A 20-year epidemiological review of the seroprevalence of varicella-zoster virus infection among children and adolescents in Singapore

Introduction

Chickenpox, also known as varicella, is a highly contagious illness caused by primary infection with the varicella-zoster virus (VZV). It is a common childhood disease in Singapore, and outbreaks have been reported in childcare centres, kindergartens, schools and other educational institutions.\(^1,2\) Chickenpox was removed from the list of legally notifiable diseases in December 2008.

In Singapore, the overall disease incidence rate declined after 1996 (Fig. 1). Between 1997 and 2007, the lowest incidence rate was observed in 2003 (371 per 100,000 population) and the highest incidence was in 1999 (798 per 100,000 population). Among the cases of chickenpox notified from 1998 to 2007, children below 5 years of age constituted about one-fourth of the total, while those aged 5-14 years comprised about 29% to 38%. Adolescents and young adults aged 15-24 years constituted about 14% to 20% of the cases. The age-specific incidence rate was highest in children below 5 years of age, followed by those in the age group of 5-14 years. Among the three major ethnic groups of Singapore residents, Malays had the highest incidence rate, followed by Chinese and Indians.

After the dip in 2003 when there was an outbreak of the severe acute respiratory syndrome (SARS), there had been consecutive increases in the annual incidence of chickenpox from 482 per 100,000
population in 2004 to 666 per 100,000 population in 2007. From 2004 to 2007, majority of the cases (40.7%) among Singapore residents were in the age group of 5-14 years, while more than two-thirds of the cases among foreigners were in the age groups of 25-34 years (38.1%) and 15-24 years (30.1%).

There was a decline in the annual number of hospitalisation due to chickenpox from 546 (13.1 per 100,000 population) in 2004 to 230 (4.4 per 100,000 population) in 2011. The median age of the inpatients was in the 20s. Among Singapore residents hospitalised for chickenpox, about one-third to half were below 10 years of age. On the other hand, about half to two-thirds of the foreigners hospitalised for chickenpox were in the age group of 20-29 years. The annual number of death due to chickenpox between 2001 and 2011 ranged from 0 to 3. Majority of the deaths were observed in adults and elderly.

We conducted a national paediatric seroprevalence survey (NPSS) between 2008 and 2010, which included the estimation of the seroprevalence of VZV infection. Comparisons were made with the findings of past serological surveys in 1989-1990, 1993 and 1998 conducted by the Quarantine and Epidemiology Department of the Ministry of the Environment among healthy persons aged between 6 months and over 45 years at designated polyclinics.\textsuperscript{3,5}

\textbf{Materials and methods}

\textbf{Survey design}

The Ministry of Health (MOH) conducted a national paediatric seroprevalence survey (NPSS) involving prospective collection of residual sera following the completion of routine biochemical investigations by diagnostic laboratories in Kandang...
Kerbau Women’s and Children’s Hospital and National University Hospital between August 2008 and July 2010. This survey was carried out in accordance with Section 7 of the Infectious Diseases Act (IDA) which provides for the use of residual samples for the purpose of public health surveillance.

Sera of Singapore citizens and permanent residents who were ethnic Chinese, Malay and Indian aged between 1 and 17 years attending inpatient services or day surgery were collected. Patients were excluded if they were known to be immune-compromised, on immune-suppressive therapy, or diagnosed with mumps, measles, rubella, chickenpox, poliomyelitis, pertussis, diphtheria, hepatitis B, dengue or hand, foot and mouth disease. It was estimated that a sample size of 1200 subjects comprising 400 in each age group of 1-6 years, 7-12 years and 13-17 years was required. The stored blood sera were tested by enzyme immunoassay (ELISA) with levels ≥ 100mIU/mL considered to indicate evidence of past natural infection or vaccination against VZV.

Vaccination records of the subjects from NPSS 2008-2010 were obtained from the National Immunisation Registry (NIR) of the Health Promotion Board (HPB). In Singapore, the NIR is responsible for collecting and maintaining accurate, complete and current vaccination records of all children from birth to 18 years of age. Both public and private healthcare institutions routinely notify the NIR of all immunisations that are administered to pre-school children, although only the notifications of diphtheria and measles immunisation are mandatory under the IDA. The School Health Services keeps track of records of all immunisations carried out in schools and at the Immunisation Clinic in the Student Health Centre, HPB. While vaccination against VZV has not been included in the national childhood immunisation programme in Singapore, it is readily available at public hospitals, government clinics and private practitioners on an individual basis.

**Statistical analysis**

The 95% confidence intervals (CI) for binomial proportions were computed using Wilson’s method. Difference in proportions between 2 groups was compared using 2-sample independent z-tests, with standard error estimated using pooled value of the independent proportions. The Mantel-Haenszel chi-square test for trend was used to evaluate differences between seroprevalence in the three age groups. A $p$-value < 0.05 was considered statistically significant.

**Results**

The NPSS 2008-2010 showed that the overall seroprevalence of VZV was 55.3% (95% CI, 52.5 – 58.1%) among the children and adolescents aged 1-17 years (Table 1). The seroprevalence increased significantly from 34.5% in children aged 1-6 years to 60.5% in 7-12 year olds and 71.0% in 13-17 year olds ($p<0.001$). The seroprevalence ranged from 27.9% to 45.3% in the age group of 1-7 years, and thereafter increased steadily from 52.1% in children aged 8 years to 83.3% in adolescents aged 17 years (Fig. 2).

There was no significant difference in the seroprevalence by gender (54.1% in males versus 56.5% in females; $p=0.406$). The seroprevalence of Chinese (58.0%) was significantly higher compared to Malays ($p=0.018$), while it was similar to that of Indians ($p=0.147$). There was no statistically significant difference in the seroprevalence between Malays (49.8%) and Indians (51.2%) ($p=0.801$).
The first survey conducted in 1989/90 involved 500 sera assayed qualitatively by the ELISA method. The seroprevalence was only 4.0% in pre-school children below 5 years of age and 22.8% in children aged 5-14 years. The seroprevalence increased to 41.0% in the older age group of 15-24 years. The second survey involving 852 sera was conducted in 1993 when there was a resurgence of chickenpox. The seroprevalence was higher at 24.8% in children below 15 years of age and it was 51.3% in the age group of 15-24 years. Another survey involving 923 sera was conducted in 1998, two years after varicella vaccine was first licensed for use in Singapore. The seroprevalence increased sharply from 12.9% in children below 5 years of age to 90.8% in older children.

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Table 1

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Age group (years)</th>
<th>1 – 6 (n=400)</th>
<th>7 – 12 (n=400)</th>
<th>13 – 17 (n=400)</th>
<th>1 – 17 (n=1200)</th>
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<td>64.0</td>
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<tr>
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<td>Indians</td>
<td></td>
<td>30.0</td>
<td>45.5</td>
<td>69.6</td>
<td>51.2</td>
</tr>
</tbody>
</table>

Figure 2

Seroprevalence (%) of VZV infection by age in NPSS 2008-2010, with the bars indicating 95% confidence intervals.
years of age to 59.5% in those aged 15-24 years. In adolescents and young adults aged 15-24 years, the seroprevalence was 70.0%. There was no statistical significance in the seroprevalence by gender or ethnic group in these three surveys.\textsuperscript{5,6}

Compared to past surveys, the seroprevalence was highest in all age groups in NPSS 2008-2010, except for those in the age group of 5-14 years which was the highest in the 1998 survey (Fig. 3). In the latest survey, the seroprevalence of VZV among children aged 5-14 years was 58.0%, which was not statistically different from 59.5% in the 1998 survey ($p=0.721$).

There were no vaccination records against VZV found in the NIR for 14 of the subjects. In addition, another 1049 subjects had no vaccination history against VZV. In total, there were 1063 subjects (88.6%) with an unknown or no history of vaccination. Of the 1200 subjects, 104 (8.7%) had received at least one dose of vaccine against VZV prior to the collection of their residual samples for the NPSS. The seropositivity rate among these 104 subjects was 59.6%, which was not significantly different from the 56.1% among 1063 subjects with an unknown or no history of vaccination ($p=0.486$). There were 33 subjects who were vaccinated against chickenpox after their residual samples were collected for the NPSS 2008-2010.

**Comments**

The pattern and intensity of social interaction dynamics affect the transmission of highly infectious diseases commonly seen among children and adolescents, such as chickenpox and hand, foot and mouth disease. During the period from 1990 to 1993, a higher incidence of chickenpox was seen in the age group of 5-24 years. Since 1996, the highest age-specific incidence rate shifted to children below 5 years of age.\textsuperscript{8} Among children below 5 years of age, the incidence increased from 1991 per 100,000 population in 2004.
Epidemiological News Bulletin

The serological surveys conducted over a 20-year period showed a pattern of increasing prevalence of VZV infection in children below 5 years of age, which implied that transmission has increased in this age group. This can be partly attributed to exposure at preschool age in nurseries and childcare centres, especially with the increasing numbers of these institutions and their capacities over the years. There were 739 childcare centres providing almost 63,000 places as of end 2007, compared to 653 childcare centres providing about 54,000 places in 2003.\(^9\) As of end 2011, the number of childcare centres increased further to 955 with the provision of about 85,800 places.\(^1^1\) The supply and enrollment of childcare centres are expected to continue rising over the next few years in view of the demand of infant care, childcare and student care centres.

The latest survey indicated that the seroprevalence of VZV in children below 5 years of age was nearly 3 times that carried out more than 10 years ago in 1998. A limitation of the study was that the findings from NPSS may not be directly comparable to that of past surveys due to the different study designs and cut-off values in defining serostatus. The higher seroprevalence among young children found in NPSS 2008-2010 may be attributed to the increased uptake of the chickenpox vaccine, and/or increase in natural infection due to larger cohort of children attending childcare centres and student care centres which facilitates virus transmission.

The increasing seroprevalence of VZV infection in older children, adolescents and young adults in the four surveys corresponded to a decreasing incidence of reported chickenpox cases in this age group. In 2007, the incidence was 2875 per 100,000 population among children below 5 years of age and 2181 per 100,000 population in the age group of 5-14 years, and it reduced further to 684 per 100,000 population in adolescents and young adults aged 15-24 years.

Although chickenpox is no longer a legally notifiable disease in Singapore, passive sentinel surveillance has been put in place and outbreaks reported to MOH are monitored. In 2012, the total number of polyclinic attendances for chickenpox was 85.9 per 100,000 population. Among Singapore residents who sought treatment for chickenpox at polyclinics, children below 5 years of age and those in the age group of 5-14 years constituted 18.4% and 44.3%, respectively. About 56.9% of the foreigners with chickenpox seen at polyclinics were aged 20-29 years.

While NPSS 2008-2010 showed relatively higher level of VZV seroprevalence among children and adolescents except for the age group of 5-14 years, a considerable proportion remained susceptible. Nearly two-thirds of children aged 1-6 years and 39.5% of children at primary school age did not possess antibody against VZV. Among adolescents aged 13-17 years, 29.0% were also susceptible to VZV infection. Thus, outbreaks of chickenpox are expected to continue unless the vaccination coverage is increased.

It is of concern that chickenpox tends to be more severe and prolonged with a greater risk of complications and higher mortality in older individuals. It has been reported that the epidemiology of primary VZV infection differs between tropical and temperate countries. While chickenpox is a childhood disease in temperate
countries with near-universal seroconversion by late childhood, VZV infection occurs later in life in the tropics and is common in adolescents and adults. As severe cases occur more in adults than in children and seroconversion occurs at older age in tropical countries, it has been suggested that tropical countries may be at a greater risk of morbidity and mortality of VZV infection. New Zealand has a temperate climate. While both Singapore and New Zealand have not included chickenpox vaccine in their respective national immunisation programmes, the seroprevalence of VZV infection in children and adolescents was found to be higher in a serosurvey conducted in New Zealand in 2009 compared to that of Singapore during the period from 2008 to 2010. In New Zealand, the seroprevalence was 87.3% in children aged 6-10 years and 94.4% in the older age group of 11-15 years. In Singapore, the seroprevalence was 50.8% in children aged 6-10 years and 67.6% in the older age group of 11-15 years.

The majority of the fatal cases in Singapore died of respiratory complications followed by other systemic complications such as septicemia and encephalitis. Groups at increased risk of developing severe VZV infection and resultant complications include infants below 1 year of age, older children and adults above 15 years and immunocompromised persons. These individuals are encouraged to be vaccinated against chickenpox.

Previous surveys conducted prior to 1996, when varicella vaccine was first licensed for use in Singapore, indicated lower seroprevalence of VZV infection in children. Data from the NIR of HPB indicates an increasing trend in the uptake of chickenpox vaccine in children from 24.3% in 2006 to 52.0% in 2010. A study had been carried out to assess the economic burden of chickenpox and the cost-benefit of adding the vaccine to the existing immunisation schedule in Singapore. Based on data from 1994 to 1995, it was estimated that for every dollar invested in a vaccination programme, US$2 dollars would be saved from a societal point of view. Further studies to quantitatively model the cost and public health impact of adding chickenpox vaccination to the national childhood immunisation programme based on the latest set of data available are warranted.

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References

A cluster of imported falciparum malaria cases in Singapore in December 2012

Introduction

Malaria is a mosquito-borne disease caused by the *Plasmodium* parasite. Human infections characterised by symptoms such as fever, shaking chills, sweats, headache, weakness, and nausea result from bites of infective female *Anopheles* mosquito carrying the malaria parasite while feeding. In humans, four species of the *Plasmodium* parasite are typically known to cause malaria: *P. malariae*, *P. ovale*, *P. vivax* and *P. falciparum*, of which *P. falciparum* is known to cause severe malaria infections. Between 2010 and 2012, there were a total of 479 laboratory-confirmed malaria cases notified to the Ministry of Health (MOH) of which almost all (99.3%) of these cases were imported from other malaria-endemic countries.

Between 26 Dec 2012 and 28 Dec 2012, MOH was notified of four *Plasmodium falciparum* cases who were admitted into two public hospitals in Singapore. MOH immediately carried out epidemiological investigations of these cases and obtained relevant
information such as the cases’ personal particulars (i.e. age, gender and ethnicity), clinical signs and symptoms, date of onset of illness, laboratory results, and travel history.

Epidemiological findings

Epidemiological investigations revealed that these cases were Singaporeans who had all travelled to the same island in a neighbouring country for recreational activities prior to their onset of illness. This report summarizes the outcome of the epidemiological investigations into this cluster of imported malaria cases.

Cases’ details

Case 1:

Case 1 is a 50-year-old engineer who developed fever, chills, rigors and myalgia on 20 Dec 2012. He was admitted to Hospital A’s Intensive Care Unit on 23 Dec 2012 before being transferred to the general ward between 3 Jan 2013 and 8 Feb 2013.

Case 2:

Case 2 is a 32-year-old engineer who developed fever, chills, rigors, headache and myalgia on 19 Dec 2012. He sought outpatient treatment on 24 Dec 2012 and was subsequently admitted to Hospital A between 26 Dec 2012 and 3 Jan 2013.

Case 3:

Case 3 is a 50-year-old landscaper who developed intermittent fever with chills, headache and myalgia on 20 Dec 2012. He sought outpatient treatment on 22 Dec 2012 and was subsequently admitted to Hospital A between 26 Dec 2012 and 31 Dec 2012.

Case 4:

Case 4 is a 52-year-old self employed businessman who developed fever, chills and rigors on 23 Dec 2012 and was admitted to Hospital B between 27 Dec 2012 and 31 Dec 2012.

Overseas movement history

Cases 1 and 2 had travelled to an island in a neighbouring country with 15 other friends for a cycling trip in the southern part of the island on 8 Dec 2012 and had stayed overnight at a ‘kelong’ (an offshore wooden platform for both fishing and dwellings purposes) before returning to Singapore on 9 Dec 2012.

Cases 3 and 4 had travelled to the same island with 5 other friends on 8 Dec 2012 and had stayed overnight at the same ‘kelong’. They then travelled to another neighbouring island the next day for jet-skiing activities. They returned to the ‘kelong’ and stayed there from 10 – 12 Dec 2012 before returning to Singapore.

The timeline of events and date of onset of illness for the cases are illustrated in Fig. 4. Both groups mentioned that they did not take anti-malaria chemoprophylaxis and did not use insecticide-treated mosquito nets when sleeping in the ‘kelong’.

Laboratory investigations

As part of the epidemiological investigations for this cluster of cases, the Malaria Reference Centre (MRC) in the National Public Health Laboratory (NPHL) of MOH performed additional molecular investigations on the blood samples received from these four cases.
*P. falciparum* infection was confirmed for all cases using both morphological and molecular approach – reading of Giemsa-stained thick and thin blood smears, and real-time PCR using DNA extracted from the blood samples.

Subsequently, molecular typing of the *P. falciparum* strains for each case and comparisons of the genotypes within the cases were performed to assess the possibility of an infection by the same strain of the parasite. Two different protocols of genotyping were used. The first protocol utilizes a comparison of three highly polymorphic genes – *Pfmsp1*, *Pfmsp2* and *Pfglurp* – following the genotyping protocol of the WHO (2007). The results showed that the strains of *P. falciparum* for the four cases belonged to the same subtype and harboured the same fragment sizes for each target. The second protocol compares six polymorphic microsatellites markers, which revealed identical profiles for the four cases. The results from these two protocols confirmed that the four cases were infected by the same strain of *P. falciparum*.

The results of the molecular and epidemiological investigations for these four imported *P. falciparum* cases are congruent and substantiated the epidemiological link highlighted above.

**Actions taken**

To further understand the extent of the outbreak, MOH conducted active case detection and surveillance for other *P. falciparum* cases who had travelled to this island.

Phone interviews with the leaders of the two groups were conducted immediately to enquire on the health status of the other members who had also been on the trips. Even though the remaining members...
were found to be well, they were advised to monitor themselves for symptoms and to seek early medical treatment if unwell.

Through retrospective review of malaria cases notified to MOH in 2012, another three *P. falciparum* cases involving Singaporeans who had travelled to the same island in 2012 for recreational activities before their onset of illness were identified. Their travel dates ranged from Jun to Sep 2012, and they had stayed between 2 and 17 days on the island. These cases did not know one another, and are also unrelated to this latest cluster of 4 cases.

The neighbouring country’s health authorities was notified of this cluster of 4 cases and provided with the epidemiological details of the cases for their necessary public health actions.

**Comments**

Genotyping of the *P. falciparum* samples from these four cases showed identical results by two different approaches, confirming that they were the same strain. In view of the epidemiological links and the common travel history, supported by the molecular findings, these four cases were classified as a cluster of imported *P. falciparum* malaria cases from the neighbouring island.

Singapore has been certified malaria-free by the World Health Organization (WHO) since November 1982. However, Singapore remains at risk of the reintroduction of malaria due to the large numbers of people moving through our borders. These people include Singaporeans who may be infected after travelling to malaria endemic regions or countries. Travellers to these areas should adopt measures to protect themselves from mosquito bites by using insect repellent, covering exposed skin and sleeping under insecticide-treated mosquito nets. They should also consult their doctors or visit travel medicine clinics 4-6 weeks prior to their departure to obtain advice about appropriate anti-malarial chemoprophylaxis.


**References**


Bovine spongiform encephalopathy and variant Creutzfeldt-Jakob disease

Background

Bovine spongiform encephalopathy (BSE), also known as “mad cow disease”, is a progressive neurological disorder in cows caused by an unusual transmissible agent called prion. Prions are abnormal, pathogenic agents that are able to induce abnormal folding of specific normal cellular proteins called prion proteins that are found most abundantly in the brain. There are two different types of BSE, namely:

a. Typical BSE strain - This is responsible for most of the BSE-infected cattle in Canada and the United Kingdom (UK). It is believed to be caused by consumption of BSE-contaminated feed, and has been causally linked to variant Creutzfeldt-Jakob disease (vCJD) in humans.

b. Atypical BSE strain - In July 2007, the UK Spongiform Encephalopathy Advisory Committee (SEAC) suggested that atypical BSE could be a separate strain of prion disease. It may have happened spontaneously, although the possibility of transmission through animal feed or the environment cannot be excluded. Notwithstanding, there were still uncertainties in the aetiology of atypical BSEs including their zoonotic potential as suggested by some animal studies.

Variant CJD is a human neurodegenerative condition that is rare but fatal. Because of its ability to transmit, and the characteristic spongy degeneration of the brain that results from this condition, variant CJD is classified under transmissible spongiform encephalopathies (TSE). TSEs are a group of rare degenerative brain disorders characterized by tiny holes that give the brain a “spongy” appearance. Other diseases classified under TSEs include Creutzfeldt-Jakob disease (CJD), kuru, fatal familial insomnia (FFI), and Gerstmann-Straussler-Scheinker disease (GSS). vCJD was first described in the UK in March 1996 and was linked with exposure to BSE infected cattle, first reported in the country in 1986. vCJD is different from the classic CJD, which is another human prion disease. Unlike vCJD, the classic CJD occurs spontaneously or is hereditary.

Transmission

Epidemiological evidence suggests that the BSE outbreaks among cattle in the UK during the 1990s were caused by the consumption of contaminated high protein animal feeds that comprised of meat-and-bone meal (MBM) derived from TSE infected animal carcases. Humans are believed to be infected with vCJD after being exposed to BSE-infected cattle, and the most likely mode of transmission is through the consumption of contaminated bovine brain or other central nervous system tissue. There is strong evidence of causal association between vCJD in human and BSE outbreaks in cattle in the UK. The time interval between the most likely period of initial human exposure to potential BSE-contaminated food (from 1984 to 1986) and the onset of initial vCJD cases (from 1994 to 1996) is consistent with the known incubation periods for human prion disease. Both vCJD and BSE are observed to have long incubation periods that measure up to several years.
Surveillance

Intensive surveillances in the European countries have detected high incidence of vCJD cases in the UK. As of February 2013, the National CJD Research & Surveillance Unit (NCJDRSU) reported 176 fatal cases of vCJD (122 definite and 54 probable) in the UK, of which three were infected through blood transfusion (secondary cases). The number of vCJD peaked in 2000 with 27 cases and 28 deaths reported. The number of cases has since decreased to one or two cases of diagnoses/death in the recent years.

As of December 2012, a total of 227 cases of vCJD have been reported in 12 countries worldwide (Table 2). Most of the cases were detected in the UK, while some of the cases diagnosed in other countries were suspected to have been exposed to BSE while residing in the UK previously.

Cases of BSE in the United States and Brazil

On 24 April 2012, the United States Department of Agriculture (USDA) reported a case of bovine spongiform encephalopathy (BSE) in a dairy cow. Several months later, Brazil reported her ever first case of BSE-infected cow to the World Organisation for Animal Health (OIE) on 7 December 2012. However, the notification was only made two years after the death of the animal.

The United States

Till date, four cases of BSE infected cows have been detected in the US. The first case was reported in late 2003, the second and third cases in 2005 and 2006, respectively. The first case was a classical BSE case and the latter three cases were classified as atypical BSE cases.

Table 2

<table>
<thead>
<tr>
<th>Country</th>
<th>Total number of primary cases (Number alive)</th>
<th>Total number of secondary cases: blood transfusion (Number alive)</th>
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<tr>
<td>United Kingdom</td>
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<tr>
<td>France</td>
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<td>-</td>
</tr>
<tr>
<td>Republic of Ireland</td>
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<td>-</td>
</tr>
<tr>
<td>Italy</td>
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<td>-</td>
</tr>
<tr>
<td>United States</td>
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<td>-</td>
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<tr>
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<tr>
<td><strong>Total</strong></td>
<td>227 (2)</td>
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</table>

The last case occurred in a ten-year-old dairy cow from a farm in Tulare County of central California. The cow was euthanized after it developed difficulties with movement and became recumbent. Biological samples of the dairy cow were sent to the California Animal Health and Food Safety Laboratory and National Veterinary Services Laboratories (NVSL) for enzyme-linked immunosorbent assay (ELISA) on 19 and 21 April 2012, respectively. Both ELISA results were uncertain, and further confirmatory tests were conducted two days later. The results for immunohistochemical and western blotting tests were both positive for BSE. Following epidemiological investigation, USDA classified the case as atypical BSE.

Brazil

On 18 December 2010, Brazil detected the country’s first BSE case in a 13-year-old beef breeding cow from the municipality of Sertanópolis of state of Paraná. The bovine was found to be recumbent with limb stiffness during the routine inspection, and died the following day. Biological samples from the bovine tested negative for rabies. Samples were then subjected to BSE testing, which initially yielded negative results on histopathological testing on 11 April 2011. The samples eventually tested positive for BSE on 15 June 2012 via immunohistochemical testing. The BSE positive result was confirmed by an OIE Reference Laboratory in the UK on 6 December 2012. According to the Brazilian authorities, epidemiological investigation excluded BSE as a cause of death in the bovine. Laboratory tests also determined the BSE agent to be of the H-type atypical BSE. In addition, investigations also revealed that the affected animal was reared in an extensive farming system on grazing (as opposed to intensive farming system where the farming practice of recycling of animal protein in ruminant feed has been associated with the development of BSE in animals).

BSE surveillance system in the United States and Brazil

The United States

Based on information provided by the United States, the USDA has in place the following three key measures to protect human and animal health against BSE, including (a) removal of specified risk materials (SRM) such as the nervous systems, tonsils and distal ileum from all animals presented for slaughter; (b) implementation of a strong feed ban that prohibits the feeding of mammalian proteins to ruminant animals; and (c) ongoing BSE surveillance programme to detect BSE among cattle. In addition, non-ambulatory cattle, fallen stock and cattle showing signs consistent with BSE are banned from entering the human food chain.

BSE surveillance programme targets high risk cattle such as non-ambulatory cattle, fallen stock and cattle which exhibit signs of central nervous disorders and other BSE associated signs. In addition, routine sampling of cattle from slaughter facilities is also carried out. According to the USDA, the surveillance system conducts testing at a level that is ten times higher than what is recommended by the OIE.

Brazil

In Brazil, measures have also been established against the introduction of BSE to the local live cattle. The use of animal feeds containing all animal-derived protein to ruminants is banned by the Brazilian government. Regular inspections of feed manufactur-
ing and distributing facilities are carried out by the Department of Livestock Input (DFIP) to ensure that the feed regulations are complied with. Both beef and dairy cattle are raised in extensive grazing system in more than 90% of the farms in the country, where grass and minerals are used as the only feeds. As vegetable protein is available in large quantities in Brazil, MBM is not generally used for cattle feeds. In addition, SRM such as head, vertebral column, spinal cord, distal ileum of the cattle are removed before meat is exported. Since 2003, the processing of dead animals has been legally prohibited in Brazil.11

The Brazilian Ministry of Agriculture Livestock and Food Supply (MAPA) implemented the BSE surveillance system in 1997, together with the rabies surveillance system. BSE was made a notifiable disease and active surveillance has been carried out since 2002. As part of the BSE surveillance, cattle with chronic disease of unknown causes, central nervous disorders, progressive debilitating disease and fallen stock are tested for BSE. In addition, mature cattle that have been tested negative for rabies will be tested to BSE.12 Surveillance sampling and BSE testing of cattle, including those subject to routine slaughter, dairy cattle, as well as beef cattle raised in intensive/semi-intensive systems, is also carried out.

Recommendations by the World Health Organisation (WHO)

The World Health Organisation (WHO) recommends the following regulations to the food safety and agriculture industries1:

a. Tissue that is likely to contain BSE agent, as well as part or product of any animal which shows signs of TSE should not enter the human or animal food chain. The use of ruminant tissues in ruminant feed should be banned in all countries;

b. The use of bovine materials and materials from other animal species in which TSEs naturally occur should be avoided in the pharmaceutical industry. If their use is absolutely necessary, materials should be obtained from countries which have an established surveillance system and report zero cases of BSE;

c. The “Guidelines on tissue infectivity distribution in transmissible spongiform encephalopathies” in 2006 serves as a guide to inform and assist national regulatory authorities in conducting risk assessments of vCJD transmission.

AVA’s import requirements and risk mitigation measures for beef imports from the US and Brazil

Beef from the US and Brazil are imported into Singapore under AVA’s regulation. AVA conducts a documentary and onsite evaluation of exporting countries, which must be accredited by AVA to export beef to Singapore. AVA also takes into consideration the BSE risk status of the country. Countries that are of OIE’s negligible BSE risk category will be allowed export of different types of beef and beef products. For those in OIE’s controlled BSE risk category, only deboned beef cuts from cattle under 30 months of age will be allowed export to Singapore. In addition, AVA reinforces the risk mitigation measures established in these countries with stringent import conditions such as removal of BSE specified risk material. The US has applied to the OIE for the classification of their BSE status to be upgraded to “negligible risk”. This would be considered at the coming OIE General Assembly in May 2013. If the US is successful, there could be a review of import of beef from the US.
Surveillance programmes of infectious diseases in Singapore

In Singapore, vCJD/CJD are currently not a notifiable disease under the Infectious Diseases Act (IDA). Nonetheless, disease surveillance programmes have been established locally for the early detection of cases of infectious diseases which result in neurological disorders including classical CJD and vCJD.

The Severe Illness and Death from Possible Infectious Causes (SIDPIC) programme is implemented in collaboration with the restructured hospitals to investigate critical illnesses and deaths potentially resulting from infectious agents. The programme covers syndromes consistent with a possible infectious aetiology, including neurological syndrome. To date, no cases of vCJD have been reported in Singapore.

Risk assessment

The incidence of BSE in cattle in Brazil and the US is very low. The BSE cases in both Brazil and the US were detected through the local surveillance system, and the affected cattle did not enter the food chain. The OIE maintains that the risk of BSE in Brazil and the US does not change with the report of the isolated cases of atypical BSE as there is no evidence of a failure of the BSE risk mitigating measures established in these countries.13, 14

Thus far, investigations indicated that both cases of BSE in Brazil and the US were likely to be sporadic cases. As the cases were categorised as atypical BSE, they were unlikely to be infected with the disease from consuming contaminated cattle feed.

AVA has put in place a set of stringent import requirements and measures to ensure that beef imported from the US and Brazil are safe for consumption. The risk of BSE-infected meat being imported to Singapore is currently assessed to be very low. In Singapore, disease surveillance programmes have been established for the early detection of cases of infectious diseases which result in neurological disorders, including classical CJD and vCJD.

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References


**Vertical transmission of hepatitis B despite immunoprophylaxis**

Several cases of vertical transmission of hepatitis B (HB) despite immunoprophylaxis with both HB immunoglobulin (HBIG) and HB vaccine have been reported to the Health Sciences Authority of Singapore (HSA). These infants were born to HB carrier mothers and had received a single dose of HBIG at birth and completed a three-dose regimen of HB vaccine. As of end-September 2012, HSA has received a total of 21 reports of HB immunoprophylaxis failure.

In Singapore, two brands of monovalent HB vaccine are currently marketed (Engerinx-B®, GlaxoSmithKline and HBvaxPRO®, Merck Sharp & Dohme). Hexavalent vaccines such as Infanrix Hexa®, which contains HB antigen, may be used for second or third dose of HB vaccination. Three brands of HBIG are available in the market, namely HyperHEP B® (previously named BayHEP B®) from Skyquest, Anti-Hepatitis B Immunoglobulin Grifols® and Niuliva® Solution, both from Grifols Asia Pacific.
Review of the case reports

The 21 case reports of HB immunoprophylaxis failure were submitted to HSA in 2012 following screening for HB status (conducted in 2011 or 2012) or captured via a retrospective review. The screening was possibly triggered by Ministry of Health’s (MOH) 2011 advisory to screen infants born to HB carrier mothers after they had completed their primary course of HB vaccination, as well as an ongoing research study at a tertiary hospital.

Of these reports, six cases involving children born before 2009 were excluded from HSA’s causality assessment due to a lack of critical information such as the brand of the implicated HBIG and HB vaccine and/or whether or not the children were infected within the first two years of life. The remaining 15 cases all involved the use of HyperHEP B® and Engerix-B®. Details of the HB vaccination schedule and brand of HB vaccine implicated are provided in Table 3.

Of the 15 cases that were assessed, only one infant tested negative for HB virus (HBV) DNA viral load, HBe antigen (HBeAg) and HB surface antigen (HBsAg) but positive for antibodies against HBe and HBs (anti-HBe and anti-HBs) at two years of age, indicating transient infection.

As shown in Table 3, there were slight differences in the HB vaccination schedule among the 15 infants included in the assessment. With regard to the use of different brands of HB vaccine, monovalent HB vaccines are considered immunologically comparable based on studies conducted. It is recommended for infants born to HB carrier mothers to use monovalent HB vaccines for all three doses for optimal protection due to lack of data on the interchangeability between hexavalent and monovalent HB vaccines for these infants. Although two infants did not receive monovalent HB vaccine as the third dose or as scheduled, the first two doses of the vaccine should confer some protection. In addition to the HB vaccine, all the 15

### Table 3

Details of the vaccination schedule and the brand of HB vaccine implicated in cases of hepatitis B vertical transmission despite immunoprophylaxis

<table>
<thead>
<tr>
<th>Year of birth</th>
<th>Number of cases</th>
<th>Vaccination schedule for HB vaccine (Engerix-B®)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>At birth, month 1, month 6</td>
<td>Day 3, month 1, month 6</td>
</tr>
<tr>
<td>1997, 2003, 2004, 2005</td>
<td>1 per year</td>
<td>Excluded from causality assessment due to lack of critical information</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>6</td>
<td>5&lt;sup&gt;[a]&lt;/sup&gt;</td>
<td>1&lt;sup&gt;[b]&lt;/sup&gt;</td>
</tr>
<tr>
<td>2010</td>
<td>8</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>2011</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>11</td>
<td>3</td>
</tr>
</tbody>
</table>

<sup>[a]</sup> Infanrix Hexa® was given as the third dose for 1 infant
<sup>[b]</sup> HBvaxPRO® was given as the second dose
infants received HBIG at birth for immunoprophylaxis against HB.

For these cases, the rates of immunoprophylaxis failure were estimated using data from the National Immunisation Registry (NIR) on the number of infants receiving HBIG at birth. The failure rates of 0.90%, 1.35% and 0.16% in 2009, 2010 and 2011, respectively, were found to be within the expected incidences reported in the literature.

Factors associated with immunoprophylaxis failure

HB vaccination and one dose of HBIG, administered within 24 hours after birth, are 85-95% effective in preventing both HBV infection and the chronic carrier state, whereas HB vaccine, administered alone within 24 hours after birth, is 70-95% effective in preventing perinatal HBV infection. The use of HBIG alone reduced HBV occurrence by an average of 50%, dependent on the maternal HBeAg status.

In several prospective trials, immunoprophylaxis failure ranging from 8% to 32% has been reported among HBeAg positive mothers with high HBV DNA levels. Risk factors analysis suggested that maternal HBeAg positivity and detectable HBV DNA were the most important factors associated with mother-to-child transmission despite immunoprophylaxis. This may be attributed to intrauterine transmission, which is estimated to occur in <5% infants. Further studies indicate that a serum HBV DNA level ≥8 \( \log_{10} \) copies/mL was considered an important factor leading to immunoprophylaxis failure. In addition, HBV DNA in cord blood was a significant independent risk factor for such failure.

While some studies have identified mutations in surface HBsAg, such as those in the “a” determinant to which HBIG/HB vaccine elicits antibodies to bind, as possible causes of immunoprophylaxis failure, others suggest that the mutations account for only a marginal role. In contrast, other obstetrical and perinatal factors such as the mode of delivery, premature birth, low birth weight and birth length have not been found to be conclusively linked to immunoprophylaxis failure.

Discussion

a) Possible causes of the increase in the number of reports

A more in-depth analysis of the immunoprophylaxis failure cases to determine their possible cause is difficult due to the lack of information on the serologic profile of the mothers at birth. In addition, the increase in the number of reports could also be due to heightened awareness among healthcare professionals following MOH’s advisory in 2011 to screen infants born to HB carrier mothers for seroconversion three months after completing the primary course of HB vaccination. More cases of vertical transmission of HB may have surfaced through proactive screening.

b) Assessment of product quality

A total of nine batches of Engerix-B® and four batches of HyperHEP B® were implicated in the cases of vertical transmission. A review of the certificates of analysis for the implicated batches found them to conform to the current registered product specifications before lot release. Registered changes since 2009 to the chemistry, manufacturing and controls (CMC) of Engerix-B® and HyperHEP B® have been examined to reconfirm that the changes have no impact on product quality and safety.
Conclusion

It is difficult to identify the root cause of vertical transmission of HB in these cases in view of incomplete data and the multi-factorial nature of immunoprophylaxis failure. Literature reports of failures of within 5% to 32% have been reported due to multiple reasons.

As HSA continues to monitor the issue, healthcare professionals are strongly encouraged to report all cases of HB infection despite immunoprophylaxis to the Vigilance Branch of HSA.

(Based on HSA Adverse Drug Reactions News Bulletin Vol 14, No. 3, Dec 2012)

References