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CONTENTS

Safety monitoring of H1N1
vaccines in Singapore during
the H1N1 pandemic pg 22

Epidemiological review of
cholera in Singapore,
1994-2009 pg 27

Burden of communicable
diseases in Singapore pg 34

Laboratory-based surveillance
system of invasive
pneumococcal diseases
in Singapore: a nationwide
monitoring of vaccine
serotype coverage pg 40

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Safety monitoring of H1N1 vaccines in Singapore during the H1N1 pandemic

Introduction

In June 2009, the World Health Organisation (WHO) declared a H1N1 pandemic, and vaccines, being one of the most important medical interventions during a pandemic, were developed quickly by manufacturers in large quantities to meet the demands of the various countries.

In Singapore, the Health Sciences Authority (HSA) employed a “rolling review and submission” of pandemic vaccines, similar to the approach taken by health authorities worldwide. This allowed vaccine manufacturers to submit data sets for review by HSA as and when they became available, without having to wait until all the data was ready, as would be the case for products reviewed under normal circumstances. Two H1N1 vaccines, namely Panvax[®] H1N1 vaccine by CSL Limited, Australia and Pandemrix[®] H1N1 vaccine by Glaxo Smithkline Biologicals were approved for use by HSA in the last quarter of 2009. Both vaccines contained the A/California/7/2009 (H1N1) viral antigen.

Pandemic vaccine vigilance has challenges associated with it. As these vaccines were to be used in a very large number of patients, certain adverse events which were too rare to show up in clinical trials may become apparent when a significant number of patients were given the vaccines.

To safeguard public health, HSA, with the support of the Ministry of Health (MOH), enhanced its existing post-marketing vigilance activities to closely monitor the safety profile of H1N1 vaccines. Innovative measures were put in place to help ensure that emerging safety concerns

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associated with the vaccines were quickly picked up and also disseminated to healthcare professionals in a timely manner.

Enhanced postmarketing vigilance activities

The new initiatives to closely track the safety profile of H1N1 vaccines were developed in collaboration with MOH, the healthcare clusters and other relevant health authorities. They include the following:

1. Establishment of a registry for patients vaccinated with H1N1 vaccines in Singapore

Patient exposure data is essential for the benefit-risk assessment of H1N1 vaccines. A registry of all patients vaccinated was developed to enable MOH and HSA to keep track of the number of doses administered and calculate the incidence rate of any adverse event that may occur.

The National Immunisation Registry (NIR) worked on enhancing its existing database to allow for mass H1N1 vaccination notifications. This was made electronically available through the Health Professional Portal and forms for vaccination recording were specially prepared for this purpose.

As of March 2010, the NIR has processed more than 250,000 notifications from over 1,000 healthcare institutions and medical clinics. *Fig. 1* shows the breakdown of vaccination uptake by age group.

2. Setting up of a sentinel site for active safety surveillance of targeted patient groups

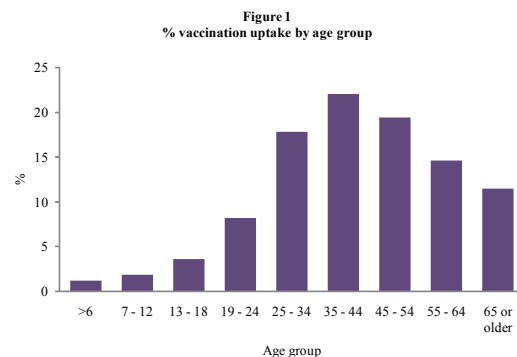
A sentinel site was set up at Kandang Kerbau Women and Children Hospital in Nov 2009 to focus

on the active safety surveillance of H1N1 vaccines in pregnant women and children. The team working on this project comprised a principal investigator from Paediatric Infectious Diseases, assisted by a co-investigator from Paediatric Allergy and Immunology and a research nurse. The programme was named HK-INSPiRE (HSA-KKH Inpatients' Surveillance of Post-vaccination Reactions). As data on vaccine efficacy and safety were limited in these groups of patients, the sentinel site served as a data collection point for these special patient groups.

Since H1N1 vaccination started on 3 November 2009, more than 1,500 pregnant women were screened. No vaccine adverse events (VAEs) relating to pregnancy outcomes has been reported.

3. Reporting of serious vaccine adverse events (VAEs)

Prior to the commencement of H1N1 vaccination, road shows were conducted by HSA to strongly encourage the reporting of all serious VAEs suspected to be associated with the vaccines. Healthcare professionals were strongly encouraged to report all fatal and life-threatening events suspected to be due to vaccination as soon as possible, preferably within **24 hours** and all other serious reports within **7 days**.



New VAE reporting forms were printed and disseminated to the healthcare institutions and medical clinics as part of the pandemic vaccination information kit. Three different platforms were established to facilitate the submission of VAE reports, namely:

- Online reporting through the Critical Medical Information Store (CMIS).
- Web-based reporting through HSA's website.
- Manual reporting through fax or mail.

The ADR/drug allergy reporting module of CMIS in the healthcare clusters was enhanced with an additional field to include batch number of the vaccine to facilitate signal detection of batch-related problems.

4. Review of adverse events of special interest (AESIs)

A list of AESIs was identified based on past experience associated with influenza vaccines. Local experts' opinion from the various medical disciplines were sought to establish the clinical relevance of the AESIs in the local context. Using the available standard case definitions from Brighton Collaboration, questionnaires were created and modified based on the recommendation from the local experts consulted.

Upon receipt of an adverse event report, the Vigilance Branch (VB), HSA, would send the relevant questionnaire to the reporting physician. The feedback obtained allowed HSA to assess the level of evidence for the reported case and allowed comparability of AESIs across international surveillance systems. In addition, the epidemiology team from MOH provided the local background incidence of the AESIs over the past few years, which formed the basis of the observed-to-expected analysis of vaccine safety signals in Singapore.

Recognising that the concern in the past that were associated with similar type of vaccines were rare neurological events such as Guillain-Barre Syndrome, HSA established a Neurology Expert Advisory Committee comprising five experienced neurologists from the healthcare clusters. The objective of this committee was to adjudicate the adverse neurological events associated with H1N1 vaccines and to determine the causality based on the assessment criteria established by the World Health Organization.

5. Working closely with product licence holders (manufacturers) on intensive monitoring of local VAEs for signal detection

The product licence holders of the H1N1 vaccines were informed of HSA's expedited timelines for VAE reporting. They were mandated to submit all known serious VAEs to their products which included the following:

- a. All fatal and life-threatening reports occurring locally to be submitted to VB within 24 hours from first notification of event and all other reports to be made within 7 days.
- b. All international fatal and life-threatening reports and adverse events of interests (AESI) to be reported to VB as soon as possible, preferably within 7 days.

In addition, the product licence holders were required to submit a monthly simplified periodic safety update report (PSUR) accompanied by a summary of vaccine distribution and patient exposure both locally and internationally.

6. Collaboration with other regulatory agencies and international surveillance

HSA worked closely with its consortium regulatory partners such as the US Food and Drug



Administration (FDA), European Medicines Agency (EMA), Australia's Therapeutic Goods Administration (TGA), Health Canada (HC) and Swissmedic to share safety signals. The VB officers also took part in weekly teleconferences organised by the WHO on H1N1 vaccine safety involving more than 20 other international drug regulators. This ensured that all participants were kept apprised of the experience of the various countries which have initiated H1N1 vaccination in their population and also of WHO's position of the safety profile of these vaccines.

7. Communication to the public and media

A significant amount of effort by MOH, the Health Promotion Board and HSA was put into providing up-to-date information for the public.

Various communications channels (media, websites, blogs) were employed and H1N1 vaccine enquiry phone lines were also set up for this purpose. This hotline was manned by MOH to manage the communications with healthcare professionals and the public regarding all pandemic queries.

A medication guide for patients was developed in four different languages. Common adverse events and their management were outlined. Rare serious events were also mentioned to ensure that an informed decision on vaccination was made by the patient. This medication guide accompanied the pandemic vaccination kits that were sent to all purchasers of the vaccines. In addition, a vaccination card was included in the kit to record the vaccines administered to the patients. This card served as an important source of information for the clinical management of patients who experienced a serious adverse event. There was considerable media coverage of these information brochures which were well received by the healthcare community.

During the monitoring period, HSA regularly shared vaccine safety information through the HSA-Adverse Drug Reactions bulletins and Dear Healthcare Professional Letters (DHPL). The serious VAEs were also made public through postings on HSA's website and updated regularly.

8. Overview of local adverse event reports associated with H1N1 pandemic influenza vaccines

The H1N1 vaccination programme began on 3 November 2009. As of 28 February 2010, approximately 425,000 doses of the vaccines have been distributed, with Panvax® accounting for majority of the sales. Over this same period, HSA has received 152 reports of suspected vaccine adverse events of which 89% were assessed as non-serious. The median age of the patients was 21 years (range: 5 months to 82 years). The majority of the events occurred within the first 3 days of vaccination. Most of the reports described already known adverse events that are associated with seasonal flu vaccines. This is consistent with the World Health Organisation's (WHO) finding that the safety profile of the pandemic vaccine is similar to that observed for seasonal flu vaccines, based on the over 300 million doses of vaccines that have been distributed globally. *Table 1* shows a breakdown of the common vaccine adverse events.

Seventeen (11%) of the adverse event reports were assessed as serious by the reporting physicians. They include six reports of allergic reactions of varying severity: a case each of anaphylaxis, exacerbation of pre-existing scleritis, Sweet's syndrome, puffy eyes and facial flushing and Churg-Strauss syndrome. Five of these patients have pre-existing medical conditions such as asthma or are known to be allergic to certain medications.



Table 1
Common adverse events associated with Panvax®

Suspected adverse reaction	% of total reactions
Hypersensitivity reactions (skin/respiratory tract)	30
Influenza-like illness	17
Application-site reactions and general disorders (e.g. fever, tiredness)	15
Nervous system disorders (e.g. giddiness, numbness, headache)	13
Musculoskeletal disorders (e.g. myalgia, body aches)	8
Gastrointestinal (e.g. nausea, diarrhoea)	6
Other system organ classes (e.g. urinary, ocular)	11

Seven other reports include a case of new onset diabetes, a case of dystonia, a case of persistent vomiting, two cases of facial palsy and two cases of H1N1 infection in patients who received vaccination more than 2 weeks prior to the onset of influenza illness. It is to be noted that no vaccine or drug is 100% effective and vaccination failure may still occur in certain instances.

Four of the other serious reports were in children and these include a case of high fever, a case of hypotonic-hyporesponsive episode and two cases of seizures. All the patients have since recovered or are recovering.

Other than the reports involving allergies such as anaphylaxis, puffy eyes, facial edema and vomiting which are known to be associated with vaccines in general, it cannot be concluded that H1N1 vaccines caused the other serious adverse events as they could be coincident events of natural progression of an

underlying disease condition. Based on the review of local reports and the global experience of the other countries, there has been no signals of any major safety concern associated with the H1N1 vaccines thus far.

Conclusion

The strong support and cooperation provided by the various stakeholders involved in the pandemic planning have enabled the establishment of a robust postmarketing surveillance system which provides for public confidence.

HSA would like to take this opportunity to thank all healthcare professionals for diligently submitting the serious VAEs suspected to be associated with H1N1 vaccines and the notifications of vaccination to NIR. This has contributed significantly to HSA's ability to closely track the risk benefit profile of the H1N1 vaccines used in Singapore.



(Reported by Chan C L, Soh S and Toh D, Vigilance Branch, Health Products Regulation Group, Health Sciences Authority)

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Epidemiological review of cholera in Singapore, 1994-2009

Introduction

Cholera was introduced into Singapore soon after it was founded as an entrepot port in 1819 during the first cholera pandemic (1819-1825).¹ Despite the implementation of stringent quarantine measures, several outbreaks of cholera were reported in Singapore during the nineteenth century in 1841, 1851, 1858, 1862 and 1864.^{2,3} El Tor cholera was first reported in Singapore in 1944 in an outbreak at Loyang involving villagers who had consumed cabbages dumped into the sea from an infected Japanese ship.⁴ It was reintro-

duced into the country in 1963 as an extension of the seventh cholera pandemic. Sporadic cases of El Tor cholera continued to be reported in subsequent years with island-wide outbreaks in 1972 (114 cases)⁵ and 1978 (83 cases).⁶ Well-defined localized outbreaks were reported among foreign construction workers in 1982⁷, inmates of an institution for the aged sick in 1987⁸, and a psychiatric institution in 1990.⁹

We present the findings of an epidemiological review of the cholera situation in Singapore from 1994 to 2009.



Findings

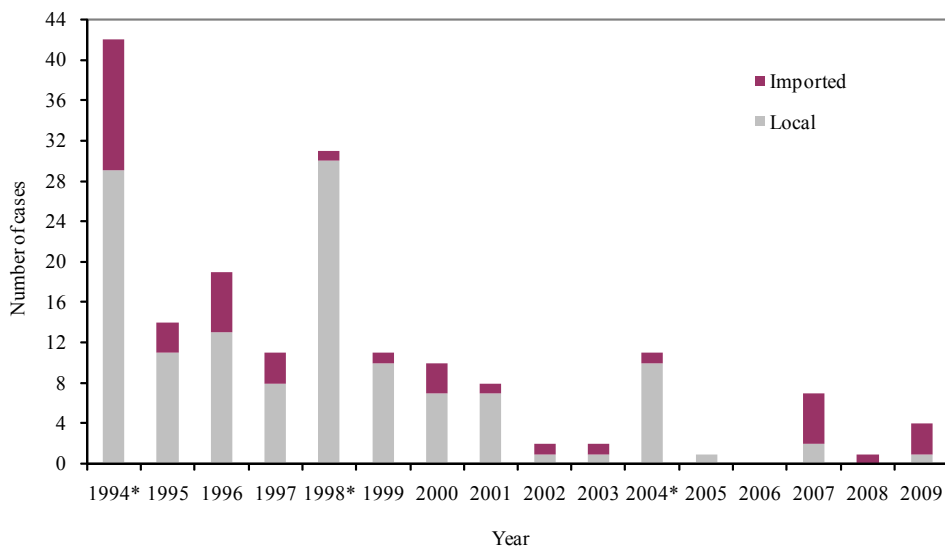
A total of 174 cases were reported over the 18-year period from 1994 to 2009, and the annual number ranged from 0 in 2006 to 42 in 1994. The incidence showed a downward trend from 42 cases in 1994 to 10 cases in 2000 and 4 cases in 2009 (Fig. 2). The incidence rate depicted some cyclical patterns with the peaks declining from 1.2 per 100,000 in 1994 to 0.8 per 100,000 in 1998, 0.3 per 100,000 in 2004 and 0.1 per 100,000 in 2009.

Cases were evenly distributed between the two genders. Adults had a higher incidence rate than children and those above the age of 55 years had the highest mean age-specific incidence rate (Table 2). The mean annual proportion of cases in the 15-24 years age group decreased significantly from 16.3% in 1994-1997 to 2.3% in 2002-2005 ($p < 0.001$), and subsequently increased to 4.8% in 2006-2009. On the other hand, the mean annual

proportion of cases in the 55 years age group or older age group increased significantly from 29.9% in 1992-1995 to 88.6% in 2002-2005 ($P < 0.0005$), and subsequently dropped to 17.9% in 2006-2009. The majority of the reported cases involved local residents. Foreigners constituted between 5% and 17% of the reported cases. Among the three major ethnic groups, the mean annual ethnic-specific incidence rate of Malays was higher than that of Chinese and Indians during the period 1994-2005, while the mean annual ethnic-specific incidence rate of Indians was the highest during the period 2006-2009 (Table 3). Among the resident cases by ethnic group, the mean annual proportion of Chinese was the highest, followed by Malays and then Indians.

Imported cholera accounted for 6.9% of all the reported cases from 1994-2009 (Table 4). Most of these cases acquired the disease from countries in the region such as Malaysia, Thailand, Indonesia, India and Pakistan.

Figure 2
Number of reported cholera cases by classification, 1994-2009



* There were 4 local death cases 1 in 1994, 2 in 1998 and 1 in 2004.



Table 2
Mean annual age-specific incidence rates (per 100,000 population) of reported cholera cases, Singapore, 1994-2009

Age group (years)	1994-1997 (n=86)	1998-2001 (n=60)	2002-2005 (n=16)	2006-2009 (n=12)
0 – 14	0.1 (3.7)	0.1 (4.6)	0 (0)	0 (0)
15 – 24	0.6 (16.3)	0.2 (12.6)	0.04 (2.3)	0.03 (4.8)
25 – 34	0.5 (22.8)	0.3 (18.5)	0.1 (4.5)	0.1 (22.6)
35 – 44	0.4 (13.6)	0.5 (27.3)	0.03 (2.3)	0.1 (13.1)
45 – 54	0.9 (14.7)	0.4 (13.4)	0.04 (2.3)	0.1 (41.7)
55+	1.6 (29.9)	0.9 (23.6)	0.5 (88.6)	0.1 (17.9)
Total	0.6 (100.0)	0.4 (100.0)	0.1 (100.0)	0.1 (100.0)

Figures in brackets refer to percentage distribution

Table 3
Mean annual ethnic-specific incidence rates (per 100,000 population) of reported cholera cases, Singapore, 1994-2009

Ethnic group	1994-1997 (n=86)	1998-2001 (n=60)	2002-2005 (n=16)	2006-2009 (n=12)
Residents				
Chinese	0.6 (65.4)	0.3 (47.5)	0.1 (76.1)	0.1 (69.1)
Malay	1.1 (16.5)	0.9 (34.4)	0.2 (6.8)	0.1 (8.3)
Indian	0.6 (6.1)	0.1 (0.8)	0 (0)	0.1 (8.3)
Others	0.6 (2.3)	2.4 (3.2)	0 (0)	0.5 (9.5)
Foreigners	0.4 (9.8)	0.2 (14.1)	0.1 (17.1)	0.02 (4.8)
Total	0.6 (100.0)	0.4 (100.0)	0.1 (100.0)	0.1 (100.0)

Figures in brackets refer to percentage distribution.

Table 4
Local and imported cases of *Vibrio cholerae*, serogroup O1 biotype El Tor and serogroup O139, 1994-2009

Serogroup	1994-1997 (n=86)	1998-2001 (n=60)	2002-2005 (n=16)	2006-2009 (n=10*)
<i>Local cases</i>				
El Tor				
Ogawa	84	49	3	3
Inaba	1	9	10	0
O139	1	2	0	0
<i>Imported cases</i>				
El Tor				
Ogawa	0	0	0	5
Inaba	0	0	3	2
O139	0	0	0	0

* In 2009, 2 imported cases were excluded; one was of *Vibrio cholerae* O1 with Ogawa and Inaba, and one was of *Vibrio cholerae* with unknown serogroup.



There were 4 cholera-related deaths, 1 each in 1994 and 2004, and 2 in 1998, giving an overall case-fatality rate of 2.3%. All the 4 deaths were local cases and their ages ranged from 67 to 89 years. They all had co-morbidities and were admitted to hospital in a state of severe dehydration.

Most of the cholera cases (83.2%) were caused by *V. cholerae* O1, biotype El Tor, serotype Ogawa (Table 4). All the cases due to the O139 serogroup were imported from India, Thailand, Indonesia and China.

Based on available records of the Department of Pathology, Singapore General Hospital, both *V. cholerae* O1 and O139 were sensitive to ciprofloxacin and tetracycline. However, *V. cholerae* O139 was resistant to cotrimoxazole, but that of O1 was sensitive.

Several outbreaks of cholera were reported. In an outbreak which occurred during a Malay wedding function at Jurong in 1999, a total of 8 cases of El Tor cholera, serotype Ogawa, were reported, with 4 detected through contact tracing and one through screening of implicated foodhandlers. The incriminated food item was iced banana-flavored drink ($p=0.01$). Careful enquiries showed that the crushed ice for cooling the drink was probably cross-contaminated when it was stored in styrofoam boxes previously used for the storage and transport raw fishes and other seafood.¹⁰

In another outbreak, a total of ten cases of El Tor cholera, serotype Ogawa, with onset of illness between 3 October and 10 October 2004 were reported. An elderly man with co-morbidities died. Seven of the cases lived in Bedok and Tampines and had taken their meals from various food establishments there. Consumption of 4 seafood items (prawns in noodles, steamed prawns,

cooked squid and fried fish, was significantly associated with illness. It could not be established how the imported seafood was contaminated.¹¹

Comments

Despite Singapore being located in a cholera-endemic region, the disease incidence has been declining and the situation is currently very similar to that of other developed countries.¹²⁻¹⁵ Factors contributing to the successful control of cholera include the high standard of environmental sanitation and hygiene¹⁶, the comprehensive disease surveillance system⁶, licensing and control of food factories and retail outlets, and health education and supervision of public foodhandlers.

The declining trend of cholera as well as other foodborne diseases such as typhoid and hepatitis A over the last 16 years could be attributed to further improvements in food hygiene practices. The NEA's grading system for eating establishments and food stalls, introduced in 1997, is a structured system of appraisal for food outlets that is intended to motivate licensees to improve and maintain good personal and food hygiene, and housekeeping of their premises. This regime has yielded significant improvements in food hygiene levels in Singapore. The proportion of grade 'A' and 'B' stalls increased from 46% in 2002 to 86% in 2008, while the remaining 14% of stalls were graded "C" and they met the hygiene requirements.¹⁷ The NEA's hawker centres upgrading programme implemented in 2001 has also contributed to an improvement in overall hygiene standards at hawker centres. A total of 72 centres have since been upgraded with better facilities and toilets, amongst other improvements, while the remaining 30 centres will be upgraded by 2012.¹⁸



Cholera is predominantly an adult disease in Singapore, especially among those above 55 years of age, unlike salmonellosis which affects mainly the young. The high incidence of cholera among the elderly could be contributed by the lower levels of gastric acid¹⁹ and lower infective dose of *V. cholerae* needed to cause clinical disease in persons with hypochlorhydria.^{20,21} The incidence of cholera has decreased in all ethnic groups. However, ethnic differences in incidence rates persist. This could not be attributed to environmental hygiene, as over the last two decades, there have been vast improvements in environmental sanitation, including universal potable water supply piped to every home in all communities. One possible reason for this could be differences in food preference and methods of food preparation among the ethnic groups. For example, the Chinese prefers to consume fish and shellfish such as cockles and oysters raw or partially cooked. Foreign workers are also known to have contracted cholera by consuming wild shellfish indiscriminately picked up from sewage-contaminated areas.

Singapore remains highly vulnerable to the introduction of cholera through trade and travel. *V. cholerae* O139 was imported into the country in March 1993, just a few months after the epidemic of cholera-like illness started in Madras, India in October 1992. Of the 5 imported cases reported, one was a Singapore residents who acquired the disease during a social visit to Madras, India, and the others were all Indian tourists from Madras.²² Because of the high level of environmental hygiene, no secondary transmission occurred and *V. cholerae* O139 could not established a foothold in Singapore.

However, sporadic cases of El Tor cholera continued to be reported with occasional localized

outbreaks due to contaminated food, in particular seafood or articles cross-contaminated by it, as illustrated in the outbreak in Jurong in 1999 described above. Contaminated seafood eaten raw or inadequately cooked is a well-known vehicle of transmission.²³⁻²⁸ Steamed prawns served in a cold dish was implicated in an outbreak in which 13 persons were infected (7 symptomatic and 6 asymptomatic) following a Moon-cake Festival dinner in Chinatown in 1978.⁶ ‘Sambal sotong’ (squid) was the vehicle of transmission in an outbreak in Marine Parade in 1981.⁷ Consumption of raw sliced fish (‘Yu-sheng’) from imported fresh water carp (‘Song-he’) served with porridge in various outlets was responsible for 4 cases in 1995, 3 cases in 1996 and 12 cases in 1998.

So far, no large nationwide outbreaks of cholera due to imported food have been reported unlike other food-borne diseases such as hepatitis A traced to imported oysters from the Philippines²⁹ and imported cockles from Malaysia³⁰; paratyphoid A due to imported oysters from the Philippines³¹ and imported coconut from Malaysia³², and norovirus gastroenteritis due to imported oysters from China³³.

However, there is no room for complacency. A high level food safety and hygiene practices should be uniformly and consistently maintained at all times and the public should be discerning when consuming food, especially seafood which is served raw or undercooked. ‘Yu-sheng’ which is widely consumed during the Chinese New Year period is kept under close surveillance and samples routinely collected for testing of enteropathogens, including *V. cholerae*.

Unlike typhoid whose endemicity is maintained by chronic human carriers, cholera carriers are short-term excretors. While the source of infection of



the sporadic cases of cholera with no travel history could not be determined, there is no reason to believe that they are infected by undetected carriers in the community. Occasionally, a few implicated public foodhandlers routinely referred for screening were incidentally found to be infected with *V. cholerae* O1. Since the infective dose of *V. cholerae* O1 is high (10^{8-11} organisms), secondary cases arising from person-to-person transmission in household settings are unlikely.³⁴

Over 70% of the cholera cases in the last 3 years from 2007-2009 were imported. This reflects the significance of cholera as a travel-related disease. Singaporeans travelling to cholera-endemic countries should be educated on the importance of good food and water hygiene practices. Moreover, they should be reminded on the importance of prompt medical consultation should they develop

symptoms of cholera during and after the trip. Healthcare professionals should also consider cholera as a differential diagnosis in severe diarrhea cases, especially in those who give a recent travel history to a cholera-endemic country. They may also consider protecting travellers with an oral cholera vaccine consisting of inactivated vibrios plus B-subunit of the cholera toxin. The four cholera-related deaths which occurred during the study period were between 67 and 89 years of age, and they had other co-morbid conditions. They succumbed rapidly from severe dehydration as they sought medical treatment late. A high degree of clinical suspicion and early detection and treatment with rapid fluid and electrolyte replacement and antibiotic therapy^{35,36} should lower the relatively high case-fatality rate (1.9% compared to about 1% in Europe and Americas³⁷), especially among the elderly with co-morbidities.

(Reported by Wong CS¹, Ang LW², James L² and Goh KT³, ¹ Centre for Molecular Epidemiology, National University of Singapore, ² Communicable Diseases Division, Ministry of Health and ³ Office of the Director of Medical Services, Ministry of Health)

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Burden of communicable diseases in Singapore

Introduction

Rapid economic development over the past few decades has brought tremendous improvements in the living conditions and health status for the Singapore population. Improved sanitation and immunisation programmes in children have markedly reduced the incidence of many communicable diseases in the local community. However, the recent emergence of severe acute respiratory syndrome (SARS) and swine influenza virus (H1N1) across the world is a constant reminder that communicable diseases will continue to pose health burdens for the nation.

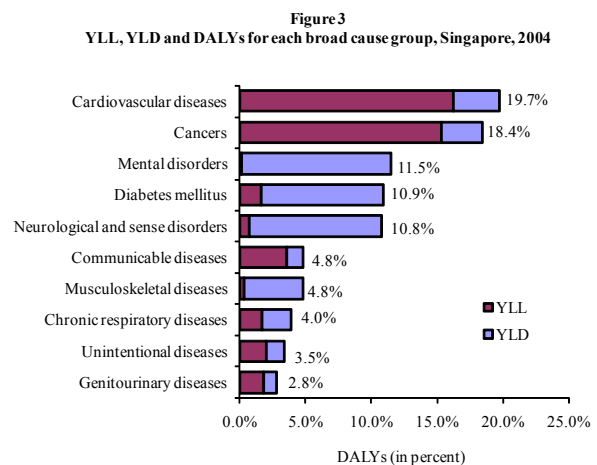
This article focuses on the burden of communicable diseases, based on the findings from the Singapore Burden of Disease Study 2004 (SBoD Study 2004). This study is the first comprehensive assessment of the health status of Singapore residents in terms of mortality and morbidity for specific diseases. The “burden of a disease” is measured by a single indicator known as disability-adjusted life year (DALY). One DALY can be thought of as one lost year of “healthy” life and is calculated as a combination of 1) years of life lost (YLL) due to premature mortality and 2) equivalent years of “healthy” life lost due to ill health or disability (YLD). These indicators provide a measure of the gap between current health status and an ideal situation in which everyone lives into old age without any disease or ill health. Full details of the methodology and data sources used in the estimation of DALYs can be found in the SBoD Study 2004 report.

Total disease burden from premature mortality and disability was 363,231 DALYs in Singapore in

2004. Communicable diseases comprising of infectious and parasitic diseases and respiratory infections made up 4.8% of total DALYs (17,431 DALYs) (*Fig 3*). A larger share of our disease burden was dominated by non-communicable diseases resulting from our sedentary lifestyles as well as an aging population. Cardiovascular diseases, cancers, mental disorders, diabetes and neurological and sense disorders were the major broad causes of non-communicable diseases that accounted for 88% of total DALYs (320,155 DALYs). Injuries, maternal, perinatal and nutritional conditions contributed the remaining 7.1% of the DALYs (25,645 DALYs). Close to three quarters of the total DALYs for the communicable diseases was attributed to premature mortality mainly due to respiratory infections.

By specific causes

Within the communicable diseases, the respiratory infections group had a slight larger share of



disease burden at 2.8% of total DALYs while the proportion for the infectious and parasitic diseases group was 2.0% (Table 5). Most of the burden from respiratory infections was because of premature deaths (91%) rather than ill-health (YLD) (9.3%). On the other hand, the distribution between years of life lost (53%) and YLD (47%) for infectious diseases was almost even.

In term of specific causes, lower respiratory tract infections (primarily pneumonia) were the most significant contributor of disease burden among all communicable diseases. It was ranked as the 7th and 4th leading causes of overall DALYs (2.7%) and YLL (5.3%), respectively (Table 5). The second largest cause was HIV/AIDS (0.5% of overall DALYs) followed by tuberculosis (0.3%) and hepatitis (mainly

Table 5
Communicable diseases burden (DALYs, YLL and YLD) by specific causes, Singapore, 2004

Specific cause	DALYs	% of total DALYs	YLL	% of total of YLL	YLD	% of total of YLD
Infectious and parasitic burden	7,177	2.0	3,835	2.2	3,342	1.8
Tuberculosis	1,093	0.3	831	0.5	262	0.1
Sexually transmitted diseases ¹	109	0	30	0	78	0
HIV/AIDS	1,840	0.5	1,215	0.7	625	0.3
Diarrhoeal diseases and gastroenteritis	471	0.1	143	0.1	328	0.2
Childhood-cluster diseases ²	1	0	0	0	1	0
Meningitis (Bact.)	102	0	99	0.1	3	0
Septicaemia	195	0.1	0	0	195	0.1
Dengue	79	0	65	0	14	0
Hepatitis	916	0.3	282	0.2	635	0.3
Hepatitis B ³	880	0.2	273	0.2	608	0.3
Malaria	21	0	21	0	0	0
Other infectious diseases ⁴	2,350	0.6	1,149	0.7	1,202	0.6
Respiratory infections burden	10,254	2.8	9,297	5.3	957	0.5
Lower respiratory tract infections	9,762	2.7	9,253	5.3	509	0.3
Upper respiratory tract infections	347	0.1	40	0	307	0.2
Otitis media	145	0	4	0	141	0.1
Total communicable diseases burden	17,431	4.8	13,132	7.5	4,299	2.3

¹ Sexually transmitted diseases include syphilis, chlamydia, gonorrhoea and other sexually transmitted diseases but exclude HIV/AIDS.

² Childhood-cluster diseases include diphtheria, whooping cough, tetanus, poliomyelitis, measles, rubella and *Haemophilus influenzae* type b (Hib).

³ Includes hepatitis C-related cirrhosis.

⁴ Other infectious diseases include chicken pox, hand, foot and mouth disease and all other infectious and parasitic diseases.



due to hepatitis B (0.3%). Owing to our effective routine immunisation programmes, the burden from childhood-cluster diseases was minimal.

There were marked differences in the attribution of total burden to deaths and ill-health or disability among the specific causes of communicable diseases. The share of total DALYs due to fatal outcomes was highest for lower respiratory tract infections (95%) followed by tuberculosis (76%) and HIV/AIDS (66%) (Fig 4). Burden due to ill-health or disability was higher among the population who suffered from septicaemia (100%), otitis media (97%), upper respiratory tract infections (88%) and diarrhoeal diseases and gastroenteritis (70%).

By sex

Overall, males experienced a higher disease burden (56% of total DALYs) compared to the females (44%) (Fig 5). This was especially in case of HIV/AIDS, hepatitis and tuberculosis where the share of burden attributed to the males was 89%, 63% and

63%, respectively compared with 11%, 37% and 37%, respectively for the females. The distribution of the total DALYs between the men and women was approximately equal for the rest of the communicable diseases.

The burden from lower respiratory tract infection was largest among men and women, accounting approximately 53% of total males DALYs (5,209 DALYs) and 60% of total females DALYs (4,554 DALYs), respectively (Fig 6). HIV/AIDS contributed another 17% in males DALYs, followed by tuberculosis (7.0%) and hepatitis (5.9%). For the women, the second and third top causes of DALYs were tuberculosis (5.3%) and hepatitis (4.4%). HIV/AIDS only accounted for 2.7% of overall burden in women. Even though more men suffered from HIV/AIDS and tuberculosis compared to women, mortality burden was higher in women than men. Other infectious diseases comprising sexually transmitted diseases, meningitis, dengue, malaria were responsible for 20% of the disease burden in both genders.

Figure 4
DALYs expressed as proportions due to YLL and YLD by specific causes, Singapore, 2004

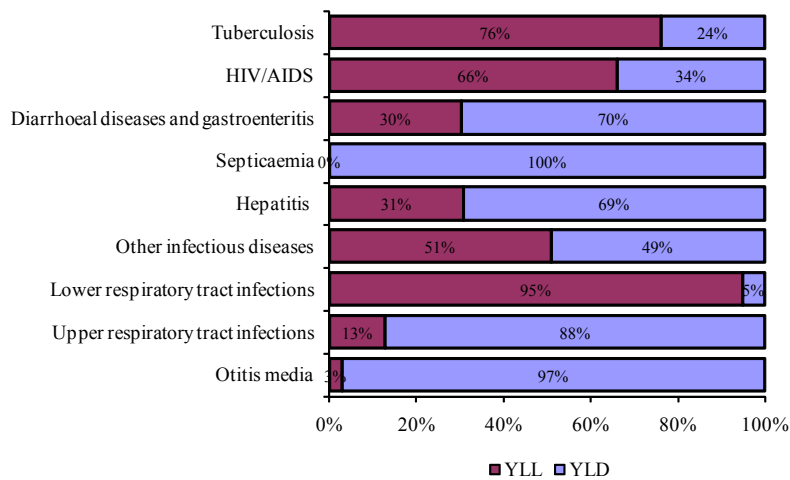


Figure 5
DALYs expressed as proportions by specific causes and sex, Singapore, 2004

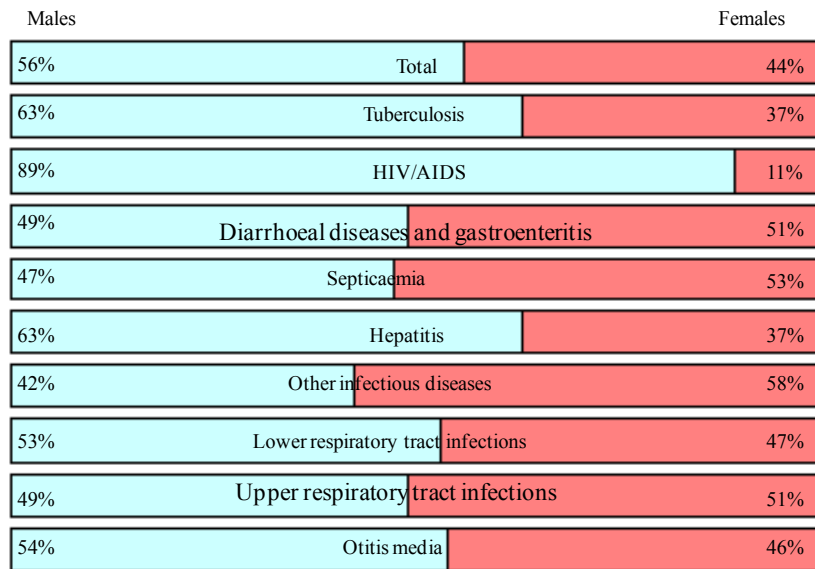
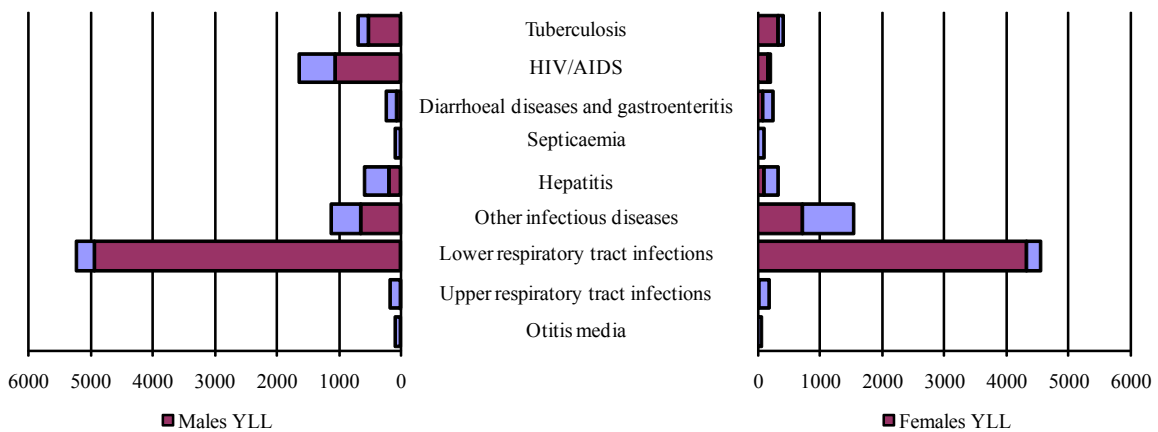


Figure 6
YLL, YLD and DALYs (in thousands) by specific causes and sex, Singapore, 2004



By age groups

In terms of age distribution, total burden per resident population peaked at birth, stabilised in older children and adulthood and subsequently increased exponentially with old age. The mortality burden per capita mirrored a similar trend as the DALYs while the burden from non-fatal outcomes increased very gradually across the age groups (Fig 7). Those aged 85 years and above registered the highest number of DALYs (2,042 DALYs, 12% of overall DALYs) predominately caused by premature mortality.

Lower respiratory tract infections were the most important single contributor to the healthy years of life lost (DALYs) and premature deaths (YLL) at birth and older ages (Fig 8). The share of lower respiratory tract infections in the overall DALYs grew progressively larger from 53% in age group 60 to 64 years

to 89% among those aged 85 years and over. HIV/AIDS contributed more than 40% of the total burden in adults aged between 35 and 44 years.

Males tend to suffer higher burden per capita compared with women across all age groups except at childhood and age 85 years and over, where the

Figure 7
YLL, YLD and DALYs rate per 1,000 resident population by age groups, Singapore, 2004

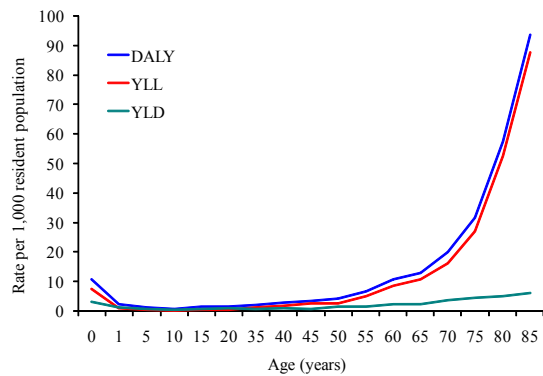
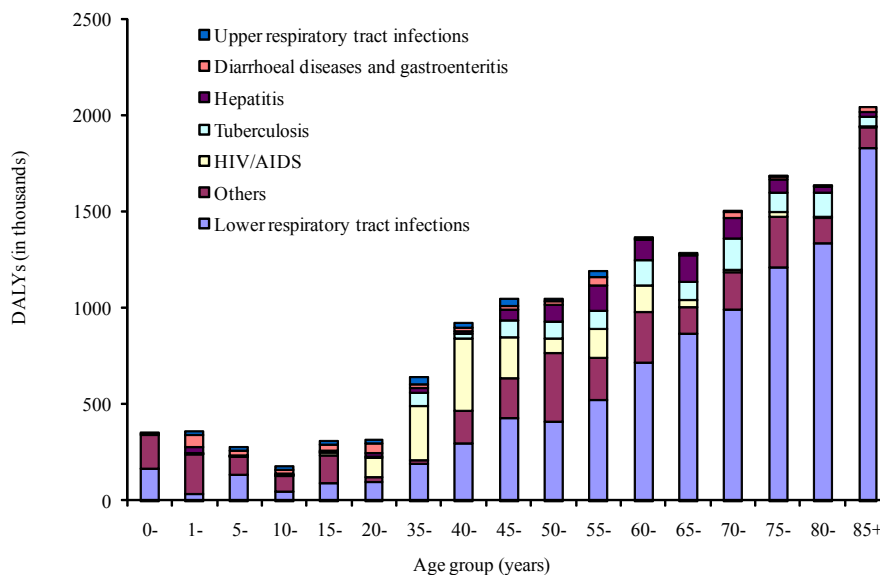


Figure 8
DALYs (in thousands) by age groups, Singapore, 2004



burden was almost equal between both genders (Fig 9). The burden gap between the males and women was most pronounced between ages 60 and 79 years.

Disease burden was greater among females aged 75 years and over compared with males (Fig 10). Men aged 45 to 64 years bore the highest share of burden compared to men in older age groups.

Conclusion

Singapore conducted its inaugural assessment of disease burden using the composite health mea-

sure - disability-adjusted life years (DALYs) based on 2004 as the reference year. This study allows comparison of the impact of one disease or groups of diseases relative to others. The total disease burden due to premature deaths and ill-health or disability was estimated to be over 363,000 DALYs. Non-communicable diseases contributed over 88% of DALYs while communicable diseases accounted for only 4.8% of the total burden. The low burden attributable to communicable diseases reflected the epidemiological transition towards a disease pattern dominated by chronic non-communicable diseases. Within the communicable diseases, lower respiratory tract infections were the main contributor of years of healthy life lost in the resident population, followed by HIV/AIDS and tuberculosis. While the Singapore population has a low burden of communicable diseases, this does not fully capture the potential disease burden or health threat posed by the emergence of epidemics like SARs or pandemic influenza. Continuous assessment of disease burden will provide valuable inputs to the future planning of healthcare strategies and the allocation of resources for the management of these conditions.

Figure 9
DALYs rate per 1,000 resident population by age groups and sex, Singapore, 2004

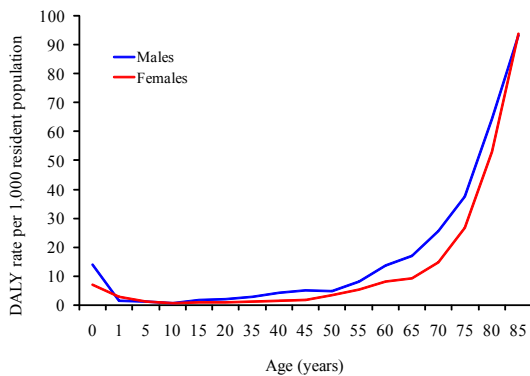
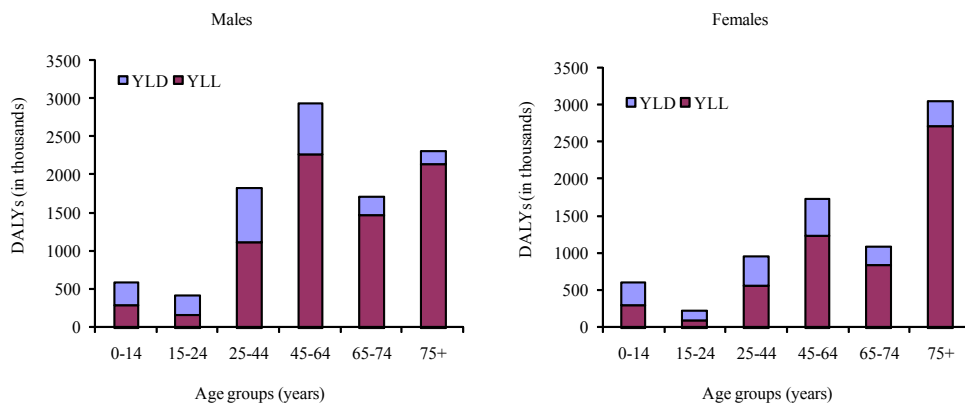


Figure 10
YLL, YLD and DALYs (in thousands) by selected age groups and sex, Singapore, 2004



(Reported by Soh I¹, Phua HP¹, Ang LW², Ma S¹, Heng D¹, ¹Epidemiology and Disease Control Division and ²Communicable Diseases Division, Ministry of Health)

Reference

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Laboratory-based surveillance system of invasive pneumococcal diseases in Singapore: a nationwide monitoring of vaccine serotype coverage

Background

Streptococcus pneumoniae is a major cause of severe bacterial infections such as pneumonia, bacteremia, sepsis and meningitis among children and elderly adults worldwide. According to the estimation of the World Health organization (WHO) in 2005, about 1.6 million deaths are caused by pneumococcal diseases every year, of which 0.7-1 million are estimated to occur in children younger than five years¹. The worldwide emergence of pneumococcal resistance to antibiotics including β -lactam, macrolides, tetracycline, cotrimoxazole and fluoroquinolones has also become a considerable concern. A significant reduction of pneumococcal disease incidence in children has been reported in countries where heptavalent pneumococcal conjugate vaccine (PCV7), a formulation of the seven most prevalent pneumococcal capsular types in the United States (4, 6B, 9V, 14, 18C, 19F, and 23F), has been introduced into the childhood immunization programme²⁻⁴. The indirect impact of PCV7 immunization of children on the overall decrease of invasive pneumococcal diseases (IPD) among older adults has also been

documented⁵. However, a gradual and continued rise in the incidence of disease due to non-PCV7 serotypes has been observed, though it remains low relative to decreases in vaccine serotypes⁴. In addition to PCV7, pneumococcal conjugate vaccines that include 9, 10, 11 and 13 serotypes have been developed. The 10-valent formulation (PCV10) which adds serotypes 1, 5, and 7F to those contained in PCV7 is approved for use in Canada and Australia and was recently authorized for use in Europe. A 13-valent formulation (PCV13) covering PCV7 serotypes and serotypes 1, 3, 5, 6A, 7F, and 19A is currently in global phase III clinical trials in adults.

In Singapore, two pneumococcal vaccines are currently licensed. The first one is the 23-valent polysaccharide pneumococcal vaccine (PPV23), which was approved by the Health Sciences Authority (HSA) for use in Singapore in 1988. The second vaccine (PCV7) was licensed for use in Singapore by the HSA in 2002⁶. In November 2009, the PCV7 vaccination officially became part of the National Childhood Immunization Programme (NCIP). Information on the epidemiology and serotype distribution



of IPD in Singapore during the period of pre-, peri- and post-PCV7 introduction is important for the evaluation of prevention and control strategies of the disease, but national data on the pneumococcal epidemiology has been limited⁶. To date, there has only been a limited study of invasive pneumococcal isolates from adult patients at the Singapore General Hospital (SGH)⁷, and from paediatric cases at the KK Women's and Children's Hospital (KKH)^{8, 9}. In 2009, clinicians were required by the Ministry of Health (MOH) to notify cases of invasive pneumococcal infections. It is defined as the isolation of *Streptococcus pneumoniae* from normally sterile sites. Pneumonia is considered an invasive disease but would be excluded if blood or pleural fluid cultures are sterile. Otitis media is not considered an invasive disease but may be included as IPD if *Streptococcus pneumoniae* is isolated from normally sterile middle ear fluid. A nationwide pneumococcus surveillance programme has been conducted in the National Public Health Laboratory (NPHL) since May 2009. The aim of the programme is to serotype sterile site pneumococcal isolates collected from the whole of Singapore and to monitor the serotype distribution of IPD among Singapore population. In this report, we present data from pneumococcus serotyping performed by NPHL and KKH in 2009.

Methods

National University Hospital, Tan Tock Seng Hospital, Alexandra Hospital and Singapore General Hospital sent positive *S. pneumoniae* isolates from sterile site cultures, e.g. blood, cerebrospinal fluid (CSF), pleural and peritoneal fluid, to NPHL for serotyping from May 2009 to December 2009. The laboratory at KKH serotyped their invasive

pneumococcal isolates from Jan 2009 to December 2009. Information on culture site of specimen and pneumococcal vaccination history of patient was obtained where available. Serotyping was performed on fresh culture isolates using Quellung reaction with the Pneumotest kit (Statens Serum Institut, Copenhagen, Denmark) which consisted of 12 pneumococcal pool antisera and with different factor antisera (Statens Serum Institut, Copenhagen, Denmark).

Results

Serotyping was performed on a total of 89 *S. pneumoniae* isolates. Of these, 63 isolates (70.8%) were serotyped by NPHL and 26 isolates (29.2%) were serotyped by KKH. The numbers of invasive pneumococcal isolates from paediatric patients and adult patients were 36 (40.4%) and 53 (59.6%), respectively. The cases were aged from 11 months to 82 years old. *Table 6* illustrates the distribution of pneumococcal isolates according to culture sites. The majority of isolates were obtained from blood culture specimens: 27 of the 36 isolates (75%) from paediatric patients and 49 of the 53 isolates (92.4%) from adult patients.

The serotyping results of paediatric isolates are reported in *Table 7*. Of the 36 isolates, one was untypable due to auto-agglutination. The most common serotypes observed among children were 6B, 14 and 23F which are included in the PCV7, comprising 77.8% of all isolates. The numbers and percentages of IPD cases caused by pneumococcus with serotypes included in the different vaccine formulation were also calculated. The proportions of paediatric IPD cases that would be covered by PCV7, PCV10 and PVC13 were 80.1%, 80.1% and 91.2%, respectively (*Table 8*).



Table 6

Distribution of pneumococcal isolates according to culture sites

Case category	Isolates obtained from culture of			
	Blood (n = 76) (%)	CSF (n = 5) (%)	Pleural fluid (n = 4) (%)	Miscellaneous (n = 4) (%)
Paediatric cases (n = 36)	27 (75.0)	4 (11.1)	3 (8.3)	2 (5.6)
Adult cases (n = 53)	49 (92.4)	1 (1.9)	1 (1.9)	2 (3.8)

Table 7

Distribution of pneumococcal serotypes among paediatric cases in 2009

Pneumococcus serotype / group	Number of isolates (n = 36) (%)
Type 6A	2 (5.5)
Type 6B*	14 (39.0)
Group 11	1 (2.8)
Type 14*	7 (19.4)
Group 15	1 (2.8)
Type 19A	2 (5.5)
Type 19F*	1 (2.8)
Type 23F*	7 (19.4)
Untypable	1 (2.8)

* serotype included in PCV7

Table 8

Number of IPD cases with serotypes included in PCV7, PCV10, PCV13 and PPV23

Case category	Coverage			
	PCV7 (%)	PCV10 (%)	PCV13 (%)	PPV23 (%)
Paediatric cases (n = 36)	29 (80.1)	29 (80.1)	33 (91.2)	
Adult cases (n = 53)	14 (26.4)	26 (49.1)	42 (79.2)	47 (88.7)

PCV7: 7-valent pneumococcal conjugate vaccine;

PCV10: 10-valent pneumococcal conjugate vaccine;

PCV13: 13-valent pneumococcal conjugate vaccine;

PPV23: 23-valent pneumococcal polysaccharide vaccine.



The distribution of pneumococcal serotypes among adult cases is shown in *Table 9*. Serotype 7F, 3 and 19A, which are non-PCV7 serotypes, were the most common among adults, and they accounted for 45.3% of all adult IPD cases. The proportions of adult IPD cases covered by serotypes contained in PCV7, PCV10, PCV13 and PPV23 were 26.4%, 49.1%, 79.2% and 88.7%, respectively (*Table 8*). Overall serotypes included in PCV7 accounted for 48.3% of all IPD cases in 2009 (*Fig. 11*).

Discussion

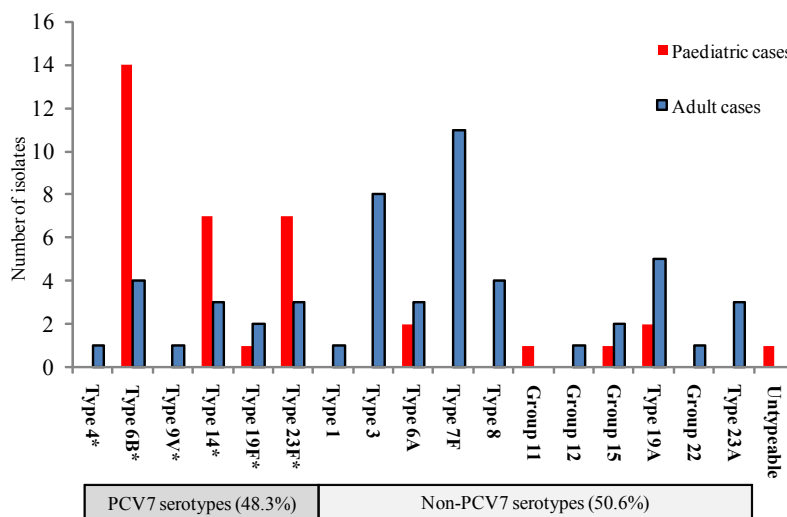
Surveillance started in NPHL in May 2009 and is based on specimens received by NPHL and KKH microbiology laboratory for serotyping. In 2009, there were 251 cases of invasive pneumococcal infections notified via the Communicable Diseases Live and Enhanced Surveillance (CD-LENS) at MOH. Of these, 124 cases met the criteria for IPD as defined by positive bacterial cultures from blood, CSF, pleural

Table 9
Distribution of pneumococcal serotypes among adult cases in 2009

Pneumococcus Serotype / group	Number of isolates (n = 53) (%)
Type 1	1 (1.9)
Type 3	8 (15.1)
Type 4*	1 (1.9)
Type 6A	3 (5.7)
Type 6B*	4 (7.5)
Type 7F	11 (20.8)
Type 8	4 (7.5)
Type 9V*	1 (1.9)
Group 12	1 (1.9)
Type 14*	3 (5.7)
Group 15	2 (3.8)
Type 19A	5 (9.4)
Type 19F*	2 (3.8)
Group 22	1 (1.9)
Type 23A	3 (5.7)
Type 23F*	3 (5.7)

* serotype included in PCV7

Figure 11
Distribution of pneumococcal serotypes among tested cases in 2009



* serotype included in PCV7



fluid and other sterile sites. In our investigation we serotyped 89 cases which correspond to 71.8% of notified IPD cases. The distribution of the serotypes causing IPD might thus not be fully representative.

Our results suggested that PCV7 includes serotypes responsible for 80.1% of paediatric IPD cases in Singapore. This is comparable to that observed in a previous study by Chong C.Y. *et al.*⁸ on children aged < 5 years in KKH and to that reported in other Asian countries such as Thailand (73.9%), Hong Kong (89.8%) and Korea (54%) prior to the introduction of vaccine¹⁰. Similarly, the predominant serotypes/groups observed in 2009 (6B, 14 and 23F) were also reported as the most common ones in previous studies^{8, 10}. However, replacement of vaccine types with non-vaccine types, such as serotype 19A^{4, 11, 12}, due to the selective pressure exerted by vaccines or horizontal transfer of the serotype genes between genetically unrelated strains, could become a real threat in some countries. Here we estimated the coverage of future vaccines (PCV10 and PCV13) in comparison with PCV7; the coverage of serotypes causing IPD might be increased 11.1% with the use of PCV13, but not with the use of PCV10.

Similar to what is reported previously by Hsu L.Y. *et al.*⁷ among adult invasive pneumococcal cases hospitalized in SGH from 2000 to 2007, it seems likely that the PCV7 coverage has been modest (26.4% in our study and 43.8% in the study of Hsu L.Y. *et al.*), but PPV23 would include serotypes responsible for the majority of IPD cases (88.7% in our study and 82.8% in the study of Hsu L.Y. *et al.*). PCV10 would

include 49.1% and PCV13 would include 79.2% of serotypes, respectively. Our data showed that the predominant serotypes were non-PCV7 types (7F, 3 and 19A) which have previously been found to be associated with significantly high case-fatality rates (serotype 3) or with lower case-fatality rates but having high invasive disease potential (serotypes 7F and 19A)¹³. Given that the non-vaccine serotypes 7F, 3 and 19A can be covered by the future vaccine PCV13, it is possible that PCV13 could indirectly provide more protection from IPD than PCV7 among adults due to herd immunity. In addition, fluctuation of serotype distribution in the absence of vaccine should be taken into account when the effects of PCVs are evaluated and the new conjugate vaccines are considered¹⁴. It is therefore important to monitor the clonal structure among circulating strains over time using DNA typing methods, such as multilocus sequence typing (MLST), to gain a more complete picture of IPD-associated pneumococcus population.

Conclusion

The ongoing laboratory-based surveillance system has provided a useful tool to monitor the pneumococcal serotypes in order to allow evaluation of pneumococcal immunization programme. The data would be more representative if additional isolates from notified cases could be typed. Thus, strengthening this surveillance system by recruiting the participation of more public and private healthcare sectors in Singapore is necessary. On the other hand, continued integration of serotyping and genotyping surveillance should be implemented in the future.

(Reported by La MV¹, Siti Zulaina MS¹, Jureen R^{1,3}, Tee WSN², Lin RVTP^{1,3}; National Public Health Laboratory¹, Ministry of Health, KK Women's & Children Hospital² and National University Hospital³)

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