**Timeliness of childhood vaccination coverage: the Growing Up in Singapore Towards healthy Outcomes Study**

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**Abstract**

#### Studies investigating timeliness for childhood vaccination are limited especially in Asia. We examined the timeliness of vaccine administration and associated factors among infant and young children in Singapore. Total of 782 children born between November 2009 and July 2011 from a prospective cohort in Singapore were studied. Vaccination records from birth to 24 months of age were obtained from the National Immunization Registry of Singapore. Multivariable logistic regression models were performed. By 2 years of age, 92.8% of children in our cohort experienced a delay in receiving 1 or more vaccine doses according to the recommended national immunization schedule. When vaccinations were reviewed by series for each vaccine, 15.6% received all vaccine series outside the recommended age ranges. Factors associated with receiving vaccination series outside the recommended ages included maternal aged ≤35 years (OR 2.00; 95% CI 1.09, 3.66), Malay (1.71; 1.01, 2.89) or Indian ethnicity (2.06; 1.19, 3.59), low monthly household income (1.91; 1.14, 3.18), having at least four children (3.46; 1.62, 7.38), private (3.42; 1.80, 6.48) and multiple vaccination providers (3.91; 1.23, 12.48). These findings show an unacceptably high proportion of children experienced a delay in the receipt of their vaccinations. The identification of several demographic, socioeconomic, health-seeking behavioural and vaccine provider factors provides opportunities for targeted interventions to enhance the timeliness of childhood vaccination in Singapore.

***Keywords:*** Age-appropriate, childhood immunization, coverage, timeliness, vaccination

**Introduction**

In Singapore, the National Childhood Immunization Programme recommends children should be vaccinated against 11 different diseases by 2 years of age (Ministry of Health 2015). This includes vaccinations against Tuberculosis; Hepatitis B; Diphtheria, Pertussis, Tetanus; Poliomyelitis; Measles, Mumps, Rubella; Pneumococcal disease and *Haemophilus influenzae* type b. Of these, vaccinations against diphtheria and measles are compulsory by law and a requirement before admission to primary school (Ministry of Health 2015). The National Childhood Immunization Schedule (NCIS) for these vaccine preventable diseases were based on prior data on the efficacy and safety of the vaccines to provide optimal protection against potential infectious risks, and to minimize adverse events following immunization (Centers for Disease Control and Prevention 2006; Ministry of Health 2015).

Globally, infant and childhood vaccination coverage reports usually document the level of coverage at two time points, around 12-24 months and pre-school (3-5 years old) depending on the local immunization schedule. Similarly, published reports of Singapore national childhood immunization data have focused on coverage, showing completeness of recommended vaccine administration by age of 2 years and primary school level (Ministry of Health 2014; Ministry of Health 2015). Such coverage reports are limited in their ability to accurately assess timeliness of vaccination and subsequently the real impact of vaccination programs. Poor schedule adherence whether early or delayed could potentially diminish the benefits of immunizations at individual and community levels (Ventola 2016). High levels of population susceptibility due to delays in vaccination could increase the likelihood of outbreaks and eliminate the benefits of herd protection in the population.

Vaccination timeliness has been examined mainly in developed countries where different rates of timely vaccinations were observed, usually depending on the type of vaccines and criteria used for timely vaccination. In the United States, only 13.2% of Michigan children were vaccinated on time by age 24 months (Wagner et al. 2018). In Norway, delayed vaccinations occurred in 45% children aged <24 months (Riise et al. 2015). In Singapore, there are no reports available for vaccination timeliness although such data can help the development of targeted efforts to improve immunisation programs in children. Using data from a prospective mother-offspring cohort, Growing Up in Singapore Towards healthy Outcomes (GUSTO), we aimed to describe the timeliness of vaccination in children during their first 24 months of life. We also examined factors for the timeliness of vaccination in this cohort of children.

**Methods**

**Study design**

Data was derived from the GUSTO study (www.clinicaltrials.gov, NCT01174875) (Soh et al. 2014). The study conformed to the principles in the Declaration of Helsinki. Ethical approval was obtained from the Domain Specific Review Board of Singapore National Healthcare Group (reference D/09/021) and the Centralised Institutional Review Board of SingHealth (reference 2009/280/D). Informed written consent was obtained from all mothers.

Mothers were recruited from antenatal clinics of the KK Women’s and Children’s Hospital and the National University Hospital, between June 2009 and September 2010. They were at least 18 years old, citizens or permanent residents who were of Chinese, Malay or Indian ethnicity. Among recruited mothers, those who disagreed for their child’s medical information to be extracted from the National Immunization Registry (NIR) were excluded from this analysis.

**Participant characteristics**

Data on maternal socio-demography, education and health history were ascertained using interviewer-administered questionnaires in the clinics at recruitment (≤14 weeks’ gestation). Maternal body mass index (BMI) was computed from body weight and height which were measured in the first trimester, and classified into BMI<23 kg/m2 and ≥23 kg/m2 using Asian cut-offs (World Health Organisation 2004). After delivery, data on neonatal sex was obtained from the medical records. Duration of gestation was determined by ultrasound scans dating at 7-12 weeks’ gestation. Neonatal weight was measured and classified as low birth weight if born with weight <2500g.

**Vaccination data**

Vaccination records of children from birth until 24 months of age were obtained from the NIR of Singapore. For each child, the age at which primary doses of the six vaccines administered was recorded in days, namely of Bacille Calmette-Guérin (BCG) vaccine, hepatitis B (Hep B) vaccine, diphtheria, tetanus toxoid and acellular pertussis (DTaP) vaccine, polio vaccine [either oral polio vaccine (OPV) or injectable polio vaccine (IPV)], mumps, measles and rubella (MMR) vaccine and pneumococcal vaccine (PCV). We also recorded primary doses of the *Haemophilus influenzae* type B (HiB) vaccine; this was available as part of a combination vaccine. Both primary doses and booster doses were studied.

We recorded the type of providers for each dose of vaccine administration and categorized children into 3 groups: Public (received 75% or more of their vaccinations in restructured hospitals or polyclinics); Private (received 75% or more of their vaccinations in private hospitals or General Practitioner clinics); or Multiple providers (did not fulfil criteria for either Public or Private).

**Definitions**

According to 2011 NCIS, the immunization schedule recommended for children up to 24 months of age comprised 1 primary dose of BCG, 3 primary doses of Hep B, 3 primary doses and 1 booster dose of DTaP, 3 primary doses and 1 booster dose of polio, 2 primary doses of MMR, 2 primary doses and 1 booster dose of PCV. In 2011, MMR vaccination was changed from a 2-dose schedule with first dose at 1-2 years followed by second dose at 6-7 years, to first dose at 12 months followed by second dose at 15-18 months. For PCV vaccination, a 2-dose primary series at 3 months for the first dose and 5 months for the second dose was recommended under the NCIS. However, 3 doses in the primary series were recommended by the manufacturers. Thus, it was permissible to give an additional dose at 2 months of age, followed by the second and third doses at 3-4 months and 5-6 months respectively. To account for this, in this study we considered the recommended age of administration for the PCV vaccination to be 2-4 months for the first dose and 3-6 months for the second dose. Regardless of the number of doses received in the primary series, the booster dose of PCV was recommended at 12 months of age. We also included 3 primary doses and 1 booster dose of Hib in our analysis, taken as part of combination vaccines. We analysed the receipt of these vaccine components according to the acceptable and recommended ages based on the 2011 NCIS; the NCIS after 2013 did not differ in recommended ages for each vaccine dose except for the introduction of Hib and combination vaccines (Table 1).

Because the number of days in a month varies, we converted the age recommended in months and weeks, to age in days, with any recommended age expressed in a range, starting with the fewest number of days possible in any given month and ending with the greatest number of days possible. Hence, for example, a recommended age of 1 month would equate to an age range of 28 through 61 days. This interpretation would reflect real-life interpretations of what a recommended age could mean. For each vaccine dose, we analysed the percentages of children receiving vaccinations according to 5 time frames: 1) too early to be considered valid (invalid), 2) timely, 3) late, 4) very late and 5) never. The American Advisory Committee on Immunization Practices allows a grace period of up to 4 days before the minimum acceptable age for the administration of vaccination to be considered valid. Hence, “Too early to be considered valid” is defined by more than 4 days before the start of the minimum acceptable age. “Timely” is defined based on the grouping of criteria for both “acceptably early” and “within the recommended time frame”, where “acceptably early” is defined as from 4 days before the start of the minimum age required until the start of the recommended age range and “within the recommended time frame” is defined by the recommended age range in the National Childhood Immunization Schedule. “Late” is defined as from the end of the recommended age range up to 6 months (defined as 180 days) after the end of the recommended age range. “Very late” is defined as beyond 6 months (defined as 180 days) after the end of the recommended age. “Never” is defined as not receiving the vaccine dose by age 24 months.

Based on the above time frames, we subsequently categorized the children into 2 groups as defined by timely and non-timely (i.e. too early, late, very late and never) vaccine receipts. We quantified the total doses of timely receipt of any vaccine for each child (range 1-21 doses). We also analysed the percentages of children with non-timely vaccine receipt of each and all vaccine series (excluded single dose of BCG vaccine).

**Statistical analysis**

Statistical analyses were performed using IBM SPSS statistics, Version 19 (USA). Categorical data were presented as frequencies and percentages, while continuous data were presented as means and standard deviations (SD). Independent Student *t*-tests and Chi-squared tests were used to compare continuous and categorical characteristics between groups of children with non-timely receipt of all vaccine series vs. counterparts.

Multivariable logistic regression analysis was performed to examine factors associated with the lack of timely receipt of all series of vaccines by age 24 months. We determined these potential factors based on clinical judgement, literature review (Luman et al. 2002; Walton et al. 2017) and by using a directed acyclic graph. As PCV vaccine was newly introduced at that time and could be unfamiliar among the population, we conducted a sensitivity analysis by excluding PCV vaccine series in the examination of factors to be associated with non-timely receipt of vaccine series. Results were expressed as odds ratios (OR), with associated 95% confidence intervals (CI). Additionally, we also performed ordinal logistic regression (cauchit link) by treating the outcome as six ordinal levels based on the number of non-timely receipt of vaccine series (i.e. 0-1, 2, 3, 4, 5 and 6 series). Result was expressed as β coefficient and 95% CI, and interpreted based on the direction of relationship.

**Results**

Of 1237 enrolled mothers with singleton pregnancies, 66 mothers withdraw from the study by delivery and 69 mothers did not agree for their child’s vaccination data to be retrieved from the NIR, leaving 1058 children who were eligible for this study. Out of these children, we excluded 29 who had received at least 1 vaccine dose overseas, as the vaccine schedules in other countries may vary from the NCIS in Singapore. We also excluded 150 children from the analysis due to discrepant data, whereby the NIR contained a record of the second dose of a particular vaccination series but did not contain a record of the first. For complete case analysis, we excluded children in whom maternal anthropometric and socio-demographic data were unavailable. We included 782 children born between November 2009 and July 2011 with complete data for analysis (Fig. 1).

**Participant characteristics**

Table 2 summarizes the participant characteristics. The majority were of Chinese ethnicity (51.0%), educated below university level (71.2%), from middle-income family (58.3%) and did not have pre-existing type 2 diabetes or hypertension (97.1%). The mean gestational age at birth was 38.3 (SD 1.5) weeks, with 8.3% born with low birth weight. Most children received vaccine injections at public clinics (89.3%). Compared to children receiving at least one vaccine series on time, those with non-timely receipt of all vaccine series were more likely to be of Malay (37.7% vs. 29.2%) or Indian (26.2% or 17.0%) ethnicity, to come from a low-income family (26.2% vs. 15.3% with household income ≤1999 Singapore dollars), to have more siblings (13.1% vs. 5.8% with ≥4 children), to be born as low birth weight babies (15.6% vs. 7.0%) with a shorter gestational age at birth (37.8 vs. 38.4 weeks), and were less likely to receive vaccines from public clinics (81.1% vs. 90.8%).

**Timeliness of vaccinations**

Table 3 shows the numbers and percentages of children who received each individual and/ or combined vaccine doses within different time frames. Timeliness and coverage for birth vaccine doses i.e. BCG and first dose of Hep B vaccine was nearly 100%. For Hep B, DTaP and polio vaccines, where the schedule begins before 6 months of age, there was a downward trend for timeliness and upward trend for low coverage with subsequent vaccine doses. In contrast, for MMR, where the schedule begins at 12 months of age, timeliness was very low for the first dose (14.8%) and higher (50.6%) for the second dose. However, MMR first dose coverage by 2 years old was 96.3% although second dose coverage remained low at 81.5%. Timeliness and coverage for both PCV and HiB vaccines in the cohort were low, with PCV vaccine being the least timely of the two.

Overall, 0.6% children received at least 1 dose of vaccine too early. Although all children received at least 1 dose of any vaccine on time; 92.8% children had at least 1 or more doses of any vaccine that were administered later than recommended age window. In addition, 81.2% children had yet to receive at least 1 or more doses of recommended vaccines by the age of 24 months. Fig. 2 presents the distribution of children according to their total doses of vaccines received timely (1-21 doses) by age 24 months. More than 50% of children (n=432) received at least 15 doses of vaccines on time, but only 0.3% (n=2) children received all vaccine doses on time.

Table 4 shows the numbers and percentages of children with non-timely receipt of vaccine series by age 24 months. For Hep B vaccine, the non-timely receipt rate for any dose within the series was the lowest at 28.1%. This was followed by Polio vaccine series, where 34.3% children received at least 1 out of 4 vaccine doses in a non-timely manner. The PCV vaccine series had the highest out of window receipt rate, where 94.6% children received first and/ or second doses at inappropriate ages. Similarly, Hep B vaccine had the lowest rate (0.3%), while PCV vaccine had the highest rate (61.9%) of non-timely receipt of all doses within the series. In total, there were 15.6% children who received all vaccine series outside the recommended ages. For children who received the first vaccine dose in the series on time, less than one-third of them had their subsequent vaccine doses outside the recommended ages (16.4% for MMR vaccine series to 30.9% for DTaP vaccine series), except for PCV vaccine series (85.7%) (Fig. 3).

**Factors associated with timeliness of vaccinations**

Table 5 shows the factors associated with non-timely receipt of all vaccine series in children by age 24 months. In multivariable logistic regression analysis, women aged ≤35 years (OR= 2.00; 95% CI 1.09, 3.66), Malay (1.71; 1.01, 2.89) or Indian ethnicity (2.06; 1.19, 3.59), low monthly household income (1.91; 1.14, 3.18), having at least four children (3.46; 1.62, 7.38), private (3.42; 1.80, 6.48) and multiple vaccination providers (3.91; 1.23, 12.48) were significantly associated with increased odds of receiving all vaccine series outside recommended ages. A trend of association was also observed between low birth weight and an increased odds of non-timely receipt of all vaccine series (2.00; 0.95, 4.23). In the sensitivity analysis excluding PCV vaccine, no substantial changes in ORs of predictive factors were found (Online Resource 1). When additional analysis was performed using the ordinal logistic regression by treating the number of non-timely receipt of vaccine series as an ordinal outcome variable, similar trends of associations were observed (Online Resource 2).

**Discussion**

In this cohort of children, approximately 9 in 10 children had a delay in the recommended time to receive at least 1 dose of vaccine by 2 years of age. Approximately 1 in 7 children received all series of vaccine outside the recommended age ranges. Maternal age, Malay or Indian ethnicity, household income, number of children and type of vaccine provider were associated with the odds of receiving all series of vaccine outside the recommended ages. We also found that when children received the first dose of vaccine in each vaccination series in a timely manner, they were less likely to receive non-timely vaccinations for subsequent vaccine doses.

Timely vaccinations provide maximal protection to children as early as possible (Centers for Disease Control and Prevention 2011). Proportions of children with on-time vaccine receipt were the highest for BCG and the first dose of Hep B vaccine, likely because these vaccines are offered at hospitals where almost all deliveries take place in Singapore. Few children had doses administered at too young an age to be considered valid, which can lead to a suboptimal immune response (Centers for Disease Control and Prevention 2011). This may require vaccine re-administration that can potentially increase the risk of adverse reactions (Feikema et al. 2000; Centers for Disease Control and Prevention 2011).

We found that delay in age-appropriate vaccination was highest for MMR and PCV vaccine doses. These were possibly caused by two successive changes in the NCIS that occurred in 2009 (introduction of PCV) and 2011 (change in MMR schedule due to a resurgence of measles in the community) (Ministry of Health 2015). The lack of timeliness for PCV vaccination may in part be due to a lack of familiarity with a new vaccine, where the public and providers are gaining understanding for its need. As for the lack of timeliness for MMR vaccination, there may have inadequate communication for the rationale of bringing both doses to less than age 2 years, leading to concern of vaccine crowding and poor timeliness.

Our data concur with that published by Luman et al. (2002) and Odutola et al. (2015), suggesting that a significant proportion of children in many countries may not be receiving their vaccinations in a timely manner. Overall, there was a decline in the receipt of age-appropriate vaccines as children grew older, as found by other studies (Odutola et al. 2015; Walton et al. 2017). The receipt of vaccine doses from 12 months onwards was substantially delayed among children. Potentially, as the child gets older the mother or caregiver may be pre-occupied with more job-related matters and/ or household duties, thereby forgetting or keep delaying vaccination appointments for their child (Odutola et al. 2015). Generally, immunization delay could negatively impact the receipt of other preventive health care services (Rodewald et al. 1995). Additionally, delayed administration of the first vaccine dose has been shown to predict the subsequent incomplete immunization (Guyer et al. 1994), in line with our findings.

This study showed that children born to mothers of young age have higher odds of not receiving vaccines at appropriate ages, as supported by others (Luman et al. 2002; Restivo et al. 2015). This may be possibly due to lack of experience or knowledge in child vaccinations (Ventola 2016). We also found that Malay and Indian children have higher odds of not receiving all series of vaccines on time, highlighting the need to have targeted interventions for these population groups. Our findings are in agreement with others that vaccination rates are influenced by socio-economic status (Odutola 2015; Ventola 2016). Children from low income families may have competing needs, fall sick more frequently and face difficulties in getting timely vaccinations. We also noted that children with more siblings in the household were less likely to receive vaccinations on time, which could be due to divided attention and lack of parental time (Luman et al. 2002; Restivo et al. 2015; Walton et al., 2017). Children of low birth weight have been reported to be at risk of delayed vaccinations (Davis et al. 1999), though our findings required further confirmation. These children may have been born with health issues that required long-term clinical care, where the treatment procedure could have disrupted the vaccination timeline.

Finally, receiving vaccination from private or multiple vaccine providers was associated with increased odds of receiving all series of vaccines outside the recommended age ranges. Owing to the longer operating hours of the clinics from private than public sector providers, parents who had missed their child vaccination in the public clinics may visit private clinics for vaccinations after working hours. It is also possible that parents may perceive private sector providers as being more accessible compared to public sector clinics, and paradoxically this may reduce their motivation to have timely vaccinations. Meanwhile, the finding as for multiple providers may be due to “doctor-shopping” behaviour.

This is the first study performed to explore the timeliness and associated factors of childhood vaccinations in Singapore. Our study is limited by the sample that was obtained from a prospective cohort which might not be representative of the children population in Singapore. However, coverage estimates for most vaccines in this study were comparable with the data from NCIS report (Ministry of Health 2015), suggesting our findings may still be valid. In addition, our findings are limited by the lack of information on environmental conditions, and parental knowledge and attitude on the importance of timely vaccination, which restricted our ability to identify specific components in the effort to improve compliance. Nevertheless, our study provides useful baseline information with which to compare future local studies on timeliness of vaccination, and to implement related interventions.

**Conclusion**

By 24 months of age, while coverage rates were high, the overall compliance with recommended vaccination schedules at specific ages was low. An unacceptably high proportion of children had a delay in the receipt of at least 1 dose of their vaccines and a number of them experienced delays receiving all series of vaccine outside the recommended age ranges during the first 2 years of their lives. Further studies and interventions are urgently needed locally, to improve age-appropriate vaccination rates for optimal protection against vaccine-preventable diseases.

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**Compliance with Ethical Standards**

**Conflicts of Interest**

KMG, YSC and FY have received reimbursement for speaking at conferences sponsored by companies selling nutritional products. KMG and YSC are part of an academic consortium that has received research funding from Abbott Nutrition, Nestle and Danone. Other authors declared that they have no conflict of interest.

**Ethical Approval**

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed Consent**

Informed written consent was obtained from all mothers of infants included in the study.

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**Fig. 1**

*Flow chart of the study*

**Fig. 2**

*Total dose of timely receipt of any vaccine in children by age 24 months*

**Fig. 3**

*Non-timely administration of subsequent vaccine doses based on receipt of first vaccine dose on time. HepB, Hepatitis B vaccine; DTaP, diphtheria, tetanus toxoid and acellular pertussis vaccine; Polio [oral polio vaccine (OPV) or inactivated polio vaccine (IPV)]; MMR, mumps, measles and rubella vaccine; PCV, pneumococcal conjugate vaccine; HiB, Haemophilus influenzae type B vaccine*

**Supplementary Materials:**

**Online Resource 1**

*Factors associated with non-timely receipt of all vaccine series in children by age 24 months, excluding PCV vaccine (n=782)*

**Online Resource 2**

*Factors associated with the number of non-timely receipt of vaccine series in children by age 24 months (n=782)*