39th year of publication

Epidemiological News Bulletin

QUARTERLY

APRIL - JUNE 2013 VOL. 39 NO. 2 A PUBLICATION OF THE MINISTRY OF HEALTH, SINGAPORE

CONTENTS

Suggested citation:
Ministry of Health, Singapore. [Article title]. Epidemiol News Bull [Year]; [Vol]:[inclusive page numbers]

MOH Weekly Infectious Diseases Bulletin
http://www.moh.gov.sg/content/moh_web/home/statistics/infectiousDiseasesStatistics/weekly_infectiousdiseasesbulletin.html

ISSN 0218-0103

http://www.moh.gov.sg/content/moh_web/home/Publications/epidemiological_newsbulletin.html

Immune status of the childhood population against vaccine-preventable diseases in Singapore

In Singapore, seropidemiological surveys were conducted periodically to assess the changing herd immunity of the population against various vaccine-preventable diseases. Another national seroprevalence survey was conducted from August 2008 to July 2010 to determine the immune status of children and adolescents against measles, mumps, rubella, hepatitis B, poliomyelitis (polio), diphtheria and pertussis.

Methods and materials

Residual sera were obtained from Singapore citizens and permanent residents of the three major ethnic groups aged between 1 year and 17 years attending either inpatient services or day surgery at Kandang Kerbau Women's and Children's Hospital and National University Hospital. The blood samples were collected for routine biochemical investigations by the diagnostic laboratories. Children known to be immunocompromised, on immunosupressive therapy, or who had been diagnosed with infectious diseases such as measles, mumps, rubella, chickenpox, diphtheria, pertussis, poliomyelitis and hepatitis B were excluded. Vaccination history of the subjects was obtained from the National Immunisation Registry (NIR), Health Promotion Board.

A total of 1200 serum samples were collected, comprising 400 in each of the three age groups 1-6, 7-12, and 13-17 years. The age, gender and ethnic distribution of the subjects was comparable to that of the Singapore resident population aged 1-17 years in 2009.

Laboratory assays

The IgG antibody against measles and mumps was determined using enzyme immunoassay (Euroimmun kit, Germany). A titre of 250 mIU/mL or greater was considered to be immune against measles, while a titre of 20 RU/mL or greater indicated immunity to mumps. The rubella IgG antibody was measured using chemiluminescent immunoassay (Abbott Architect, Abbott Laboratories, USA). A titre of 10 IU/mL or greater was considered to be immune.

Hepatitis B surface antigen (HBsAg) and antibody against HBsAg (anti-HBs) were tested by the chemiluminescence immunoassay method (Abbott Architect, Abbott Laboratories, USA). Children with anti-HBs levels ≥10 mIU/ml were considered to have immunity to hepatitis B virus (HBV).

Human IgG antibodies against *Bordetella pertussis*, diphtheria toxoid, and poliovirus (all 3 serotypes simultaneously) were measured by using commercial enzyme-linked immunosorbent assay kits (IBL-America, Minneapolis, MN, USA), in accordance with the manufacturer's instructions. The quantitative cut-off IgG antibody values for immunity were 0.1 IU/ml for diphtheria, 22 U/ml for pertussis, and 12 U/ml for poliovirus.

Statistical analyses were performed using SPSS software, version 19. A p value < 0.05 was considered statistically significant.

Results

Measles[1]

The overall prevalence of antibody against measles among subjects aged 1-17 years was 83.1% (95% CI, 80.9 – 85.1%) (*Table 1*). The seroprevalence in adolescents aged 13-17 years (75.8%) was significantly lower than that of the other two younger

Table 1
Prevalence (%) of antibody against measles, mumps, rubella, hepatitis B*, polio, diphtheria and pertussis by age group, gender, and ethnic group

	Measles	Mumps	Rubella	Hepatitis B	Polio	Diphtheria	Pertussis
Overall	83.1	71.8	88.5	40.0	92.3	99.4	60.8
Age group (years)							
1 - 6	84.3	61.5	87.3	63.8	89.3	98.5	64.0
7 - 12	89.3	73.3	90.0	32.8	93.3	100.0	63.3
13- 17	75.8	80.5	88.3	23.5	94.3	99.8	55.0
Gender							
Male	84.1	70.2	88.9	42.6	91.2	99.5	62.8
Female	82.1	73.2	88.1	37.5	93.2	99.4	58.9
Ethnic group							
Chinese	84.8	76.3	90.4	40.6	91.5	99.4	62.0
Malay	77.9	59.4	82.9	37.0	93.4	99.7	59.5
Indian	83.7	70.5	89.1	42.6	94.3	99.2	55.7

* anti-HBs ≥10 mIU/ml/

groups (p=0.005), while the seroprevalence in the 1-6 year olds (84.3%) was also significantly lower than that of the 7-12 year olds (89.3%) (p<0.05). The seroprevalence increased from 62.3% in one-year olds to between 83.3% and 95.6% in children aged 2-13 years, followed by a dip to 64.1% in those aged 15 years before it increased again to 83.3% in adolescents aged 17 years.

There was no significant difference in the seroprevalence by gender (84.1% in males vs. 82.1% in females; p=0.372). The seroprevalence of Malays (77.9%) was significantly lower compared to that of Chinese (p=0.008), while it was similar to that of Indians (p=0.176). The seroprevalence of Chinese (84.8%) and Indians (83.7%) was similar (p=0.750). The difference in age-standardized seroprevalence of Chinese and Malays was also significant (p=0.016).

Mumps[1]

The overall prevalence of antibody to mumps was 71.8% (95% CI, 69.1 – 74.2%) (*Table 1*). The seroprevalence increased significantly with age from 61.5% in the 1-6 year olds to 73.3% in the 7-12 year olds and 80.5% in adolescents aged 13-17 years (test for trend, p<0.0005). The seroprevalence increased from 47.8% in one-year olds to between 55.2% and 71.1% in children aged 2-6 years, followed by a dip to 64.5% in those aged 10 years before it increased again to between 76.7% and 86.7% in adolescents aged 12-17 years. The seroprevalence was lower than that of measles and rubella among children aged 1 to 13 years.

The prevalence of mumps antibody was 70.2% among males and 73.2% among females, with no significant difference detected (p=0.249). However, there were significant differences in the seroprevalence by ethnic group (p<0.0005). The prevalence of Malays (59.4%) was significantly lower compared to that of Chinese (p<0.005) and Indians (p<0.031). Similar differences were observed in age-standardized seroprevalence of Malays compared to that of Chinese (p<0.005) and Indians (p=0.008). The prevalence of Chinese (76.3%) and Indians (70.5%) was similar (p=0.156).

Rubella[1]

The overall prevalence of antibody against rubella was 88.5% (95% CI, 86.6 – 0.2%) (*Table 1*). The seroprevalence was not significantly different among the three age groups; 87.3% in the 1-6 year olds, 90.0% in the 7-12 year olds and 88.3% in the 13-17 year olds. The seroprevalence increased from 59.4% in one-year olds to about 92.6% in children aged 2-14 years, followed by a dip to about 81.0% in adolescents aged 15-17 years.

No significant difference by gender was observed (88.9% in males vs. 88.1% in females; p=0.696). The seroprevalence of Malays (82.9%) was significantly lower compared to that of Chinese (p<0.005), while it was similar to that of Indians (p=0.102). The age-standardized seroprevalence of Malays was also significantly lower compared to that of Chinese (p=0.001). The seroprevalence of Chinese and Indians was similar at 90.4% and 89.1%, respectively (p=0.662).

Hepatitis B[2]

The prevalence of HBsAg was 0.3% (4/1200) (95% CI, 0.1 – 0.9%) among children and adolescents aged 1-17 years. The four children tested positive for HBsAg were all Chinese, and one child was a girl in the age group of 7-12 years, and other three were boys in the age group of 13-17 years. Older age was

not significantly associated with higher prevalence of HBsAg (test for trend, p=0.066). None of the children aged 1-6 years was positive for HBsAg, while the increase from 0.3% (95% CI, 0.04 – 1.4%) in children aged 7-12 years to 0.8% (95% CI, 0.3 – 2.2%) in adolescents aged 13-17 years was also not significant (p=0.805).

The prevalence of HBsAg was 0.5% (3/584) among males and 0.2% (1/616) among females, which was not statistically different (p=0.362). The differences in the prevalence of HBsAg among the three ethnic groups were also not statistically significant (p=0.353).

The proportion of children and adolescents aged 1-17 year with immunity to HBV was 40.0% (95% CI, 37.3 – 42.8%) (*Table 1*). Older age was significantly associated with a lower proportion with immunity to HBV (test for trend, p<0.0005). The proportion with immunity to HBV decreased significantly from 63.8% (95% CI, 58.9 – 68.3%) in children aged 1-6 years to 32.8% (95% CI, 28.3 – 37.5%) in 7-12 year olds, and 23.5% (95% CI, 19.6 – 27.9%) in 13-17 year olds.

The difference in the proportion with immunity to HBV between the genders was not statistically significant (p=0.077); 42.6% among males had immunity to HBV compared to 37.5% among females. The differences in the proportion with immunity to HBV among the three ethnic groups were also not statistically significant (p=0.460); 40.6% (321/790) for Chinese, 37.0% (104/281) for Malays, and 42.6% (55/129) for Indians.

The proportion with immunity to HBV by age showed a general decreasing trend. Among children aged 1-6 years, the proportion with immunity to HBV decreased at an average of 10% per year. The proportion with immunity to HBV among those aged 8-16 years reached a steady state at approximately 31%. While there was a drastic dip in the proportion with immunity to HBV among adolescents aged 17 years, the number of samples was the smallest by individual age.

The mother of the girl who tested positive for HBsAg was a known hepatitis B carrier, and there was no record of vaccination against hepatitis B found in the NIR for the child. Of the three boys tested positive for HBsAg, one child had the first dose of the hepatitis B vaccine at birth, the second dose at one month, and the third dose at 6 months; one child had the first dose at 8 months, the second dose at 9 months, and the third dose at 14 months; while one child had the first dose when he was 3 years old, the second dose one month later after the first dose, and the third dose when he was about 4 years old.

Polio[3]

The seroprevalence of antibodies against all three serotypes of poliovirus among Singapore children was 92.3% (95% CI, 90.6 – 93.6%). It increased with age from 89.3% in children aged 1-6 years to 93.3% in 7-12 years and 94.3% in 13-17 years (p=0.008) (*Table 1*). The prevalence rate of poliovirus antibodies generally remained at around 90%. The gender-specific seroprevalence of poliovirus antibodies was 93.2% for females and 91.2% for males, and were not significantly different (p=0.207). The seroprevalence for Indians was the highest at 94.3%, but this was not significantly different from that of Chinese (91.5%) and Malays (93.4%) (p=0.395).

Diphtheria[3]

The survey revealed an overall immunity level of 99.4% (95% CI, 98.8 – 99.7%) for diphtheria, and the seroprevalence was uniformly very high between genders and among the three ethnic groups (*Table 1*).

Pertussis[3]

The presence of pertussis antibody was demonstrated in only 60.8% (95% CI, 58.0 – 63.5%) of the subjects. The seroprevalence decreased significantly from 64.0% in subjects aged 1-6 years to 63.3% in those aged 7-12 years, and further down to 55.0% in subjects aged 13-17 years (p=0.009) (*Table 1*). Two peaks were observed at the age of 2 years and 11 years, corresponding with the booster doses given to children at 18 months and 10-11 years. No significant differences in the seroprevalence of pertussis for the two genders (p=0.168) and the three ethnic groups (p=0.374) were observed.

Seroprevalence among vaccinated subjects

Measles, mumps and rubella

Of the 1200 subjects, 92.2% had received at least one dose of vaccine against measles, 91.7% against mumps and 91.8% against rubella, prior to the collection of their residual samples. These subjects were either vaccinated with the monovalent vaccine or with the combination measles, mumps and rubella (MMR) or MMR-varicella vaccines. The prevalence of antibody against measles, mumps and rubella (MMR) were all significantly higher among subjects with a past history of vaccination compared to those with an unknown or no history of vaccination (p<0.005). For measles, it was 86.5% vs 42.6%; for mumps, it was 75.3% vs 33.0%; and for rubella, it was 92.9% vs 39.4%.

A total of 1083 subjects (90.3%) were known to have received only the MMR vaccine. Of these subjects, 544 (50.2%) had only received one dose, while the others who had received 2 doses were aged 6 years or older. The seroprevalence of all of MMR was lowest in those who were last vaccinated 10 years or longer. For measles, it declined from 89.9% at one year post-vaccination, to 79.6% at 3 to 4 years post-vaccination, and increased to between 84.6% and 92.3% at 5 to 9 years post-vaccination, before it dropped to 67.6% at 10 years or longer post-vaccination.

The prevalence of antibody against mumps decreased significantly since the date of the last MMR vaccination (p<0.0005). It decreased from 74.4% at 7 years or longer post-vaccination to below 50% at 10 years or longer post-vaccination.

The post-vaccination seroprevalence of rubella was highest compared to measles and mumps. It was between 88.8% and 99.3% within 9 years post-vaccination but declined to 78.4% at 10 years or longer post-vaccination.

Hepatitis B

A high proportion (96.6%) of the population surveyed had been vaccinated against hepatitis B. In total, there were 41 subjects with an unknown or no history of vaccination. The proportion with immunity to HBV was 39.7% among 1159 subjects with history of vaccination prior to the collection of their residual samples, which was not statistically different from 48.8% among 41 subjects with an unknown or no history of vaccination (p=0.709).

Pertussis

Of the 1200 children, 91% were known to have completed at least the primary course (three doses) of pertussis vaccination by the age of 2 years. Among these 1092 vaccinated subjects, the seroprevalence of pertussis decreased with time since vaccination. The seroprevalence was 85.0% (95% CI, 79.7 – 89.2%) among children who received their last pertussis vaccination within a year prior to the study, but decreased to 75.0% (95% CI, 64.5 – 83.2%) in the group who had their last vaccination about one year prior to the study. Among children who were given their last pertussis vaccination about two and three years prior to the study, the seroprevalence was 63.1% (95% CI, 50.9 – 73.8%) and 59.4% (95% CI, 47.2 – 70.5%), respectively. The seroprevalence remained at about 50% in those children who had their last pertussis vaccination four years or longer prior to the study.

Comments

The national childhood immunisation programme is effective in raising the herd immunity of the childhood population against MMR, hepatitis B, polio, diphtheria and pertussis. The high proportion of the study population with vaccination records is consistent with that of the national immunisation coverage rate. As expected, seroprevalence of the vaccinated children declined over time, and it is important to ensure that booster doses are administered.

For MMR, the seroprevalence of rubella was the highest and that of mumps was the lowest. This was somewhat reflected in the age-specific incidence of these diseases. The incidence of rubella among children aged below 15 years decreased from 6.6 per 100,000 in 2008 to 2.8 per 100,000 in 2010. The incidence of mumps in this age group decreased from 54.2 per 100,000 to 31.1 per 100,000 in 2010. On the other hand, the incidence of measles among children aged below 15 years was 3.9 per 100,000 in 2010, which was more than 3 times that of 1.2 per 100,000 in 2008. The highest incidence of measles was in children below 5 years of age, in particular, infants below 12 months of age who are not included in the vaccination programme. With effect from 1 December 2011, the first dose of MMR vaccine was brought forward from 15 months to 12 months of age so as to protect unvaccinated children aged 12-15 months. Furthermore, to reduce the number of children which may not respond to the first dose of MMR vaccination, the second dose was brought forward from 6-7 years to between 15 and 18 months of age. With this change in the immunization schedule, children would have received 2 doses of MMR vaccine by 2 years of age, thus reducing the pool of susceptibles among young children.

The successful implementation of the national childhood hepatitis B immunisation programme has virtually eliminated acute hepatitis B and resulted in a low HBsAg prevalence among children and adolescents.

In the case of polio and diphtheria, indigenous cases have been eliminated. On the other hand, a total of 22 pertussis cases were reported between 1993 and 2006[4]. A sharp increase in the notification of pertussis was observed in 2007 and 2008, followed by a decline in 2009 and 2010. The peak incidence of pertussis occurred in infants aged less than 6 months, and about 90% of the reported cases occurred in this age group.

References

1. *Ang LW, Lai FY, Tey SH et al. Prevalence of antibodies against measles, mumps and rubella in the childhood population in Singapore. Epidemiol Infect 2012:1-10. doi:10.1017/S0950268812002130.*
2. *Ang LW, Tey SH, Cutter J et al. Seroprevalence of hepatitis B virus infection among Singapore children and adolescents in Singapore, 2008-2010. J Med Virol 2013;85:583-8. doi:10.1002/jmv.23496.*
3. *Lai FY, Thoon KC, Ang LW et al. Comparative seroepidemiology of pertussis, diphtheria and poliovirus antibodies in Singapore: waning pertussis immunity in a highly immunised population and the need for adolescent booster doses. Vaccine 2012;30:3566-71.*
4. *Liew F, Ang LW, Cutter J et al. Evaluation on the effectiveness of the National Childhood Immunisation Programme in Singapore. Ann Aca Med Singapore 2010; 39:532-41.*

Replacement of oral polio vaccine with inactivated polio vaccine and inclusion of *Haemophilus influenzae* type b vaccine in the national childhood immunisation schedule

Polio in Singapore

Singapore, along with the Western Pacific region, was certified free of poliomyelitis (polio) by the World Health Organization (WHO) on 29 Oct 2000 following the introduction of polio vaccination in Singapore in 1962[1]. With more countries being declared polio-free, global eradication of polio is becoming increasingly likely. As of Jan 2012, only three countries in the world remain polio-endemic (Afghanistan, Nigeria and Pakistan)[2].

Rationale for the use of oral polio vaccine (OPV)

Contact immunity

The trivalent OPV contains live-attenuated strains of all three poliovirus subtypes. Following the first dose, there is short-term shedding of the vaccine strains in the stools of the immunised person. In areas of poor hygiene and sanitation, this rapidly transmits the vaccine strains and hence immunity to contacts of the vaccinated. This is useful in populations with poor immune coverage to polio.

Intestinal immunity

The OPV produces superior intestinal immune responses[3]. This is important to interrupting the transmission of the poliovirus which is spread by the faeco-oral route. Intestinal immunity will prevent subsequent infection or invasion by the poliovirus.

Ease of administration

Aside from the low cost of the vaccine, the OPV can be administered easily through the oral route. This is important especially for developing countries as it obviates the need for sterile equipment for injections.

Risks associated with OPV

Vaccine-associated paralytic poliomyelitis (VAPP)

Although the OPV was designed to prevent polio infections, it can paradoxically cause polio infections not only in the vaccinated but also in their close contacts. Following the first oral dose of the live-attenuated polio vaccine, the poliovirus replicate in the gut of immunocompetent individuals. Rever-

sion of attenuating mutations present in the vaccine strains can lead to VAPP in the vaccinated as well as their close contacts.

The WHO reports a low incidence rate of VAPP (one case per million). However, higher rates have been reported in the US (one per 750,000)[4], in England (one per 400,000) and in India (one per 143,000)[5]. The higher rate of VAPP in India has been postulated to be due to the higher usage of OPV[6].

Locally, no indigenous cases of VAPP have been reported post-certification, except for an imported case which could have been vaccine-related[1].

Outbreaks from vaccine-derived poliovirus (VDPV)

Although the OPV uses attenuated viruses, it has the potential to mutate to become more transmissible and virulent. VDPV strains which have regained their virulence and transmissibility can lead to polio outbreaks in pockets of populations with poor immunity.

Globally, outbreaks of VDPV have been well documented. More recent outbreaks have been reported in the Philippines, China and Nigeria. In these outbreaks, the VDPV were estimated to have been circulating for at least one to two years before they were detected in clusters of acute flaccid paralysis.

Concerns over the isolation of VDPV in outbreaks and VAPP have prompted WHO, in its 2004-2008 Global Polio Eradication Initiative Strategic Plan, to recommend ceasing OPV administration as soon as possible after interruption of wild-type poliovirus circulation[7].

Inactivated polio vaccine (IPV)

Although the global decline in polio would not have been possible without the OPV, American, European and Australian governments have already stopped routine immunisations with OPV. In recent years, a number of countries in the Western Pacific region had made a transition to an IPV immunisation schedule (e.g. Brunei Darussalam, Japan, and Malaysia)[8].

In Singapore, although IPV had been available only on request and at full cost, more doses of IPV than OPV had been administered. The proportion of IPV administered had steadily increased from 62% in 2005 to 75% in 2009 (excluding vaccinations administered by School Health Services)[9].

Immunogenicity

IPV produces IgG-mediated immunity which prevents the progression of polio infection to viraemia and hence protects the motor neurons against paralysis. Numerous clinical trials using IPV alone or in combination vaccines have been conducted.

A randomised controlled trial commissioned by the WHO in 2001 reported approximately 90% seroconversion rates in combination vaccines[10]. Subsequent studies confirmed that 99%-100% of children develop protective antibodies to all three types of poliovirus after three doses of IPV[11].

Herd immunity

Concerns exist over the lower levels of mucosal immunity induced by IPV and the inability of inactivated viruses to spread to unvaccinated contacts as OPV does. The IPV does induce an intestinal immune response

although it is weaker compared to that of OPV; the pharyngeal immune responses induced by both types of vaccines are similar[2]. Experiences with IPV in developed countries have led to the postulation that the intestinal immune response may not be as important as perceived. Rather, the elimination of pharyngeal shedding achieved by IPV may be more important for preventing the transmission of the wild virus[12].

It is also conceivable that the marked reduction in pharyngeal shedding and, to a lesser extent, intestinal viral excretion achieved by IPV can still limit the spread of polio in the community and contribute to herd immunity.

Safety

An extensive review by the Institute of Medicine has shown no increased risk for serious adverse events with the use of IPV[13].

Switch from OPV to IPV

In recommending the switch from OPV to IPV, the Ministry of Health (MOH)'s Expert Committee on Immunisation (ECI) took into considerations the following points:

Increasing foreign worker population

As of Dec 2012, Singapore was reported to have 952,100 work permit holders[14]. This number has risen over the years. Without any form of screening for exposure or vaccination, cohorts with poor polio immunity can accumulate in Singapore. The resultant pockets of polio-susceptible individuals who often reside in close proximity, increases the local risk of VAPP and circulation of VDPVs if OPV continues to be used locally.

High standards of healthcare

Having the benefit of learning from the experiences of other countries which have adopted IPV immunisation schedules, and considering MOH's mission to pursue medical excellence, it would be unacceptable for even a single case of VAPP or an outbreak arising from VDPV to occur in Singapore. The loss in public and international confidence in Singapore's healthcare standards would be hard to regain.

Recommendation

The ECI recommended that the all-OPV vaccination schedule be replaced with the sequential IPV-OPV schedule. The advantage of this approach is that it significantly reduces the risk of VAPP, as the risk is highest with the first dose of OPV, while preserving the purported benefits of the OPV. The first IPV dose also reduces the risk of VAPP significantly by preventing viraemia from subsequent OPV doses.

The recommended vaccination schedule for polio vaccine is as follows:

a) A four-dose IPV schedule with three primary doses to be given at 3, 4 and 5 months of age and the first booster dose at 18 months of age;

b) A fifth dose using OPV (second booster) at 10-11 years of age (Primary 5).

The IPV currently registered in Singapore consist of the standalone IPV (Imovax [Sanofi-Aventis]) and two types of combination vaccines: the combined diphtheria, tetanus, acellular pertussis, IPV and *Haemophilus influenzae* type b vaccine - DTaP-IPV-Hib (Infanrix IPV+Hib [GSK] and Pediacel [Sanofi-Aventis]); and DTaP-IPV-Hib combined with hepatitis B vaccine - DTaP-IPV-Hib-HepB (Infanrix Hexa [GSK])[15].

Haemophilus influenzae type b (Hib) vaccine

Hib disease

Hib is a gram-negative aerobic coccobacillus that lives in the human nasopharynx and causes a spectrum of diseases which are important causes of morbidity and mortality, especially in young children below five years of age. Only a small fraction of those who harbour this organism on their respiratory mucosa will subsequently develop clinical disease. However, as the main mode of transmission is via droplets from nasopharyngeal secretions, those who carry it are important disseminators of the disease.

The most serious manifestation of Hib disease is meningitis and pneumonia. This is seen mainly in children below five years of age, with the disease burden highest among those aged between four months and 18 months. Immunisation against Hib is currently available to protect against the disease. The WHO strongly encourages the inclusion of conjugate Hib vaccines into all routine infant immunisation programmes. In countries where it has been implemented; e.g. USA, UK, New Zealand and Australia, there has been a decline in the incidence of Hib related diseases. Studies have also shown that nasopharyngeal colonization of Hib drops dramatically in populations where Hib immunisation has achieved high coverage, as a consequence of the herd immunity effect induced by the conjugate vaccines.

However, there is also concern about the long-term effectiveness of Hib immunisation programmes and possible disease replacement by other *H. Influenzae* strains[16].

Hib vaccination has been incorporated into the childhood immunisation programmes of a number of countries in the Western Pacific region. This has been achieved through the support of GAVI Alliance (e.g. Cambodia, Lao People's Democratic Republic, Mongolia, Myanmar, Papua New Guinea, and Vietnam) or self-funding (e.g. Australia, Brunei Darussalam, Japan, Malaysia, and the Philippines)[8,17].

Situation in Singapore

In a hospital-based retrospective analysis on the incidence, characteristics and clinical sequelae of invasive Hib diseases in Singaporean children admitted from 1994-2003 to Singapore General Hospital, Tan Tock Seng Hospital and KK Women's and Children's Hospital, 53 children with invasive Hib disease were identified, of whom two died and 22 had serious sequelae (46%). The types of long-term sequelae identified included cerebral palsy, epilepsy and variable degrees of developmental delay. The most common invasive Hib disease manifestations observed in Singaporean children was meningitis (58%, n=31; 29 were < 5 years of age) and pneumonia (26%, n = 14; 11 were < 5 years of age). During the 11-year period, the annual incidence of invasive Hib disease was estimated to be 4.4/100,000 children < 5 years old. However, even with such low rates, it was estimated that there were four to five children a year with invasive Hib disease, in whom two will suffer long-term morbidity, and one death every five to six years[18].

The rates of invasive Hib were shown to have peaked in 1998-2001 and declined sharply after, possibly due to the increased uptake of the vaccine as well as the acceptance of the combination vaccines amongst the more affluent parents. It was suggested that the magnitude of vaccine uptake after the late 1990s may have been sufficient enough to confer the benefits of herd immunity. This indicated a likely

benefit of the vaccine in the setting of a relatively low disease burden even with partial vaccine uptake[18].

The local incidence of Hib continues to remain low and appears to have decreased further. In the six year period from 2004-2009, 12 out of 9, 531 admissions for pneumonia in Singapore residents aged 12 years and below were due to Hib (0.1%). Eight out of 164 admissions for meningitis in Singapore residents aged 12 years and below were due to Hib (4.9%). There was one death documented for *Haemophilus* pneumonia in 2004[19].

Conjugate Hib vaccines

Hib vaccines are formulated to contain purified capsular polysaccharides (PRP) covalently bound to a carrier protein in liquid or freeze-dried preparations. These vaccines induce both protective circulating antibodies as well as immunological memory in all age groups.

The Hib vaccines currently registered in Singapore consist of standalone vaccines (ACT-Hib [Sanofi-Aventis] and Hiberix [GSK]) and three types of combination vaccines: DTaP-Hib (Actacel [Sanofi-Aventis] and Infanrix Hib [GSK]), DTaP-IPV-Hib (Pediacel [Sanofi-Aventis] and Infanrix IPV+Hib [GSK], and DTaP-IPV-Hib-HepB (Infanrix Hexa [GSK]). The carrier protein used in all the available vaccines is the tetanus toxoid protein[15].

Hib conjugate vaccines have not been associated with any serious adverse effects. However, redness, swelling and pain at the injection site may occur in as many as 25% of its recipients. Less commonly, children may develop a fever[20].

The uptake of the Hib-containing combination vaccines have been progressively increasing in Singapore. Between 2005 and 2009, the number of doses of hexavalent vaccines administered had increased by 85%[21].

Recommendation

The ECI recommended that Hib vaccination be included in the National Childhood Immunisation Schedule (NCIS) to reduce the risk of serious complications such as meningitis and pneumonia which may lead to long-term disabilities and deaths. The recommended vaccination schedule is as follows:

a) A four-dose Hib schedule, in line with the schedule for DTaP and IPV at 3, 4 and 5 months of age and a booster dose at 18 months of age;

b) Combination vaccines containing IPV and Hib may be used for the routine schedule;

c) Children who previously received DTaP and OPV but have not completed their primary and/or booster doses should complete their vaccination series up to first booster dose at 18 months of age with DTaP, IPV and Hib combination vaccines (i.e. direct 1-for-1 replacement of DTaP and OPV with DTaP, IPV, and Hib combination vaccines). Catch-up doses for Hib are not required for those who did not receive earlier doses.

Both the pentavalent, 5-in-1 (DTaP-IPV-Hib) and hexavalent, 6-in-1 (DTaP-IPV-Hib-HepB) combination vaccines may be used in place of individual vaccines. A hexavalent (DTaP-IPV-Hib-HepB) combination vaccine can be used in place of a pentavalent (DTaP-IPV-Hib) and standalone HepB vaccines (with the exception of infants born to HepB positive mothers). The minimum interval between the first and second doses of HepB-containing vaccine is four weeks; and 16 weeks between the first and third doses of HepB-containing vaccine.

Infants born to HepB positive mothers should continue to receive standalone HepB vaccine at birth and at one month of age to reduce the risk of vertical transmission of hepatitis B virus infection. A hexavalent (DTaP-IPV-Hib-HepB) combination vaccine however, can be used for the third dose at 5-6 months of age.

Implementation

MOH has accepted the recommendations of the ECI. The revised NCIS as shown in *Table 2* became effective from 1 Jun 2013. By 1 Jan 2014, the new schedule will be recommended as the standard of care. Prior to 1 Jan 2014, all medical clinics (i.e. polyclinics, GP clinics and paediatric clinics) with existing stocks of DTaP and OPV vaccines can use up the vaccines before the replacement of OPV with IPV-containing combination vaccine.

To encourage higher uptake of childhood vaccinations and better protect the children, the use of Medisave was extended to all vaccinations in the NCIS with effect from 1 Jun 2013[22].

Table 2

National childhood immunisation schedule, Singapore

Vaccination against	Birth	1 Month	3 months	4 months	5 months	6 months	12 months	15 months	18 months	10-11 years^
Tuberculosis	**BCG**									
Hepatitis B	**HepB (D1)**	**HepB (D2)**			**HepB (D3)#**					
Diphtheria, Tetanus, Pertussis			**DTaP (D1)**	**DTaP (D2)**	**DTaP (D3)**				**DTaP (B1)**	**Tdap (B2)**
Poliovirus			**IPV (D1)**	**IPV (D2)**	**IPV (D3)**				**IPV (B1)**	**OPV (B2)**
Haemophilus influenzae type b			**Hib (D1)**	**Hib (D2)**	**Hib (D3)**				**Hib (B1)**	
Measles, Mumps, Rubella							**MMR (D1)**	**MMR (D2)##**		
Pneumococcal Disease			**PCV (D1)**		**PCV (D2)**		**PCV (B1)**			
Human Papillomavirus	***Recommended for <u>females 9 to 26 years</u>; three doses are required at intervals of 0, 2, 6 months***									

<u>Notes:</u>

BCG	Bacillus Calmette-Guérin vaccine	^	Primary 5
HepB	Hepatitis B vaccine	#	3rd dose of HepB can be given at the same time as the 3rd dose of DTaP, IPV, and Hib for the convenience of parents.
Hib	*Haemophilus influenzae* type b vaccine		
DTaP	Paediatric diphtheria and tetanus toxoid and acellular pertussis vaccine	##	2nd dose of MMR can be given between 15 and 18 months
Tdap	Tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine		
MMR	Measles, mumps, and rubella vaccine		
OPV	Oral polio vaccine		
IPV	Inactivated polio vaccine		
PCV	Pneumococcal conjugate vaccine		
D1/D2/D3	1st dose, 2nd dose, 3rd dose		
B1/B2/B3	1st booster, 2nd booster, 3rd booster		

(Contributed by Kita Y, Tiong WW, Ooi PL, and Cutter J, Communicable Disease Division, Ministry of Health)

References

1. Lee HC, Tay J, Kwok CYH et al. Certification of poliomyelitis eradication in Singapore and the challenges ahead. Ann Aca Med Singapore 2012; 41:518-28.
2. World Health Organization. India records one year without polio cases. News release 12 Jan 2012. Available at http://www.who.int/mediacentre/news/releases/2012/polio_20120113/en/ (Accessed 17 June 2013).
3 Onorato IM, Modlin JF, McBean AM et al. Mucosal immunity induced by enhanced-potency inactivated and oral polio vaccines. J Infect Dis 1991; 163: 1-6.
4. Centers for Disease Prevention and Control. Poliomyelitis prevention in the United States. MMWR Morb Mortal Wkly Rep 2000;49:RR-5.
5. John TJ. Vaccine-associated paralytic polio in India. Bull World Health Organ 2002:80:917.
6. SK Mittal, JL Matthew. Vaccine associated paralytic poliomyelitis. Indian J Pediatr 2003;70:573-7.
7. World Health Organization. Global Polio Eradication Initiative: strategic plan 2004-2008. 2003. Available at: http://www.polioeradication.org/content/publications/2004stratplan.pdf (Accessed 17 June 2013).
8. World Health Organization. WHO vaccine-preventable diseases: monitoring system. 2013 global summary. Available at http://apps.who.int/immunization_monitoring/globalsummary/schedules (Accessed 17 June 2013).
9. Health Promotion Board, Singapore. Percentage of IPV and OPV administered from 2005 to 2009 in Singapore. 2010.
10. Cuba IPV Study Collaborative Group. Randomized, placebo-controlled trial of inactivated poliovirus vaccine in Cuba N Engl J Med. 2007;356:1536-44.
11. Faden H, Modlin JF, Thoms ML et al. Comparative evaluation of immunization with live attenuated and enhanced-potency inactivated trivalent poliovirus vaccines in childhood: systemic and local immune responses. J Infect Dis 1990;162:1291-7.
12. Böttiger M. The elimination of polio in the Scandinavian countries. Public Health Rev 1993-1994;21:27-33.
13. Stratton KR, Howe CJ, Johnston RB Jr. Adverse events associated with childhood vaccines other than pertussis and rubella. Summary of a report from the Institute of Medicine. J Am Med Assoc. 1994 25;271:1602-5.
14. Ministry of Manpower, Singapore. Foreign Workforce Numbers. Available at:http://www.mom.gov.sg/statistics-publications/others/statistics/Pages/ForeignWorkforceNumbers.aspx (Accessed 17 June 2013).
15. Health Sciences Authority, Singapore. Online Medicinal Product Search. Available at: http://eservice.hsa.gov.sg/prism/common/enquirepublic/SearchDRBProduct.do?action=load (Accessed 17 June 2013).
16. Ladhani S, Slack W MPE, Heath PT et al. Invasive Haemophilius influenzae disease, Europe, 1996-2006; Emerg Infect Dis 2010;16:455-63.
17. GAVI Alliance. Countries approved for support by GAVI for pentavalent vaccine as of March 2013. Available at: http://www.gavialliance.org/results/countries-approved-for-support/ (Accessed 17 June 2013).
18. Thoon KC, Chong CY, Ng WY et al. Epidemiology of invasive Haemophilus influenzae type b disease in Singapore children, 1994-2003. Vaccine 2007;25:6482-9.
19. Ministry of Health, Singapore. Communicable Disease Surveillance, unpublished data.
20. Centers for Disease Prevention and Control. Vaccine information statement - Haemophilus influenzae type b (Hib) vaccine. Available at: http://www.cdc.gov/vaccines/vac-gen/side-effects.htm#hib (Accessed 17 June 2013).
21. Health Promotion Board, Singapore. Pentavalent and hexavalent combination vaccines administered from 2005 to 2009 in Singapore. 2010.
22. Ministry of Health, Singapore. MOH Circular 16/2013. Changes to the National Childhood Immunisation Schedule. 23 May 2013.

Laboratory data on surveillance of invasive pneumococcal diseases in Singapore, 2012

Introduction

Streptococcus pneumoniae is a major cause of severe bacterial infections such as pneumonia, bacteremia, sepsis and meningitis among children and elderly adults worldwide[1]. To date, 93 serotypes, including two recently identified serotypes 6C and 6D, have been identified based on antigenic differences in their capsular polysaccharides[2,3]. Vaccines against pneumococcal infections, such as the 23 capsular polysaccharide vaccine (PPV23), and the 7-, 10-, and 13-valent pneumococcal conjugate vaccines (PCV7, PCV10, and PCV13) have been available.

The PCV7 (covering serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) was introduced in the National Childhood Immunization Programme (NCIP) of Singapore in October 2009, followed by the PCV13 (covering six more serotypes 1, 3, 5, 6A, 7F, and 19A in addition to the PCV7 serotypes) in December 2011. A surveillance programme has been implemented in order to understand the dynamics and the impact of PCVs on the epidemiology of invasive pneumococcal infection. As required by Ministry of Health (MOH) since December 2008, clinical and laboratory confirmed cases of invasive pneumococcal diseases (IPD) are notified via the Communicable Diseases Live and Enhanced Surveillance (CD-LENS) database within the framework of the nationwide surveillance programme. A case of IPD is defined as a patient who had a positive culture for *S. pneumoniae* in blood, cerebrospinal fluid (CSF) or other normal sterile sites. The pneumococcal serotyping of isolates from IPD cases are performed by the KK Women's and Children's Hospital (KKH) and the National Public Health Laboratory (NPHL). Following the previous reports on the pneumococcal serotyping for surveillance of IPD from 2009 to 2011, we describe herein the data of pneumococcal serotyping obtained in 2012.

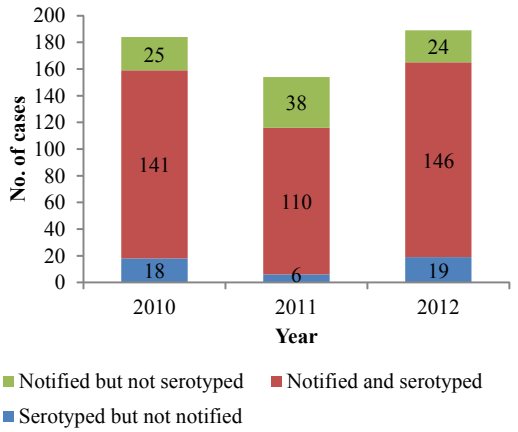
Materials and methods

As described in the previous reports[4,5], six public hospitals' laboratories submitted *Streptococcus pneumoniae* isolates from sterile site cultures (blood, CSF, pleural and peritoneal fluid, or tissue) to NPHL for serotyping. The microbiology laboratory at KKH serotyped their invasive pneumococcal isolates. Serotyping was performed using Pneumotest kit (Statens Serum Institut, Copenhagen, Denmark) and serotypes were identified based on the observation of agglutination reaction with serum antibodies (Quellung reaction) under a phase-contrast microscope. The serotyping data obtained from NPHL and KKH in 2012 were compiled for analysis. In addition, the numbers of IPD cases notified via CD-LENS database at MOH were also extracted from the database and reviewed.

Results

In 2012, there were 271 cases of pneumococcal infections notified via CD-LENS at MOH. Of these, 170 were laboratory confirmed IPD cases. However, some cases were notified but not serotyped or vice versa (*Fig. 1*). After merging and filtering the data extracted from CD-LENS, NPHL and KKH, we obtained a total of 189 laboratory confirmed IPD cases. The number of serotyped cases was 165, which correspond to 87.3% of laboratory confirmed IPD cases.

Figure 1
Distribution of notified and serotyped IPD cases, 2010-2012



Of the 165 cases serotyped in 2012, the number of paediatric and adult cases were 31 (18.8%) and 134 (81.2%), respectively. Majority of isolates were obtained only from blood culture specimens (92.1%), and some isolates were from CSF and pleural fluid. The proportions of pneumococcal isolates according to culture sites are shown in *Table 3*.

The isolates from paediatric IPD cases were mainly serotyped by the KKH laboratory (24/31; 77.4%). Serotype 19A, which accounted for 51.6% of paediatric IPD cases, was the most common serotype observed among children. The second and third most common serotypes observed were type 6B (22.6%) and type 3 (16.2%). Non-PCV13 serotypes were encountered in 2 cases (6.7%) with type 20 and group 15 (*Table 4*). The percentages of IPD serotypes covered by different vaccine formulations were also calculated. The proportions of paediatric IPD cases that would be covered by PCV7 and PCV13 were 25.8% and 93.5%, respectively (*Fig. 2A*).

The distribution of serotypes observed among adult cases is shown in *Table 5*. Serotypes 3, 23F, 7F, 6B, and 19A, in decreasing order, were the most common among adults in 2012 and accounted for 44.8% of all adult IPD cases. Besides, 11 cases (8.2%) were ungroupable/ untypeable due to auto-agglutination, or lack of antisera for further typing of non-vaccine-related serotypes or groups. The proportions of IPD cases that would be covered by PCV7, PCV13, and PPV23 were 31.3%, 67.9%, and 75.4%, respectively (*Fig. 2B*).

Table 3
Proportions of pneumococcal isolates according to culture sites, 2012

Case group	Culture sites		
	Blood* (%)	CSF** (%)	Pleural fluid** (%)
Paediatric (n = 31)	24 (77.4)	1 (3.2)	6 (19.4)
Adult (n = 134)	128 (95.6)	1 (0.7)	5 (3.7)

Isolates were from *blood only, ** CSF with/without blood, or pleural fluid with/without blood

Table 4

Distribution of pneumococcal serotypes among paediatric cases, 2012

Pneumococcal serotype/group	Number of isolates (%) (n = 31)
Type 6B *§	7 (22.6)
Type 14 *§	1 (3.2)
Type 3 §	5 (16.2)
Type 19A §	16 (51.6)
Group 15	1 (3.2)
Type 20	1 (3.2)

* serotype included in PCV7, § serotype included in PCV13

Discussion

We present herein the data collected for approximately one year after introduction of PCV13

Figure 2
Potential coverage rates of PCV7, PCV13, and PPV23 for paediatric (A), and adult IPD cases (B), 2012

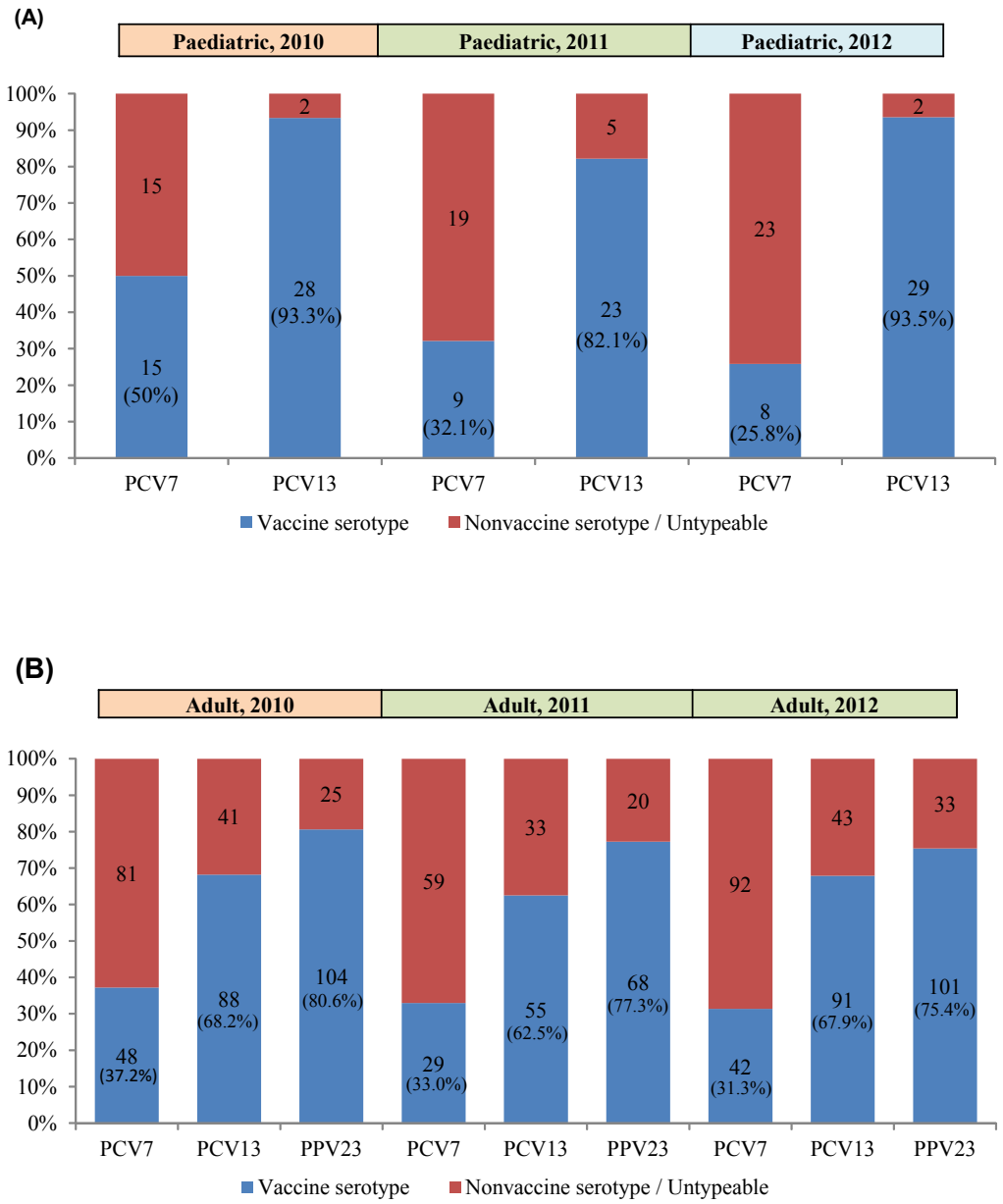


Table 5

Distribution of pneumococcal serotypes among adult cases, 2012

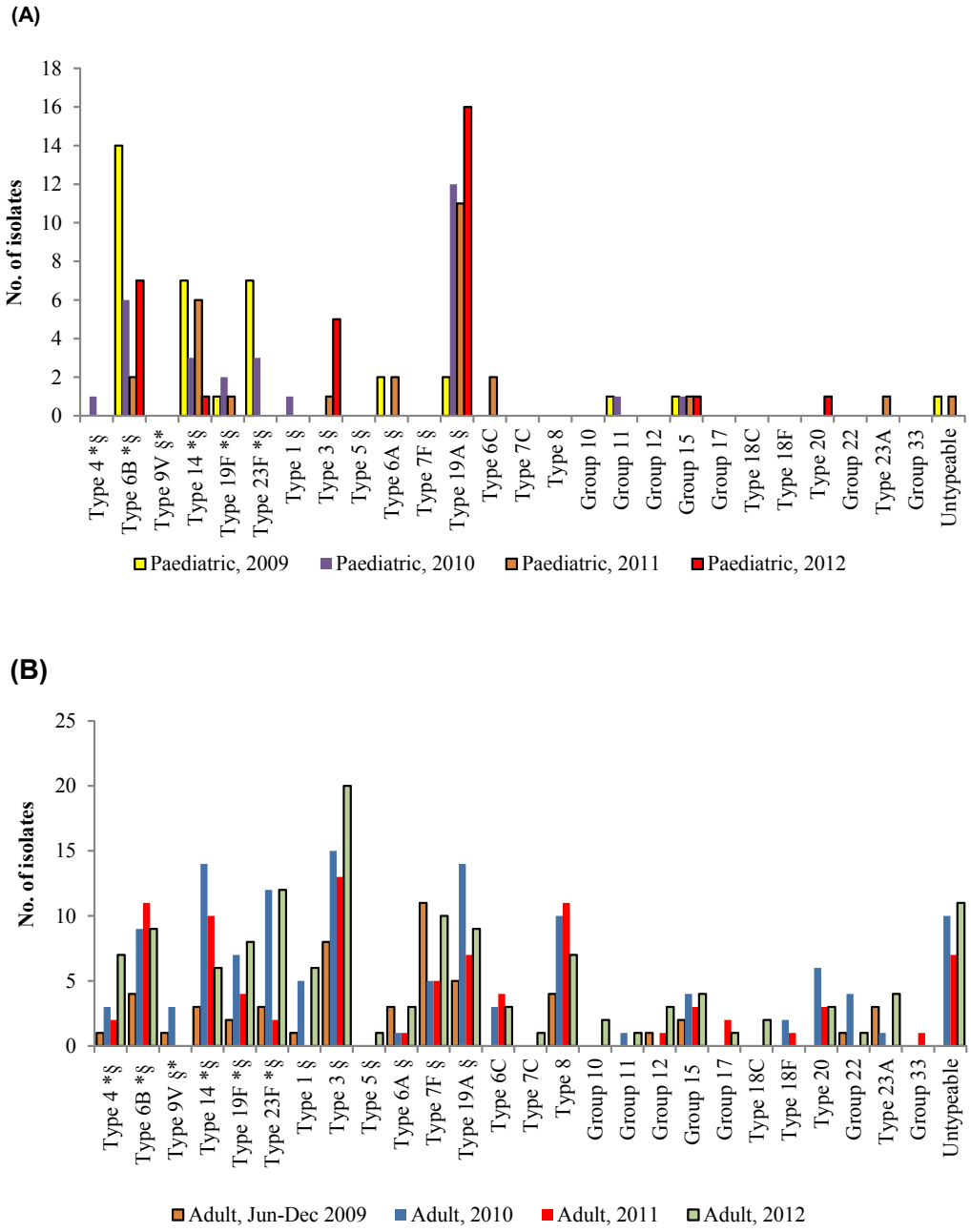
Pneumococcal serotype/group	Number of isolates (%) (n = 134)
Type 4 *§	7 (5.2)
Type 6B *§	9 (6.7)
Type 14 *§	6 (4.5)
Type 19F *§	8 (6.0)
Type 23F *§	12 (9.0)
Type 1 §	6 (4.5)
Type 3 §	20 (14.9)
Type 6A §	3 (2.2)
Type 7F §	10 (7.5)
Type 19A §	9 (6.7)
Type 5 §	1 (0.7)
Type 6C	3 (2.2)
Type 7C	1 (0.7)
Type 8	7 (5.2)
Group 10	2 (1.5)
Group 11	1 (0.7)
Group 12	3 (2.2)
Group 15	4 (3.0)
Group 17	1 (0.7)
Type 18C	2 (1.5)
Type 20	3 (2.2)
Group 22	1 (0.7)
Type 23A	4 (3.0)
Non-groupable	11 (8.2)

* serotype included in PCV7, § serotype included in PCV13

into NCIP. When comparing the data obtained within the period 2009-2011 to those in 2012, the decreasing trend in the proportion of PCV7 serotypes seems to be more evident among paediatric IPD cases: 80.1% (in 2009) decreasing to 50% (in 2010), 32.1% (in 2011), then to 25.8% (in 2012)[4,5]. The decreased coverage of PCV7 serotypes has also been noticed in a retrospective study in KKH during the late PCV7 introduction period (64.4%) versus the early PCV7 introduction period (78.6%), despite a gradual increase in PCV7 coverage to approximately 45% of the birth cohort receiving one or more doses of PCV7 (data in 2009 from the National Immunization Registry (NIR), Health Promotion Board)[6]. Based on data in 2011 from the NIR, the vaccination coverage for pneumococcal vaccines (PCV7 and/ or PCV13) was 52% for children aged one year who received two doses of PCV (personal communication). The coverage for the vaccine appears to be further improving after it was introduced into the national immunization schedule since 2009.

Data in 2012 revealed that the potential coverage of PCV13 was significantly higher in comparison with PCV7 (93.5% versus 25.8%, $p<0.001$), mainly due to the high proportion of the serotype 19A (51.6%) and the emergence of serotype 3 (16.2%) in children. Such high prevalence of non-PCV7 serotype IPD, in particularly IPD caused by 19A, may be due to selection pressure after widespread use of PCV7[7]. However, fluctuation of serotype distribution may not be driven entirely by vaccine pressure, and therefore needs to be considered when the vaccine effects are evaluated[8]. While observing the serotype composition of paediatric IPD from 2009-2012, the fluctuation of distribution of the PCV7 serotype 6B has been encountered, and non-PCV13 IPD cases (group 11, 15, type 20 and type 23A) were also observed (*Fig. 3A*). Hence monitoring closely changes in the composition of non-vaccine types is crucial, since replacement of vaccine types with non-vaccine types is a complex phenomenon which has occurred in most populations[9].

Figure 3
Comparison of IPD serotype distribution among paediatric (A), and adult IPD cases (B), 2009-2012



Compared to the distribution among children, the serotype distribution among adult cases looked more heterogeneous. The proportions of PCV7, PCV13, and PPV23 associated serotypes were 31.3%, 67.9%, and 75.47%, respectively, among adults in 2012. Similar to what was observed previously, the potential PCV7 coverage was modest (35.5%) compared to PCV13 (65.9%), and PPV23 (79.3%) during the period 2010-2011[5]. Although PCV13 is not directly given to adults, it is possible that PCV13 could indirectly protect adults from IPD more than PCV7 due to herd immunity. However we did not observe any significant changes in pneumococcal population dynamics for the past few years. Serotype 3, which has been found to be associated with significantly high case-fatality rates[10], still predominated. Meanwhile other serotypes which are less predominant, such as 6B, 7F, 8, 14, 19A, 23F, varied over this period (*Fig. 3B*).

Enhanced surveillance is required after the inclusion of PCV13 so that any changes in the serotype composition can be appropriately analyzed. Detection of new emergence of one serotype should trigger further epidemiological investigation.

(Reported by La MV[1], Zulaina S MS[1], Foo K[2], Jureen R[3],Tee WSN[2,4] and Lin RVTP[1,3]; National Public Health Laboratory[1], Communicable Diseases Division, Ministry of Health[2], National University Hospital System[3], KK Women's & Children Hospital[4])

Acknowledgements

We thank the laboratories, especially the Microbiology laboratory at KKH , which have contributed to the data collection.

References

1. *World Health Organisation.Pneumococcal conjugate vaccine for childhood immunization - position paper. Wkly Epidemiol Rec 2007;82:93-104.*
2. *Park IH, Pritchard DG, Cartee R et al. Discovery of a new capsular serotype (6C) within serogroup 6 of* Streptococcus pneumoniae. *J Clin Microbiol 2007;45:1225-33.*
3. *Jin P, Kong F, Xiao M et al. First report of putative* Streptococcus pneumoniae *serotype 6D among nasopharyngeal isolates from Fijian children. J Infect Dis 2009;200:1375-80.*
4. *Ministry of Health, Singapore. Laboratory-based surveillance system of invasive pneumococcal diseases in Singapore: a nationalwide monitoring of vaccine serotype coverage. Epidemiol News Bull 2010;36:40-5.*
5. *Ministry of Health, Singapore. Pneumococcal serotyping for surveillance of invasive pneumococcal diseases in Singapore, 2010-2011. Epidemiol News Bull 2012;38:29-35.*
6. *Thoon KC, Chong CY, Tee NW. Early impact of pneumococcal conjugate vaccine on invasive pneumococcal disease in Singapore children, 2005 through 2010. Int J Infect Dis;16:e209-15.*
7. *Pai R, Moore MR, Pilishvili T et al. Postvaccine genetic structure of* Streptococcus pneumoniae *serotype 19A from children in the United States. J Infect Dis 2005;192:1988-95.*
8. *Jefferies JM, Smith AJ, Edwards GF et al. Temporal analysis of invasive pneumococcal clones from Scotland illustrates fluctuations in diversity of serotype and genotype in the absence of pneumococcal conjugate vaccine. J Clin Microbiol;48:87-96.*
9. *Weinberger DM, Malley R, Lipsitch M. Serotype replacement in disease after pneumococcal vaccination. Lancet 2011;378:1962-73.*
10. *Jansen AG, Rodenburg GD, van der Ende A et al. Invasive pneumococcal disease among adults: associations among serotypes, disease characteristics, and outcome. Clin Infect Dis 2009;49:e23-9.*

Norovirus gastroenteritis outbreak at a nursing home in Singapore

Notification

On 28 Dec 2012, the Ministry of Health (MOH) was notified of a possible outbreak of gastroenteritis at a nursing home involving 15 individuals (14 residents and 1 staff) who developed diarrhoea and vomiting since the evening of 22 Dec 2012. The 4-storey nursing home had a total of 149 residents and 47 staff. Between 35 and 40 residents were housed at each level.

Epidemiological investigations

MOH conducted an epidemiological investigation on 26 Dec 2012 to determine the extent and cause of the outbreak, and possible modes of transmission. The age, gender and ethnicity of the cases were recorded. The symptoms experienced and type of medical treatment sought were obtained. Active case detection was carried out among all residents as well as administrative staff, nurses and food handlers working in the nursing home. Stool samples were obtained from the symptomatic residents and staff and submitted to the laboratory for detection of bacterial and viral enteropathogens (*Shigella*, *Campylobacter*, *Vibrio*, *Salmonella*, rotavirus and norovirus).

The kitchen was inspected and food handlers were referred to the Communicable Disease Centre, Tan Tock Seng Hospital, for testing of enteropathogens.

A case was defined as a previously well individual residing or working at the nursing home who developed watery diarrhoea (at least 2 times a day) and/or vomiting with or without other symptoms such as abdominal pain, fever and nausea between 22 Dec 2012 and 6 Jan 2013.

Findings

A total of 60 cases with onset of illness between 22 Dec 2012 and 6 Jan 2013 were identified, giving an overall attack rate of 31%. Out of these cases, 54 were residents and 6 were staff giving an attack rate of 36% for residents and 13% for staff. The mean age of the 54 affected residents was 83 years and ranged from 55 years to 95 years. Most of the cases were residents from the second and third levels. The attack rates were 15% at level 1, 67% at level 2, 57% at level 3 and 6% at level 4. All the cases had moderate to severe functional and cognitive disabilities with about 83% bed-ridden.

The index case, a 57 year-old male resident at level 2, came down with gastroenteritis on 22 Dec 2012. The second case who resided next to him reported ill within 72 hours after onset of illness of the index case. Based on the intervals between onset of illness of the cases and close contacts of the first 10 reported cases between 25 and 28 Dec 2012, the mean incubation period was 47hr (range 20h – 55hr).

Clinical features comprised watery diarrhoea (75%), vomiting (68%), abdominal cramps (23%) and fever (7%). A total of 13 residents (22%) were hospitalized for observation while the rest were treated by the

nursing home's medical team. Among those hospitalized, an 81-year-old male resident died; the cause of death was due to pneumonia. All the remaining cases recovered. The epidemic curve is shown in *Fig. 4*.

Meals were prepared and cooked at an in-house kitchen and consumed by all staff and residents. The kitchen was found to be clean and satisfactorily maintained. No major hygiene lapses in the kitchen area were observed.

All seven stool samples collected from the cases tested positive for *Norovirus*. Further genetic analyses of the viruses carried out by the National Public Health Laboratory (NPHL), showed that all were of GII.4 variant Sydney 2012.

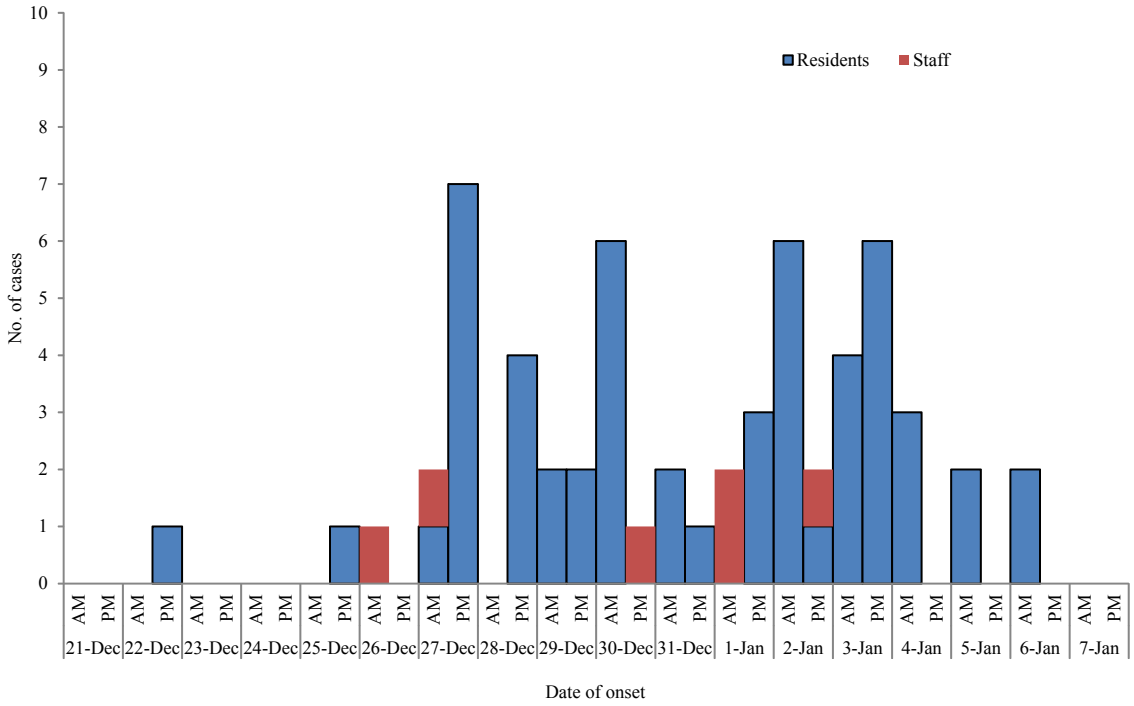
All the four food handlers had been well prior to the outbreak and none tested positive for enteropathogens.

Prevention and control

MOH advised the nursing home to isolate cases early, step up measures for hand hygiene and stop all communal activities. Due to insufficient isolation rooms, cohort nursing was recommended. Advice was also given to discourage visitors to the nursing home temporarily and stop taking new residents until

Figure 4

Onset of illness of 60 gastroenteritis cases at a nursing home in Singapore, 22 Dec 2012 to 6 Jan 2013



the outbreak was over. To ensure that the recommended prevention and control measures were put in place, another site visit was made on 2 Jan 2013.

Discussion

The epidemiological and clinical findings suggested that this was an outbreak of norovirus gastroenteritis. The reported symptoms (predominantly diarrhoea and vomiting) with a mean incubation period of 47hr (range 20h – 55hr) for the first 10 reported cases between 25 and 28 Dec 2012 are compatible with the symptoms and known incubation period (usually about 12-48hr) for norovirus gastroenteritis. This is further supported by the isolation of norovirus genogroup (GII.4 variant Sydney 2012[1]) from the stools of seven cases (2 staff and 5 residents) in this outbreak.

Norovirus is a highly contagious pathogen and the leading cause of viral gastroenteritis outbreaks worldwide. It is transmitted through direct person-to-person contact, contaminated food or water, and contaminated environmental surfaces[2]. The virus is usually present in very high amounts in the stool and vomitus of those who are unwell, and it can be transmitted rapidly to other cases. In health care and long-term care settings, with close living quarters, shared bathrooms, and incontinent patients, the risk of person-to-person transmission[3] is increased, as in this outbreak. Healthcare facilities are the most commonly reported settings for norovirus gastroenteritis outbreaks in the United States and other industrialized countries including Singapore[4]. Nearly two-thirds of all norovirus gastroenteritis outbreaks reported in the United States occurred in long-term care facilities[5]. In addition, studies have shown that healthcare workers could play a role in the transmission of norovirus in healthcare settings. According to a study in the Netherlands in 2008, the average number of all subsequent cases attributable to the downstream branch of one single infected healthcare worker in the transmission tree was 4.4[6].

Noroviruses in humans belong to one of three norovirus genogroups (GI, GII, or GIV), which are further divided into more than 25 genetic clusters. Over 75% of confirmed human norovirus infections are associated with genotype GII[7]. We isolated norovirus genogroup (GII.4 variant Sydney 2012[8]) from the stools in this outbreak. This strain had been responsible for outbreaks in Japan, Australia and the United States in 2012[9] and has gained importance in outbreaks in closed institutions.[10,11]

The index case, a 57 year-old male resident, presented with symptoms on 22 Dec 2012. He could have been infected by an asymptomatic relative or through consumption of contaminated food brought in by a visitor which was a common practice observed in the nursing home. However, this hypothesis could not be confirmed as the index case denied consuming food brought into the nursing home or meeting with relatives prior to his onset of illness.

It is also unlikely that this outbreak was due to contaminated food prepared at the in-house kitchen, as the meals prepared by the kitchen were consumed by all the staff and residents, and out of 47 staff, only six were affected. A much higher attack rate among the staff would have been expected if the in-house meals were the cause of this outbreak.

The following factors could have also contributed to the explosive nature of the outbreak:

1) The nursing home did not implement cohort nursing for affected cases at an earlier stage of this outbreak;

2) Nurses were not assigned to a specific floor for their duties. Thus asymptomatic healthcare workers might also have spread the virus to the susceptible residents at the other levels. During inspection of the nursing home, some lapses in hand hygiene were observed among healthcare workers especially after contact with symptomatic cases. The healthcare workers did apply the alcohol rub; however, it was observed that their hand rubbing with alcohol was about 15 to 20 seconds. Studies of hand hygiene reveal that healthcare workers on average wash their hands 6-10 seconds. Similarly, healthcare workers typically apply 3cc or less of alcohol-based hand sanitizers, and this volume may be insufficient to permit the 30 seconds of contact time required for >99% kill of vegetative bacteria and non-enveloped viruses. It is definitely an insufficient volume for inactivation of calciviruses such as norovirus[12];

3) The manager of the nursing home confirmed that there were episodes of vomiting by some of the cases in common areas during their physical activity. Vomiting can give rise to infectious droplet aerosols and widespread contamination of the environment.

4) The sharing of facilities such as toilets and common sitting areas could also facilitate the transmission of the infection to other susceptible residents in the same ward.

In conclusion, epidemiological investigation of this outbreak suggests direct and indirect person-to-person norovirus transmission, probably from both symptomatic and asymptomatic healthcare workers and residents. Environmental surfaces contaminated by virus aerosolized from vomitus could also have played a role. How the virus was introduced into the home could not be determined. Proper hand hygiene, environmental disinfection with household bleach, and isolation of cases in the early stage of outbreaks remain the mainstays for prevention and control of norovirus gastroenteritis.

(Contributed by Minn T, Low C, Raj P, Hishamuddin P and Tay J, Communicable Diseases Division, Ministry of Health)

References

1. *US Centers for Disease Control and Prevention. Notes from the field: Emergence of new norovirus strain GII.4 Sydney — United States, 2012. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6203a4.htm. Last accessed on 23 Apr 2013.*

2. *Ler SS, Hishamuddin P, Tay J et al. Norovirus outbreak at a primary school in Singapore. Epidemiol News Bulletin 2011; 37: 94-7.*

3. *Weber J, Rutala W A, Miller M B et al. Role of hospital surfaces in the transmission of emerging health care-associated pathogens: Norovirus,* Clostridium difficile, *and* Acinetobacter *species. Available at: http://www.sciencedirect.com/science/article/pii/S0196655310004086. Last accessed on 17 June 2013.*

4. *Minn T, Toh HY, Hishamuddin P et al. Norovirus outbreak at a nursing home in Singapore. Epidemiol News Bulletin. 2012; 38: 72-6.*

5. US Centers for Disease Control and Prevention. Surveillance for norovirus outbreaks. Available at: http://www.cdc.gov/features/dsnorovirus/. Last accessed on 10 Apr 2013.

6. Heijne JC, Rondy M, Verhoef L et al. Quantifying transmission of norovirus during an outbreak. Division of Clinical Epidemiology & Biostatistics, Institute of Social and Preventive Medicine (ISPM), University of Bern, Bern, Switzerland. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22317811. Last accessed on 17 June 2013.

7. US Centers for Disease Control and Prevention. Fact sheet: Norovirus in healthcare facilities. Available at: http://www.cdc.gov/hai/pdfs/norovirus/229110-ANoroCaseFactSheet508.pdf. Last accessed on 24 Apr 2013.

8. US Centers for Disease Control and Prevention. Notes from the field: Emergence of new norovirus strain GII.4 Sydney — United States, 2012. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6203a4.htm. Last accessed on 23 Apr 2013.

9. National Institute of Health Sciences. Division of Biomedical Food Research. Detection of Norovirus GII/4 variant in Japan. Available at: http://www.nihs.go.jp/fhm/fhm4/fhm4-nov901e.html. Last accessed on 2 April 2013.

10. Blanton LH, Adams SM, Beard RS et al. Molecular and epidemiologic trends of caliciviruses associated with outbreaks of acute gastroenteritis in the United States, 2000–2004. J Infect Dis 2006;193:413-21

11. Tan M, Jiang X. Norovirus and its histo-blood group antigen receptors: an answer to a historical puzzle. Trends Microbiol 2005; 13:285-93.

12. Florida Department of Health. Norovirus: general information, hand hygiene and contact precautions. Available at: http://www.doh.state.fl.us/chd/bay/Documents/Norovirus.pdf. Last accessed on 17 June 2013.

The Epidemiological News Bulletin is published quarterly by the Ministry of Health, Singapore

Any comments or questions should be addressed to:

The Editor
Epidemiological News Bulletin
Communicable Diseases Division, Ministry of Health
College of Medicine Building, 16 College Road,
Singapore 169854
E-mail : Goh_Kee_Tai@moh.gov.sg
Jeffery_Cutter@moh.gov.sg