Singapore’s success story in the prevention and control of hepatitis B virus infection

Hepatitis B virus (HBV) infection was recognised as a major public health problem in Singapore as it is closely associated with chronic hepatitis, liver cirrhosis and hepatocellular carcinoma. During the period 1972-1976, the mean annual number of hospital discharges was 647 for acute viral hepatitis, 368 for chronic hepatitis/cirrhosis and 271 for primary liver cancer. The annual incidence of primary liver cancer per 100,000 population per year was 18.3 for males and 5.1 for females in the period 1968-1972. Local data confirmed the significant association between hepatitis B surface antigen (HBsAg) carriage and hepatocellular carcinoma, the third most common cancer among males, with a relative risk of 41.5\(^1\).

In the 1970s, HBV infection accounted for 54% of the reported acute viral hepatitis. The annual morbidity rate for acute hepatitis B was 10.4 per 100,000 population and the case-fatality rate was 2.0%.

The prevalence of HBsAg among blood donors was 5.7% in a survey conducted in August/September 1971 and the incidence of post-transfusion hepatitis was 0.36-0.57 per 1000 transfusions\(^2\). A community survey at Toa Payoh housing estate revealed a HBsAg prevalence of 5.7% for Chinese children 5-9 years of age and 8.5% among Chinese adults. Seroepidemiological surveys of the general population aged from 6 months to over 55 years conducted from 1983-1987 showed that the prevalence of HBsAg increased from 1.6% for one-year-olds to 3.4% for 5-14 year-olds and reached 6.3% for 35-44 year-olds (Fig 1). About 6%-8% of adult males and 4% of adult females were HBsAg positive with the highest rate among the Chinese. The prevalence of
hepatitis B e antigen (HBeAg), a marker of high infectivity, among HBsAg-positive persons was high in children below 10 years of age (88.3%) and then sharply declined to 11.5% among adults aged 45 years and above. The HBsAg prevalence was high among family contacts of chronic hepatitis B carriers (38.0%), multiple-transfused patients (13.0%) \(^3\), male prostitutes (14.9%) \(^4\), the mentally handicapped (14.5%), male juvenile delinquents (13.2%) and dental surgeons (11.4%) \(^5\).

**Modes of transmission**

The main mode of transmission in the first year of life was perinatal. This mode formed the most important link in maintaining the endemicity of HBV in the country. Based on a study on maternal-child transmission conducted at Kandang Kerbau Hospital, about 43% of babies born to HBsAg-positive mothers developed the carrier state. If the mothers were also HBeAg positive, the frequency of transmission was much higher at 88%. Transmission by the intrauterine route accounted for about 8% \(^6\).

Epidemiological enquiries showed that horizontal transmission from carriers to the susceptibles occurred within the same household and in the community via various parenteral and inapparent parenteral routes; e.g. contaminated needles or syringes in tattoo parlours and medical clinics. Within the same household, sharing of various personal and household articles such as toothbrushes and razors, was significantly associated with HBV transmission \(^7\).

Sexual transmission of HBV infection was established in a cross-sectional study of male patients presenting with a new episode of sexually-transmitted disease at a government outpatient clinic. Sex-related factors significantly associated with higher HBV infection, independent of age and ethnic group, were reactive VDRL test for syphilis, participation in anal intercourse and having 10 or more lifetime sexual partners \(^8\).

**Strategies for prevention and control**

The key to the prevention and control of HBV infection is immunisation, the aim of which is to prevent acquisition of HBsAg as early in life as possible to reduce the large pool of carriers in the community. Other measures include surveillance, universal blood precautions and public health education. Clinical and epidemiological research are other important components.

When a safe and efficacious HBV vaccine became commercially available, the cost was very high. Clinical trials were conducted in Singapore...
to determine the best schedule and dosage of the childhood immunisation programme. The results indicated that immunoprophylaxis could reduce perinatal HBV transmission by 85% and that a reduced dosage of both plasma-based and yeast-derived vaccine was as efficacious as the dose recommended by the manufacturer. These findings were of practical importance since the use of a lower dose of vaccine without compromising its efficacy and immunogenicity would markedly reduce the cost of the vaccination programme.

**The childhood hepatitis B vaccination programme**

The childhood hepatitis B immunisation programme was implemented after an intensive health education campaign in the mass media. The immunisation schedule for infants has been fully integrated into the existing national childhood immunisation programme with the first dose given within 24 hours of birth, the second dose at 4-6 weeks and the third dose at 5 months. The target group was babies born to carrier mothers. It started on 1 October 1985 when laboratory facilities for the screening of pregnant women for HBsAg and HBeAg became more widely available. As mathematical modelling showed that the reduction in the incidence of HBV infection is less marked if vaccination was confined only to this group of babies, the programme was extended to all newborns on 1 September 1987 through the use of Medisave fund. Health education of the public and the medical and nursing staff was again intensified prior to the implementation of the extended programme. Routine antenatal screening continued to enable hepatitis B immunoglobulin to be administered to newborns of HBeAg carrier mothers at birth.

**Immunisation coverage**

Between Oct 1985 and Aug 1987, virtually all the babies born to carrier mothers in government institutions completed the full course of hepatitis B immunisation. With the extension of the programme to all newborns, while the coverage rate in government hospitals was more than 88% during the period September 1987 - March 1988, only about 13% of the live-births in private hospitals received the HBV vaccine. This arose because the majority of babies born to non-carrier mothers in those hospitals were immunised after discharge at government maternal and child health clinics where the cost of immunisation was considerably cheaper. With more publicity and health education, the coverage for infants who have completed three doses before one year of age increased from 49% in 1988 to 94% in 1995 and since 2005, it has been maintained at 95% and above in children under 2 years of age, with virtually all the babies born to carrier mothers immunised (Fig 2).

**Monitoring the HBV markers of vaccinees**

One cohort of children born to HBeAg carrier mothers and vaccinated with the plasma-based vaccine at birth, one month and 2 months was followed up at 2 years, 4 years, 6 years and 8 years. The prevalence of antibody against HBsAg (anti-HBs) decreased from 86% at one year to 57% at 8 years. Almost all the HBsAg were acquired during the first year of life and no carriers were detected at 4- and 8-year follow-up, even among those found to be anti-HBs negative. About 40% of the break-through perinatal infections resulted from HBV vaccine-induced escape mutant of HBV. No significant difference in seroconversion rate and geometric mean titre (GMT) was noted between the reduced dose (5 ug) and full dose (10 ug).
When the non-responders were revaccinated with a course of hepatitis B vaccine at 4-year follow-up, all of them seroconverted, the majority with an anamnestic reaction. For the responders, whose anti-HBs levels had dropped to a low level, administering a booster dose also elicited a sharp secondary antibody response. For those given a booster for the first time at 8 years, there was again a sharp anamnestic response. These phenomena indicate that once an immune response has been induced, it can be restimulated by exposure to the wild virus with active increase in anti-HBs during the early phase of the incubation period of the disease, thereby protecting against clinical illness or development of the carrier state.

Another cohort of children born to HBsAg carrier mothers and vaccinated with the yeast-derived vaccine at birth, 1 month and 6 months was followed up at 2 years, 4 years and 6 years. All the babies born to HBeAg-negative carrier mothers and vaccinated with either the reduced dose (2.5 ug) or full dose (5 ug) did not develop persistent HBsAg carrier state. No significant difference in seroconversion rate, GMT and antibody against hepatitis B core antigen (anti-HBc), a marker of infection, was observed between the 2.5 ug and 5.0 ug group throughout the duration of follow-up. Although the GMT dropped sharply from 9-month to 6-year follow-up, a booster dose given at the end of the follow-up period, including those with no detectable anti-HBs, resulted in a sharp anamnestic response.

Follow-up of these two cohorts of vaccinated children showed that perinatal transmission had been reduced by 80%-100%.

The high immunogenicity of very low dosages of yeast-derived vaccine was demonstrated in a cohort
of seronegative children aged 1-12 years followed up for 10 years. No HBsAg carrier was detected over the duration of study 14-16.

The herd immunity of the childhood population was confirmed in a seroprevalence survey conducted in 1998/1999 which showed that 90% of children below 5 years of age and 77% in children aged between 5 and 14 years possessed anti-HBs.

Catch-up vaccination programme

As more than 70% of young adults 18-29 years of age had no immunity against hepatitis B, a 4-year hepatitis B catch-up immunisation programme targeted at the student population born before 1987 and who were likely to have missed the national immunisation against hepatitis B was implemented from 2001-2004 after wide media publicity and health education.

Trends of acute hepatitis B

The incidence of acute hepatitis B declined from per 9.2 100,000 in 1985 to 3.4 per 100,000 in 1999 and 1.3 per 100,000 in 2010. In children below 15 years of age, the mean annual incidence dropped from 1.44 per 100,000 during the period 1983-1985 to 1.14 per 100,00 for the period 1995-1997 17.

Since routine screening of voluntary blood donors for HBsAg was implemented in 1973, the incidence of post-transfusion B was reduced from 13-23 cases per year to fewer than 1 per year and subsequently eliminated.

The introduction of disposable needles and syringes in healthcare institutions has resulted in a marked decrease in the horizontal transmission of acute hepatitis B associated with parenteral exposures such as injection, dental treatment, venepuncture, acupuncture and tattooing, from 62.1% in 1977 to 5.9% in 1998 and none since 1999 18.

Changing prevalence of HBV carrier state

The prevalence of HBsAg in children had declined from 5.7% in Chinese children 5-9 years of age in 1972 to 3.4% in 1987. In primary school children, the HBsAg prevalence was 4% in 1987, and 0% in 1994-1996. In the 1993 serological survey, HBsAg was detected in 1.3% of children aged 5-14 years but in none of the children below 5 years of age. In another survey carried out in 1998, no HBsAg was detected among children below 15 years of age. In the latest survey in 2008-2010, the HBsAg prevalence was 0% in preschool children aged 1-6 years, 0.25% in primary school children aged 7-12 years and 0.75% in secondary school children aged 13-17 years.

The HBsAg prevalence in antenatal women monitored through routine screening had declined from 4.4% in 1980-81 to 2.4% in 2008. Two national seroprevalence studies among Singapore adult residents aged 18-69 years showed that the HBsAg prevalence had dropped significantly from 4.1% in 1999 to 2.7% in 2005 (Fig 3) 19, 20.

Incidence of primary liver cancer

The age-standardised incidence of primary liver cancer among males decreased from 27.8 per 100,000 per year during the period 1978-1982 to 18.9 per 100,000 per year during the period 1993-1997 21 (Fig 4). This declining trend occurred before the national childhood immunisation programme against hepatitis B was implemented in 1985. Factors con-
tributing to this decline include vast improvements in socio-economic status, a high standard of environmental and food hygiene and sanitation, in particular, control of aflatoxin contamination in foodstuffs. It is still too early to assess the impact of childhood hepatitis B vaccination on the incidence of primary liver cancer which is uncommon below 40 years of age.

Conclusion

The successful control of HBV infection in Singapore is mainly attributed to the comprehensive coverage of the universal immunisation of all newborns to prevent both perinatal and horizontal transmission. The effectiveness of the reduced dosage of hepatitis B vaccine in the prevention of HBsAg carriage among vaccinated children and adults was confirmed by the 1993 national serological survey in which HBsAg was detected in 5.6% of the unvaccinated group compared with 0.3% in the vaccinated group. Despite the initial concern over the emergence of antibody escape variants of HBV, the current vaccines remain highly effective in the prevention of both acute hepatitis and chronic carrier state.

Figure 3
Age-specific seroprevalence (%) of HBsAg and anti-HBs among adults in Singapore, 1999 and 2005

Figure 4
Age-standardized incidence of primary liver cancer by sex, 1968-2007
The impact of the prevention and control programme is summarised in Table 1.

However, the problem is far from over. HBV infection continues to pose financial burden among the adult population in Singapore. A recent study estimated that the annual cost of chronic HBV infection and its complications amounted to $279 million. The 2005 national serological survey showed that a large proportion of the adult population aged 19-69 years remained highly susceptible to HBV infection with only 42% immune. Adults aged 25-44 years had the highest incidence rate of acute hepatitis B. As hepatitis B is a sexually-transmitted disease, those whose lifestyles exposed them to a high risk of acquiring HBV infection should be routinely screened and vaccinated.

Table 1

Summary of the impact of the hepatitis B prevention and control programme in Singapore

- Post-transfusion hepatitis B virtually disappeared since 1973
- Acute hepatitis B associated with parenteral procedures declined from 62.1% in 1977 to 5.9% in 1988 and 0% since 1999
- Incidence of acute hepatitis B dropped from 9.2 per 100,000 in 1985 to 1.7 per 100,000 in 2008 with no cases in children aged < 15 years since 1997
- Maternal-child transmission virtually eliminated with 97% children vaccinated by 2 years of age
- A 1993 serological survey showed that the hepatitis B carrier rate was 0.3% in vaccinated persons compared with 5.6% in unvaccinated persons
- Hepatitis B carrier rate in selected population had declined; e.g., in primary school children from 4% in 1987 to 0% in 1994; in adults from 9.1% in 1975 to 4.1% in 1999 and 2.7% in 2005; in antenatal women from 4.4% in 1980-81 to 2.4% in 2008; in children 1-17 years, it was 0.8% in 2008-2010
- It is still too early to assess the impact on the incidence of primary liver cancer as the condition affects predominantly older adults

(Based on a paper delivered by Goh KT, Sr Consultant, Office of the Director of Medical Services, Ministry of Health, at the World Vaccine Congress, Singapore, 21 June 2011)

References

1. Goh KT. Epidemiology and control of hepatitis B virus infection in Singapore. Southeast Asian Medical Information Center, Tokyo, 1992.


Introduction

Infection due to *Streptococcus pneumoniae* has played a significant role in morbidity and mortality among young children and elderly adults worldwide. Between 700,000 and 1 million deaths are estimated to occur among children younger than 5 years old every year despite the availability of vaccines and antibiotics.

To date, 93 serotypes, including two recently identified serotypes 6C and 6D, have been identified based on antigenic differences in their capsular polysaccharides. Vaccine formulation is challenging as serotype distribution varies over time and geographical area. There are a few available pneumococcal vaccine formulations which are categorized into two types: pneumococcal polysaccharide vaccine (PPV), i.e. PPV23 comprising 23 capsular polysaccharides, and pneumococcal conjugate vaccine (PCV) such as the 7-, 10-, and 13-valent pneumococcal conjugate vaccine (PCV7, PCV10, and PCV13). With the widespread use of the PCV7, which covers serotypes 4, 6B, 9V, 14, 18C, 19F and 23F, the changes in serotype distribution have been observed and the occurrence of nonvaccine serotype invasive pneumococcal diseases (IPD) has raised some concern.

In Singapore, the PCV7 was introduced in the National Childhood Immunization Programme (NCIP) 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. Since December 2008, medical practitioners and clinical laboratories are required to notify the Ministry of Health (MOH) of all clinical and laboratory confirmed cases of IPD within the framework of the nationwide surveillance programme. A case of IPD was defined as a patient who had a positive culture for *S. pneumoniae* in blood, cerebrospinal fluid (CSF) or other normal sterile sites.

In order to understand the dynamics and the impact of PCVs on the epidemiology of invasive pneumococcal infection, data on the pneumococcal serotypes have been collected. The main data source are from the Kandang Kerbau Women’s and Children’s Hospital (KKH) and the National Public Health Laboratory (NPHL). Following the previous report on the pneumococcal serotyping data in 2009, we describe herein the data from pneumococcal serotyping performed by NPHL and KKH in 2010 and 2011.

Materials and methods

Six restructured hospitals’ laboratories sent *Streptococcus pneumoniae* isolates from sterile site cultures such as blood, CSF, pleural and peritoneal fluid, or tissue to NPHL for serotyping. The microbiology laboratory at KKH serotyped their invasive pneumococcal isolates. Pneumotest kit (Statens Serum Institut, Copenhagen, Denmark) was used to perform serotyping on fresh culture isolates. Quellung reaction, based on an agglutination reaction with serum antibodies, was observed under a phase-contrast microscope to identify the serotype. The serotyping
data obtained from NPHL and KKH in 2010 and 2011 were compiled for analysis. In addition, the numbers of IPD cases notified via the Communicable Diseases Live and Enhanced Surveillance (CD-LENS) database at MOH were also extracted from the database and reviewed.

**Results**

A total of 148 laboratory confirmed cases of invasive pneumococcal infection were reported in 2011, a decrease of 10.8% from the 166 cases reported in 2010. The numbers of IPD cases serotyped in 2010 and 2011 were 159 and 116, respectively. After merging and filtering the data extracted from CD-LENS, NPHL and KKH, we obtained the numbers of IPD cases which were notified but not serotyped or vice versa (Fig 5). The percentages of IPD cases serotyped in 2010 and 2011 were 86.4% and 75.3% of the total IPD cases, respectively.

Of the 159 cases serotyped in 2010, 30 (18.9%) were paediatric cases, which were defined as those under 18 years of age in this report, and 129 (81.1%) were adult cases. The number of paediatric and adult cases serotyped in 2011 were 28 (24.1%) and 88 (75.9%) of 116 cases, respectively. Some isolates were from CSF and other body fluids, but majority of isolates was obtained only from blood culture specimens (92.5% of isolate in 2010; 88.8% in 2011). The proportions of pneumococcal isolates according to culture sites are shown in Table 2.

The serotyping results of paediatric IPD cases were mainly provided by the KKH laboratory. During the two-year period, the most prevalent serotypes observed among children were type 19A (40.0% in 2010; 39.3% in 2011), which is included in the PCV13 but not in the PCV7, followed by two PCV7-

![Figure 5](image_url)

**Distribution of notified and serotyped IPD cases, 2010-2011**

<table>
<thead>
<tr>
<th>Year</th>
<th>Case group</th>
<th>Blood* (%)</th>
<th>CSF** (%)</th>
<th>Pleural fluid** (%)</th>
<th>Miscellaneous** (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010 Paediatric (n = 30)</td>
<td>25 (83.4)</td>
<td>1 (3.3)</td>
<td>3 (10.0)</td>
<td>1 (3.3)</td>
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</tr>
<tr>
<td>Adult (n = 129)</td>
<td>122 (94.7)</td>
<td>3 (2.3)</td>
<td>2 (1.5)</td>
<td>2 (1.5)</td>
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</tr>
<tr>
<td>2011 Paediatric (n = 28)</td>
<td>18 (64.3)</td>
<td>1 (3.6)</td>
<td>9 (32.1)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Adult (n = 88)</td>
<td>85 (96.6)</td>
<td>2 (2.3)</td>
<td>0</td>
<td>1 (1.1)</td>
<td></td>
</tr>
</tbody>
</table>

Isolates were from *blood only, **CSF with/without blood, **pleural fluid with/without blood, or **miscellaneous (peritoneal fluid, pelvic fluid, brain tissue) with/without blood.
serotypes: type 6B (20%) for year 2010, and type 14 (21.4%) for year 2011 (Table 3).

The percentages of IPD serotypes covered by different vaccine formulations were calculated. The potential coverage rates of PCV7 was 50% in 2010 which decreased to 32.1% in 2011, while the PVC13 could increase coverage to 93.3% for paediatric IPD cases in 2010 and to 82.1% in 2011 (Fig 6A). Non-PCV13 serotypes appeared to have increased: 2 cases (6.7%) with serotypes belonging to group 11 and group 15 in 2010, and 4 cases (14.3%) with type 6C, group 15, and type 23A in 2011 (Table 3).

The serotype distribution among adult cases was more heterogeneous compared to the distribution among children. Serotypes 3, 14, 19A, 23F, and 8, in decreasing order, were the most common among adults in 2010 and accounted for 50.4% of all adult IPD cases; while the most common serotypes observed in 2011 were types 3, 6B, 8, and 14 accounting for 51.2% (Table 4). The proportions of IPD cases potentially covered by serotypes contained in PCV7,

### Table 3
**Distribution of pneumococcal serotypes among paediatric cases, 2010-2011**

<table>
<thead>
<tr>
<th>Pneumococcal serotype/group</th>
<th>Number of isolates</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Year 2010 (n = 30) (%)</td>
<td>Year 2011 (n = 28) (%)</td>
</tr>
<tr>
<td>Type 4 *§</td>
<td>1 (3.3)</td>
<td>-</td>
</tr>
<tr>
<td>Type 6B *§</td>
<td>6 (20.0)</td>
<td>2 (7.1)</td>
</tr>
<tr>
<td>Type 14 *§</td>
<td>3 (10.0)</td>
<td>6 (21.4)</td>
</tr>
<tr>
<td>Type 19F *§</td>
<td>2 (6.7)</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>Type 23F *§</td>
<td>3 (10.0)</td>
<td>-</td>
</tr>
<tr>
<td>Type 1 §</td>
<td>1 (3.3)</td>
<td>-</td>
</tr>
<tr>
<td>Type 3 §</td>
<td>-</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>Type 6A §</td>
<td>-</td>
<td>2 (7.1)</td>
</tr>
<tr>
<td>Type 19A §</td>
<td>12 (40.0)</td>
<td>11 (39.3)</td>
</tr>
<tr>
<td>Type 6C</td>
<td>-</td>
<td>2 (7.1)</td>
</tr>
<tr>
<td>Group 11</td>
<td>1 (3.3)</td>
<td>-</td>
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<tr>
<td>Group 15</td>
<td>1 (3.3)</td>
<td>1 (3.6)</td>
</tr>
<tr>
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<td>-</td>
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<td>Non-groupable</td>
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<td>1 (3.6)</td>
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<table>
<thead>
<tr>
<th></th>
<th>Year 2010 (n = 129) (%)</th>
<th>Year 2011 (n = 88) (%)</th>
<th>Total (%)</th>
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<tr>
<td>Type 4 *§</td>
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<td>5 (2.3)</td>
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<td>24 (11.1)</td>
</tr>
<tr>
<td>Type 19F *§</td>
<td>7 (5.4)</td>
<td>4 (4.5)</td>
<td>11 (5.1)</td>
</tr>
<tr>
<td>Type 23F *§</td>
<td>12 (9.3)</td>
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<td>5 (2.3)</td>
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<tr>
<td>Type 3 §</td>
<td>15 (11.6)</td>
<td>13 (14.8)</td>
<td>28 (12.9)</td>
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<td>Type 7F §</td>
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<td>Type 19A §</td>
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<td>Type 6C</td>
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<td>Group 15</td>
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<td>Group 17</td>
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<tr>
<td>Type 18F</td>
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<td>1 (1.1)</td>
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</tr>
<tr>
<td>Type 20</td>
<td>6 (4.7)</td>
<td>3 (3.4)</td>
<td>9 (4.0)</td>
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<tr>
<td>Group 22</td>
<td>4 (3.1)</td>
<td>-</td>
<td>4 (1.8)</td>
</tr>
<tr>
<td>Type 23A</td>
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<td>-</td>
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<tr>
<td>Group 33</td>
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<td>7 (8.0)</td>
<td>17 (7.8)</td>
</tr>
</tbody>
</table>

* serotype included in PCV7, § serotype included in PCV13
PCV13, and PPV23 were 37.2%, 68.2%, and 80.6% for year 2010; and 33%, 62.5%, and 77.3% for year 2011 (Fig 6B).

Discussion

In our previous report, we described the distribution of IPD serotypes in 2009; i.e. approximately one year prior to the inclusion of PCV7 in NCIP. This time, we present data from post-inclusion of PCV7 to just before inclusion of PCV13 into NCIP. When comparing the data obtained within the period 2009-2011, there appears to be a downward trend in the proportion of PCV7 serotypes among paediatric IPD cases: 80.1% (in 2009) decreasing to 50% (in...
A retrospective study reviewing IPD cases from 2005 to 2010 in KKH observed that the proportion of IPD serotypes covered by PCV7 during the period from post-introduction to just after inclusion of PCV7 into the NCIP (2005-2010) was not significantly different from the period of pre-introduction of PCV7 into Singapore (1998-2004) (73% versus 75.3%). This is despite the significant changes in serotype distribution, with an increased contribution of serotypes 6B and 19A, between the two study periods. Nevertheless, they noticed a decreased coverage of IPD serotypes in the late PCV7 introduction period (64.4%) versus the early PCV7 introduction period (78.6%)\textsuperscript{8}. Our data suggests that the decreasing trend of the proportion of PCV7 serotypes among IPD children seems to become more evident after the inclusion of PCV 7 in NCIP. Changes in the composition of paediatric IPD serotypes have been observed within the period 2009-2011. The non-PCV7 type 19A, followed by types 14 and 6B, predominated in 2010-2011 instead of the vaccine types 6B, 14, and 23F which were the most common in 2009 (Fig 7A). Replacement of vaccine types with nonvaccine types is a complex phenomenon which has occurred in most populations\textsuperscript{6}. The explanation for this is still unclear and it seems to be due to selective pressure exerted by vaccines, capsular switching as a survival mechanism or antimicrobial prescribing practices\textsuperscript{9-12}. Furthermore, fluctuation of serotype distribution in the absence of vaccine could play a part, and therefore needs to be considered when the effects of PCVs are evaluated\textsuperscript{13}. With the recent introduction of PCV13 into the NCIP, it may be expected to provide higher vaccine coverage, up to 82.1% of IPD cases in children, although some IPD cases positive for non-PCV13 serotypes have started to appear. It is important to closely monitor future changes in the composition of nonvaccine types. Continued genotypic surveillance to monitor clonal structure of circulating strains could allow drawing a more complete picture of IPD-associated pneumococcal population\textsuperscript{11}. Among adult IPD cases, the proportions of PCV7 and PPV23 associated serotypes were noted as 26.4% and 88.7%, respectively, based on half-year surveillance data in 2009\textsuperscript{7}. For the whole period 2010-2011, the potential PCV7 coverage was modest (35.5%) compared to PCV13 (65.9%), and PPV23 (79.3%). Similarly, Hsu LY et al previously reported that the proportions of PCV7 and PPV23 associated serotypes were 43.4% and 82.8%, respectively, among adult invasive pneumococcal cases hospitalized in Singapore General Hospital from 2000 to 2007; i.e. during the pre-introduction period and the early introduction period of PCV7 into Singapore\textsuperscript{14}. It suggests that PCV7 covers only a small proportion of adult IPD serotypes and may not be expected to make an impact on IPD among adults, and the appropriate use of PPV23 probably results in a decrease of adult IPD cases in Singapore. In terms of the IPD serotype distribution among adults, the fluctuation was also seen. Serotype 3, which has been found to be associated with significantly high case-fatality rates\textsuperscript{15}, predominated, while the less predominant serotypes (6B, 8, 14, 19A, 23F) varied over this period (Fig 7B). There are, however, several limitations to our report. Laboratory-based surveillance of IPD relies on the submission of specimens by six restructured hospitals’ laboratories to NPHL for serotyping in addition to serotyping performed at KKH. During the two-year period of this analysis, there were about 20% of confirmed IPD cases of which serotyping was not performed. Thus, the distribution of serotypes among
IPD cases presented here may not be fully representative. Additionally, as the numbers of IPD cases studied were small, serotype proportions and variation trends could be significantly distorted by small changes in the numbers of isolates.

In conclusion, despite the above limitations, continued surveillance of pneumococcal diseases is necessary to monitor the invasive pneumococcal disease dynamics and to detect emerging serotypes after the inclusion of PCV13 into the NCIP.
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References


Possible nosocomial transmission of measles in a public hospital

Introduction

Measles is an acute, highly communicable viral disease caused by the measles virus, a member of the genus *Morbillivirus* of the family *Paramyxoviridae*. The mode of transmission is by droplet spread or direct contact with the nasal or throat secretions of an infected person. The average incubation period for measles is 14 days with a range of 7-21 days. Outbreaks of measles are known to occur in settings where unvaccinated susceptible population congregates such as boarding schools, colleges, universities, factories, offices and institutions.

Measles vaccination is compulsory in Singapore since 1985. Under the National Childhood Immunisation Programme, the first dose of the trivalent measles, mumps and rubella (MMR) vaccine is to be administered by the age of 2 years and the second dose at 6-7 years of age. In view of the large proportion of reported cases among unvaccinated infants and preschool children, the MMR immunisation schedule was amended with the first dose given at 12 months of age and the second dose at 15-18 months of age with effect from 1 December 2011.

Over the past six years, the national vaccination coverage for the MMR vaccine has been consistently maintained at around 95% for the first dose, and above 90% for the second dose.

On 23 August 2011, the Ministry of Health (MOH) was notified of a cluster of five measles cases in a public hospital. Out of these cases, three had a previous admission to the institution within the past 2 weeks. We report herein the epidemiological investigations for this outbreak.

Epidemiological investigations

A clinical case was defined as a child presenting with rash, fever and one or more of the symptoms: cough or coryza or conjunctivitis. A laboratory confirmed case was defined as a clinical case with one or more of the following results: presence of measles immunoglobulin M (IgM), detection of measles virus either through immunofluorescence antigen testing (Ag IF) or measles polymerase chain reaction (PCR). A nosocomial case was defined as a confirmed case who had contact with another confirmed case in the hospital during 7-21 days before date of onset of symptoms if no other source was identified; a community acquired case was a confirmed case that had no prior travel history during the 21 days before onset of symptoms or was known to have contact with another confirmed case. Active case detection revealed a total of 14 laboratory confirmed measles cases that had been admitted to the same hospital between 2 August and 20 August 2011. Out of these cases, 7 were females and 7 were males. Their ages ranged from 4 months to 3 years. There were one Nepalese and 13 Singaporeans/ Singapore Permanent Residents comprising one Chinese, ten Malays and two Indians. All the cases had not been vaccinated against measles; 4 had missed their vaccination and the other ten were not due for their vaccination. Two family clusters were detected, one involving a pair of siblings and the other, a pair of cousins.
The epidemic curve for these 14 cases is shown in Fig 8. Of these 14 cases, seven had been previously admitted to this hospital for unrelated illnesses approximately two to three weeks before their admission for measles.

As part of our investigations into the possibility of intra-hospital (nosocomial) transmission of measles, we reviewed the movement history within the hospital for all 14 cases, to see if they had any common exposures in place and time.

Our investigations identified two general wards, Ward A and Ward B, as two areas where cases could be epidemiologically linked to each other in time and place. Cases 2 and 10 had both been admitted to Ward A, and Cases 2, 4, 5, 9, 11 and 12 had been admitted to Ward B.

Genotyping of the measles virus for Cases 2, 4, 5, 10, 12, and 13 was performed. Throat swabs were sent to the laboratory at Kandang Kerbau Women’s and Children’s Hospital for testing by real time PCR, and positive samples forwarded to the National Public Health Laboratory for genotyping. Genotyping was carried out following the protocol provided by the WHO Western Pacific Regional Office at the training workshop in Hong Kong in 2009. A 540-bp region of nucleoprotein (N) gene was amplified and sequenced. Sequences of N gene were submitted to Measles Nucleotide Surveillance (http://www.hpa-bioinformatics.org.uk/Measles/Public/Web_Front/main.php) to determine the genotypes.

Ward A

Case 2 was admitted for measles from 4 - 7 August 2011 at Ward A Bed 18. Case 10 was admitted for bronchiolitis from 7 – 9 August 2011 at Ward A Bed 13. Both beds were in the same cubicle as shown in Fig 9. They shared a common period of exposure for approximately 16 hours between 7 August 2011 0559 hrs and 7 August 2011 2200 hrs (Fig 10). Case 10 was readmitted on 21 August 2011 for measles. His onset date was 10 days after the common exposure. The measles virus isolated from both cases was of
D8 genotype and genotypically, 100% identical, thus confirming the common source of infection.

**Ward B**

Cases 2, 4, 5, 9, 11 and 12 had been admitted to Ward B, as shown in Fig 11.

Cases 2, 4 and 12 had overlapping periods of admission in Ward B, although their beds were situated in different cubicles and rooms within Ward B (Fig 11). Case 2 was admitted to Ward A on 4 August 2011, diagnosed with measles on 7 August 2011 and then transferred to Bed 26 in the isolation room of Ward B on the same day. The case was nursed in this room from 7 – 14 August 2011. Case 4 was admitted for bronchiolitis from 5 – 8 August 2011. Both Cases 2 and 4 shared an overlapping period of admission in Ward B for approximately 21 hours between 7 August 2011 22:00 hrs to 8 August 2011 17:45 hrs (Fig 12). Case 12 was admitted for upper respiratory tract illness and bronchiolitis from 6 – 8 August 2011. Cases 2 and 12 shared an overlapping period of admission in Ward B for approximately 1.5 days from 7 August 2011 22:00 hrs – 9 August 2011 11:30 hrs.

Case 4 was subsequently readmitted on 21 August 2011 for measles and the date of onset of measles symptoms was 8 days after the patient’s overlapping period of admission with Case 2. Case 12 was readmitted on 26 Aug 2011 for measles and the date of onset of measles symptoms was 16 days after the patient’s overlapping period of admission with Case 2. Cases 2, 4 and 12 were found to have been infected with measles of the same genotype D8, with a single nucleotide difference found in Case 2 (Fig 13).
Figure 11
Layout of Ward B of a public hospital

Figure 12
Common exposure period for Cases 2, 4 and 12

Case 4, bronchiolities, Bed 7
Case 2, measles, Bed 26 (Isolation Room)
Case 12, URTI, bronchiolities, Bed 3

Common exposure between 7 August 2011 2200 hrs and 8 August 2011 1745 hrs
Discussion

The epidemiological linkages of the reported cases and laboratory findings suggest nosocomial transmission of measles in Wards A and B. Case 2 could have infected Case 10 while they were both in Ward A. This is supported by the fact that their measles virus genotypes were 100% identical, they had a relatively close physical proximity within the ward and the onset of symptoms for Case 10 was 10 days after the overlapping period of admission which falls within the known incubation period of measles (7-21 days).

There are two possible hypotheses for transmission within Ward B.

(a) The first hypothesis is that Case 2 was the index case infecting Cases 4 and 12, based on the assumption that Case 2 may not have been fully compliant with isolation whilst in the ward. Cases 5, 9 and 11 could have been community-acquired infections as they did not have any exposure to Case 2 during the time they were in Ward B. Cases 2, 4 and 12 had similar genotype with only 1 nucleotide difference. Cases 4 and 12 also developed measles symptoms 8 days and 15 days, respectively, after their overlapping period of admission with Case 2, which is within the known incubation period for measles.

(b) The second hypothesis is that the index case was an unknown patient or visitor with measles (before the onset of rash) who was present in Ward B from 5 – 7 August 2011. This person could have infected Cases 4, 5, 9, 11 and 12, as all these five cases were in two neighbouring cubicles in the ward during the same period (5-7 August 2011) (Figs 11 and 14). These five cases also developed measles symptoms between 9 and 16 days after 5-7 Aug 2011, which falls within the known incubation period for measles. Genotyping was done for Cases 4, 5 and 12 and

![Figure 13: Sequence comparison of measles virus detected in Cases 2, 4 and 12](image)

| Case 2 | CAGCA|ACCC |
| Case 4 | CAGCACACCC |
| Case 12 | CAGCACACCC |

![Figure 14: Possible common exposure period for Cases 4, 5, 9, 11 and 12](image)
In the course of our investigations, we noted that some of the cases had not been immediately isolated at the start of their admission, even though they were suspected to be measles cases. They were only isolated after laboratory confirmation of measles. This may have potentially exposed other susceptible children to the virus. With effect from 24 Aug 2011, the hospital implemented a new policy to rectify this issue. All suspected measles cases will now be isolated from the start of admission and they will be de-isolated if the laboratory test results confirm that they do not have measles.

There were no reports of any frontline health-care workers from Wards A and B who were ill with measles in the months of July and August 2011. Therefore, healthcare workers as a source of infection for this cluster of cases were considered to be unlikely.

All frontline healthcare workers in this hospital are required to produce proof of measles and rubella immunity either by documentary evidence of vaccination or via serology testing.

Conclusion

This report describes a possible nosocomial outbreak of measles occurring within a healthcare setting. Similar incidents have previously been reported in the Republic of Korea\(^3\) as well as in Pennsylvania\(^4\) and Indiana\(^5\) in the United States. The risk of measles transmission within healthcare settings emphasizes the importance of early identification and isolation of suspected measles cases within the healthcare institutions as well as the need for high vaccination coverage of healthcare workers against measles. Other measures to prevent or reduce nosocomial transmission include maintaining high vaccination coverage and timely vaccination of children according to vaccination schedules.

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References


A suspected cluster of leptospirosis in Singapore in 2011

Background

Leptospirosis is a common zoonotic disease worldwide, caused by Leptospira bacteria\(^1\). Transmission occurs through direct contact with infected animals or through contact with materials contaminated by the urine of these animals, usually rodents and other small mammals\(^2\). Other leptospirosis carriers include dogs, cows, pigs and other mammals\(^2\). The disease is usually associated with rural areas and urban slums of developing nations\(^3\). However, outbreaks and clusters have been reported, where risk factors include involvement in water-related recreational activities, travel to rural areas and floods\(^1,3,4\).

Leptospirosis is not a notifiable disease in Singapore. However, medical practitioners do notify the Ministry of Health (MOH) of leptospirosis cases from time to time. Investigations will be carried out when a severe case is reported or a possible cluster of leptospirosis cases is suspected.

On 13 July 2011, MOH was notified by an infectious disease physician of a case of leptospirosis. The case had informed the physician that other members of his running group (RG) had also recently suffered from a febrile illness.

This report summarizes the epidemiological investigation into this possible cluster of leptospirosis cases.

Methods

As preliminary information pointed towards a possible cluster of leptospirosis cases, MOH carried out an epidemiological investigation as soon as the notification was received. The cases were identified and their personal particulars such as age, gender and ethnicity were recorded. Clinical signs and symptoms, date of onset of illness, laboratory results, and information on their medical treatment were obtained. Information on workplaces, residences and risk factors for leptospirosis exposure such as involvement in water-related recreational activities, travel to rural areas and floods\(^1,3,4\).

A field investigation was conducted along the running route used by the RG for a major running event. Water and muddy water samples were taken, respectively, from a wide water body and muddy field located along the route.

A case was defined as a person who tested positive for leptospiral IgM antibody, with a recent onset of flu-like symptoms followed by severe renal symptoms, and had a recent history of participation in a run along a forest trail in Bukit Batok Estate (Fig 15).

Epidemiological findings

Based on the case definition, two cases of leptospirosis were identified.

The index case (Case A) was a 48-year-old Caucasian male living in Singapore. He developed fever, chills, rigors, nausea and muscle ache on 27 June 2011 and subsequently visited a general practitioner (GP) for treatment. He was subsequently hospitalised on 3 July 2011 after his condition worsened, and
was diagnosed with acute renal failure. Serological tests showed that he was positive for leptospiral IgM antibody. He was treated with doxycycline and ceftriaxone and subsequently recovered.

The case worked in an office despatching engineers to service cranes on board ships. He reported that he did not go on board the ships.

The case lived with his family in a private apartment. The family did not rear any pets at home, nor were they aware of any recent complaints of rodent infestation around their residence. A pest control company carried out regular checks and pest control on a weekly basis at his residential area. None of his family members or any other residents in the area had been reported to be ill with similar symptoms. Furthermore, environmental survey of the vicinity around his residence had revealed no signs of a rodent infestation.

Case A stated that he often travelled to Senai Airport in Johor, Malaysia during the weekends to fly his private jet. He usually spent 3 hours at the airport and then returned to Singapore on the same day. On 25 June 2011, he had travelled to Senai Airport to fly his jet in the morning from 1000hrs to 1300hrs before returning to Singapore. The case actively participated in runs organised by RG, which were conducted every week at various locations. On the afternoon of 25 June 2011, Case A participated in a run along a forest trail in Bukit Batok Estate. The run involved 60 local members of RG and 100 foreign guest runners. Figure 15 shows the approximate running location and surrounding vicinity.

Active case finding through interviews with the lead runner and other runners in the RG revealed that three local participants (including Case A) had become ill with a febrile illness between 25 June 2011 and 13 July 2011. None of the foreign participants were reported to be ill.

One of the other 2 local participants who were ill was identified to be a case of leptospirosis (Case B). He was a 58-year-old Caucasian male Singapore permanent resident. He developed fever, cough and loose stools on 14 June 2011 but did not seek medical attention at that time as he thought he had flu. He was later admitted to Changi General Hospital on 9 July 2011 as his symptoms persisted, and he was eventually diagnosed with sepsis secondary to left lower limb cellulitis and urinary tract infection, as well as acute kidney impairment. He was tested positive for leptospiral IgM antibody although his urine culture results were negative for *Leptospira*. He was treated with ciprofloxacin and clindamycin and discharged well on 13 July 2011.

The case was a retiree who lived with his family in a private apartment. He did not keep any pets at home and was not aware of any recent rodent infesta-
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The case also had no recent history of travel overseas.

The other local participant reported feeling unwell on the day of the 25 June 2011 run, and thus only assisted on the sidelines. He subsequently developed fever on 28 June 2011 and sought treatment from a GP as well as outpatient treatment at a hospital. The GP’s diagnosis was that of a bacterial upper respiratory tract infection. No laboratory tests were done to identify the causative organism. As such, we were unable to confirm if this was a case of leptospirosis.

Description of RG’s running activities

The lead runner of RG stated that two ‘reconnaissance’ runs through the same forest trail in Bukit Batok estate were conducted on 7 June 2011 and 21 June 2011, involving about 60 local RG members each time. These were followed by the main event run on 25 June 2011.

Case A participated in all three runs on 7, 21 and 25 June 2011. Case B had assisted on 7 June 2011 to set up the river crossing ropes across a wide body of water for the reconnaissance run, spending at least 2 hours in the water. He did not participate directly in the runs held on 21 June 2011 and 25 June 2011, but only assisted on the sidelines.

The dates of onset of illness of Cases A and B in relation to these 3 runs are shown in Fig 16.

Field inspection findings

A field inspection of the forest trail was carried out on 21 July 2011. The forest trail used for the run consisted of a series of dirt trails. These trails were surrounded by moderately dense vegetation on both sides. The trail was intercepted by several small streams along the way (Fig 17). Along the trail, the runners had to cross a wide body of water measuring approximately 15 metres wide and 1.2 metres deep. This was done using ropes secured on trees across the water body, which was set up by several members of RG prior to the run.

A survey of the trail revealed no obvious signs of any rodent infestation in the vicinity. Water and muddy water samples that were taken on 27 July 2011 from the wide water body and a muddy field along the trail yielded negative results when cultured for Leptospira.

Discussion

Our investigation revealed two cases of leptospirosis who were both members of the same running group, and who had participated in a run on a forest trail in Bukit Batok estate in a 3-week period between 7 and 25 June 2011. Both tested positive for leptospiral IgM antibody and had presented with symptoms and a biphasic pattern consistent with leptospirosis (i.e. a mild initial phase characterized by flu-like symptoms followed by a second, more serious phase which included severe renal symptoms).

Interviews with Cases A and B did not identify any other potential risk factors in their occupation, residential environments, or travel history, which could have exposed them to animals or contaminated soil, vegetation or water. Given that the only common link between the two cases was their run on the forest trail and their exposure to the water body on the trail, this activity was considered to be the most likely source of infection. The date of onset of illness for Cases A and B were consistent with the incubation period for leptospirosis (usually 5-14 days, with a range of 2-30 days). Both cases mentioned that they
had suffered cuts during the course of the run(s). This increased their risk of acquiring an infection when wading through the water body along the route.

Environmental sampling did not reveal the presence of *Leptospira*, and there were no obvious signs of rodent or animal presence in the area. However, this does not exclude the possibility that the water might have been previously contaminated by urine of infected animals, as the sampling was only done 4-6 weeks after the cases were exposed to the water. Furthermore, the samples were only taken from the sides of the water body, whereas the cases had waded through the middle of the water body.

Recent reviews have reported an emerging trend of leptospirosis acquired through recreational activities in rural areas such as hiking, fresh water swimming and rafting. Recent outbreaks have been reported worldwide associated with such activities. These rural areas...
are home to small mammals such as bats, rats and other rodents, which are all potential carriers of *Leptospira*. In rural, forested areas, the best way to avoid an infection would be to avoid high-risk activities, such as traversing through bodies of water or muddy areas with dense vegetation, especially when a person has cuts or similar injuries which may increase the risk of exposure to contaminated animal urine in the environment. Vaccination against leptospirosis is a developing area, and may be a viable option for the prevention of leptospirosis infection in the future.

The number of reported cases of leptospirosis in Singapore is low (approximately 10-60 cases per year). However, recent trends observed in other developed and urban settings worldwide show that the possible emergence of leptospirosis as an important disease should not be dismissed. Measures such as chemoprophylaxis can be considered for groups with a higher risk of exposure, such as military personnel or regular outdoor activity enthusiasts. Public education to raise awareness on leptospirosis and other diseases associated with outdoor activities could also be considered.

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