year to year, with the largest number of RVGE occurring

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