Hepatitis B and Measles Immunity Seroprevalence Survey (HBMISS) Technical Report

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INTRODUCTION

Hepatitis B is an infection that can seriously affect the liver caused by the Hepatitis B virus. The infection can lead to cirrhosis of the liver, liver failure as well as liver cancer.

Chronic hepatitis B infection is estimated to cause from 60–80% of hepatocellular carcinoma (HCC) worldwide and estimated to kill 700,000 to one million people worldwide. Approximately one in 20 people worldwide are living with chronic Hepatitis B infection. Without appropriate monitoring or treatment, it is estimated that one in four of these people will die from liver cancer or liver failure.

The World Health Organisation (WHO) estimates there to be 278,000 deaths a year in the Western Pacific Region (WPRO) (of which Brunei Darussalam is part of) with an estimated prevalence of approximately $\geq$ 8%. In 2006, it was estimated that 1.9% of pregnant mothers had tested HBsAg positive. As yet, there have not been any studies to assess the prevalence of Hepatitis B carriers in Brunei Darussalam.

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In 2005, the Western Pacific Region became the first WHO region to set a time-bound goal for controlling hepatitis B infections, with 2012 as identified as the target year by which to reduce the prevalence of HBsAg, a marker of chronic HBV infection, to less than 2% among 5 year-old children.

Brunei Darussalam hopes to be able to achieve the WHO WPRO's regional goal of having a Hepatitis B chronic infection rate of less than 2% and eventually achieve the ultimate goal of less than 1%.

Measles remains a leading cause of death globally among young children, despite the availability of a safe, effective and inexpensive vaccine used for nearly 50 years. Millennium Development Goal Four (MDG4) aims to reduce overall child deaths by two-thirds by 2015 compared with 1990 level. Recognising the important contribution of measles to child mortality, routine measles vaccination mortality reduction will make an important contribution to achieving this goal.

In June 2005, the 15th meeting of Technical Advisory Group in the Western Pacific Region further reviewed the status of progress made towards measles elimination

and hepatitis B control, and recommended setting twin goals of regional measles elimination and hepatitis B control by 2012.

Background and Current Status

General introduction on Brunei Darussalam: The population of Brunei Darussalam is estimated to have been 414,400 in 2010 and is increasing at a rate of 2.0% per annum. The population structure is essentially that of a young population; about 8.5% and 34.2% of the population is under-five and under-20 years respectively, and only 3.5% are 65 years or over.

In 2010, life expectancy at birth was 76.5 years for males and 78.8 years for females, the crude birth rate had declined from 18.7 per 1000 population in 2005 to 15.5 per 1000 population in 2010, the crude death rate was 2.9 per 1000 population, and the total fertility rate was 1.6. The infant mortality rate stands at 6.1 per 1000 live births in 2010 and the under-five mortality rate at 7.2 per 1000 live births, while the death rate among mothers giving birth was 15.3 per 100 000 live births.

Brunei Darussalam is classified as a high-income country by the World Bank with an estimated per capita Gross Domestic Product (GDP) of BND40,700 in 2010. It has a multi-ethnic population, with Malays comprising 66%, the predominant ethnic community, and Chinese, with 11%, the next major group. Other races, such as Indians, other ethnic groups and expatriates, make up the rest of the population.

Comprehensive free medical and health care is provided for all citizens of Brunei Darussalam, provided via government hospitals, health centres and health clinics. A large network of health centres and clinics located throughout the country provides primary health care services, including those for mother and child. In remote areas that are not accessible or are difficult to access by land or water, primary health care is provided by the Flying Medical Services. As of 2006, there were four government general hospitals, 16 health centres, 25 maternal and child health clinics, eight travelling health clinics and four remote areas covered by the Flying Medical Services team. The Ministry of Defense also operates five medical centres that mainly provide services for its personnel and their families. In addition to the government hospitals, there is one private hospital. There are also several private clinics which provide primary healthcare around the country.

The Ministry of Health has now categorized the respective health care services available in Brunei Darussalam into two main services. The Directorate of Medical Services is responsible for hospital, nursing, laboratory, pharmaceutical, dental and renal services, while the Directorate of Health Services oversees community health, environmental health and scientific services.

The country has a comprehensive child immunisation programme to protect against vaccine-preventable diseases. All these services are provided free of charge. Medical advances in vaccines have been made widely available through the Expanded Programme on Immunisation, which is incorporated into the Child Health Services and School Health Services. The country's health services are monitoring developments to en-

sure immunisation measures and facilities continue to be in line with best practice for disease prevention. Currently, 99.5% of all births are delivered in hospitals.

Brunei Darussalam has essentially achieved its goal of universal primary education with 99% of children completing six years of primary school. Children begin primary school at the age of six or seven years of age. Primary schools are either run by the government (over 60%) or by the private sector.

Prevention and Control of Chronic Hepatitis B Infection in Brunei Darussalam: Hepatitis B is transmitted both vertically from mother to child and horizontally. The horizontal transmission is mainly intra-familial in nature due to socio-cultural practices of sharing of food, drink, sleep, intimate and close contact with family as a whole. Sexual, injectable drug use, blood transfusion, tattooing, skin piercing practices are among the least listed mode of transmission in Brunei Darussalam.

Hepatitis B notification was introduced into the disease surveillance system in 1979. Notification is compulsory under Section 3(6) of Quarantine and Prevention of Diseases Act, Chapter 47 which was then compounded by the introduction of the Infectious Disease Act more than two decades later in 2003. In addition, the Disease Control Unit was established in 1991 which was upgraded to a division in 2004. This division is currently under the Department of Health Services and also oversees issues related to hepatitis B control in the country.

In addition, to routine surveillance, all pregnant women presenting to antenatal clinics are screened for hepatitis B and regular hepatitis B screening is offered to key high-risk population groups (e.g. family contacts of HBsAg positive people (since 1994), patients on renal dialysis, blood donors, patients presenting with sexually transmitted infections (STI), prisoners). The contact tracing, counseling and immunisation of close family contacts has been done since 1994 under the purview of the Disease Control Unit since 1995. Between 2001 and 2010, it was estimated that 1.4-2.4% of pregnant mothers had tested HBsAg positive annually (Table 1), which is lower than the rate of 3.2% observed in study done before 1990.

Different studies carried out in Brunei Darussalam prior to 1995 and before introduction of Hepatitis B vaccination have shown HBV carriage rate around 6% with significant racial differences (highest rates among Chinese population).

Prevention and Control of Measles Infection in Brunei Darussalam: Age distribution

Table 1: Number of antenatal screens for HBsAg.

	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Total Screened	8275	8225	7852	7988	7170	6796	7027	7874	7458	6419	8908
Total positive	191	196	153	128	165	131	135	139	105	98	92
Est. prevalence (%)	2.3	2.4	1.9	1.6	2.3	1.9	1.9	1.8	1.4	1.5	1.1

Source: Department of Laboratory Services, Ministry of Health

Table 2: HBsAg estimated among different population groups.

Category screened	HBsAg (%)	Remarks
1. Ante-natal mothers	1.1 - 2.4%	Calculated by (HBsAg +ve mothers / all ante-natal screens) during the year. Figures from 2001-2011).
2. Family contacts of HBsAg positives	2.8 %	From 1995-2001; 4,268 family contacts of 601 carriers were screened in Hepatitis B counseling clinic in this period. In addition, 13.2% of contact were positive for anti-HBs showing natural infection with recovery.
3. Blood donors	0.7 – 1.4 %	Virology Laboratory, Ministry of Health. Figures from 2001-2008.

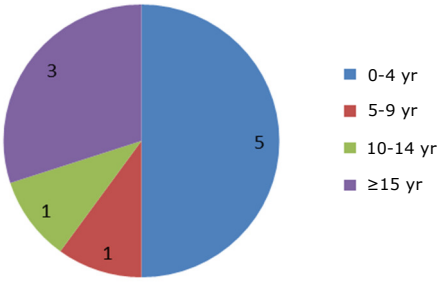

Fig. 1: Distribution of age groups among suspected measles cases in 2011.

is as shown in Figure 1. There were five cases in under-five age group, one case in 5-9 year age group, one case in 10-14 year age group and three cases in above 15 year age group. Therefore the majority of cases are from under-five age group.

Cases of suspected measles were reported in first six months in 2010. However the incidence by month is relatively high in April 2011 which three cases were reported (Figure 2). All of the suspected cases were investigated and laboratory tested.

As of 31st December 2011, the suspected measles case rate is 2.4 per 100,000 population and therefore above the required WHO target. Overall, Brunei Darussalam has achieved 9 of the 10 Measles elimination indicator targets set by WHO (Western Pacific Region).

Table 3 shows the achievement of Measles Elimination Indicator targets set by WHO (Western Pacific Region) in Brunei Darussalam.

Hepatitis B & Measles Immunisation in Brunei Darussalam: The first programme for Hepatitis B immunisation started on May 11, 1983 for high risk groups. In 1988, Hepatitis immunisation was incorporated into the Ex-

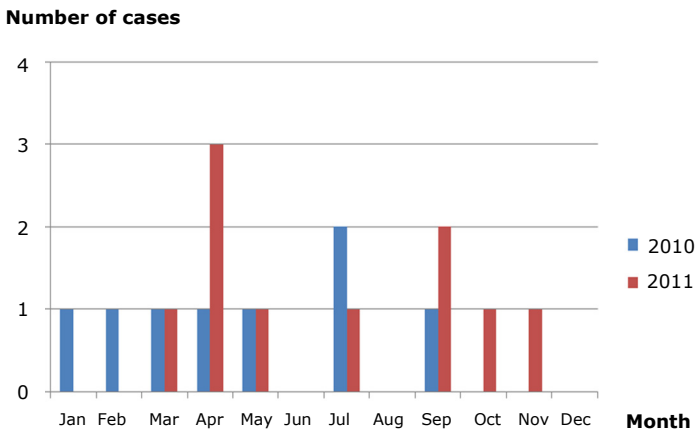

Fig. 2: Monthly distribution of suspected measles cases in 2010 and 2011.

Table 3: Measles Elimination Indicator Targets for Brunei Darussalam.

	Indicator	Target	2007	2008	2009	2010	2011
1	Confirmed cases by lab(/1000000)	<1	NA	5.09	5.09	0	9.85
2	National reporting of discarded measles cases	≥2	NA	2.3	1.5	1.8	1.5
3	% od 2nd level admin units reporting >1/100000 discarded measles cases	≥80%	50	100%	100%	100%	100%
4	% of suspected cases with adequate investigation	≥80%	100	83%	87%	86%	70
5	% of suspected cases with adequate blood specimen	≥80%	NA	78%	75%	100%	90%
6	% of specimen with Lab result <7day	≥80%	NA	NA	NA	NA	NA
7	Transmission chains (outbreaks) with sufficient samples for virus isolation	≥80%	No O/B	No O/B	No O/B	No O/B	No O/B

panded Programme on Immunisation (EPI), whereby all newborn infants are being immunised with three doses of vaccine given at birth, one month and six months of age. Additionally, the EPI was made compulsory in Brunei Darussalam in 2003 under the Infectious Disease Order 2003, requiring all children in the country to be vaccinated. The coverage for Bruneian infants in 2005 for the hepatitis B vaccine was 99.8%. The high uptake of the vaccine can be attributable to the fact that almost all live births occur in the hospitals and babies are assessed at ages one and six months with very good compliance.

Antenatal mothers are routinely tested for Hepatitis B since 1984. HBIG is given to those babies born to HBsAg positive mothers and follow the subsequent doses at one month and six months of age, which is independent of other immunisations in the schedule but still has very high coverage levels. For example, coverage with three doses of hepatitis B vaccine (HepB3) and DPT3 is almost the same both by administrative and survey methods.

Measles vaccine was introduced into the routine childhood immunisation schedule in 1974. MMR at one year old replaced the monovalent measles given to nine months old in 1988. In the same year, MMR also replaced the monovalent rubella vaccine given to girls in school at ages 12 to 13 years old. In 1996, boys were also included in the school vaccination.

Table 4: Hepatitis B Birth dose coverage.

YEAR	Hep B Birth Dose (given within 24 hours of birth) (%)	Hep B, Birth Dose (Total, including those given before and after 24 hours of birth) (%)
2008	99.60	100.00
2009	100.00	100.33
2010	95.80	95.80
2011	95.00	96.00

In 2007, the MMR booster dose were changed from primary six (11-12 years) school children to three years old. In 2008 the School Health Division carried out a nationwide catch-up vaccination programme to capture all school-aged children from primary one (six years old) to primary six (11-12 years old). In the same year, the Maternal and Child health clinics also did all children aged from ≥3 to 5 years old.

Brunei Darussalam has maintained a high coverage of nearly 100% for the past 10 years for all three doses of hepatitis B and

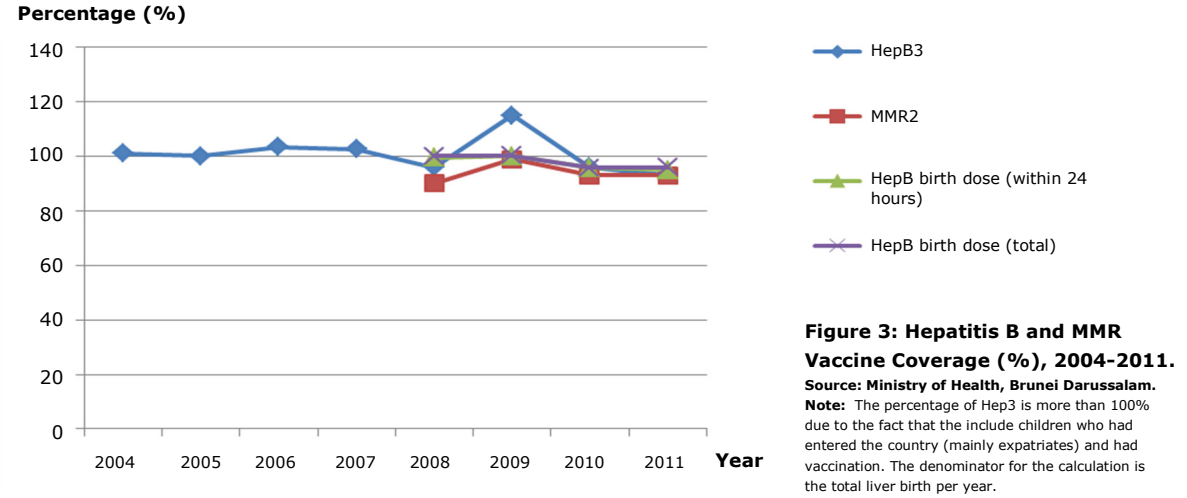

Figure 3: Hepatitis B and MMR Vaccine Coverage (%), 2004-2011.
Source: Ministry of Health, Brunei Darussalam.
Note: The percentage of Hep3 is more than 100% due to the fact that the include children who had entered the country (mainly expatriates) and had vaccination. The denominator for the calculation is the total liver birth per year.

MMR.

The Hepatitis B and Measles Immunity Seroprevalence Study (HBMISS) among Children in Brunei Darussalam

Objectives: The Hepatitis B and Measles Immunity Seroprevalence Study (HBMISS) was started in mid-2011. The main objectives of conducting this survey were:

- To determine HBsAg prevalence and presence of measles immunity in school age children in Brunei Darussalam.
- To assess the impact of existing hepatitis B and Measles prevention and control methods, particularly the Expanded Programme on Immunisation in Brunei Darussalam.
- To provide baseline information for the development and evaluation of action programmes.
- To provide the basis for future national planning for hepatitis B and Measles prevention and control.
- To be able to certify whether Brunei Darussalam has achieved the Western Pacific Regional goals of hepatitis B and measles elimination by 2012.
- To provide information on the susceptibility profile of the population.
- To further evaluate the success rate of the catch up MMR booster vaccination programme that was held nationwide in 2008 in both Maternal and Child Health clinics and Schools.

Materials and Methods

Research Design: A nationwide cross-sectional survey was carried out to estimate the prevalence of HBsAg and Measles IgG among children in Brunei Darussalam. For the purpose of this survey, all children in Year 4 in all primary schools (government and private) in Brunei were invited to participate in the survey. Children in Year 4 classes are generally 8-10 years of age. Participants who had agreed to have their blood sampled were given a small goodie bag with snacks and a $10 book voucher as appreciation.

Data Collection: The students were given data forms in advance for their parents to fill in to gather their demographic data. In addition, the parents were requested to make a copy of their child's vaccination cards to be collected on the day of data collection. Information was also gathered from the child's vaccination card if the school had a copy of it and the parents failed to bring a copy.

Five (5) ml blood was drawn from consen-

ted students. The serums derived from the bloods were sent to Department of Laboratory Services Virology laboratory for testing. ELISA test were used for detection of HBsAg, anti-HBS and measles IgG. Children with positive HBsAg tests were called for counseling and contact tracing and repeat blood tests were taken to confirm the test as soon as possible. Any children testing negative on the second test were considered to be false positives and their initial results were discarded.

The schools were visited once only for blood drawing from the students. Attempt to bleed the students was aborted when the health staff failed to bleed them after three attempts.

Any students testing positive for HBsAg were called for counseling with their families and retested for confirmation. If students tested negative during the second test, their first tests were nullified and they were considered to be HBsAg negative. The children were called for retesting almost immediately for retesting after the investigators received the results from the laboratory.

Laboratory test

HBsAg Test*:* The tests were performed on automated analyser (Cobas e601) using Electrochemiluminescence (ECLIA). The analyser automatically calculates the cut-off. The result of a sample is given either as reactive as well as in the form of a cut-off index (signal sample/cut-off). Interpretation of result are as follows:

- cut-off index <0.90 are non-reactive, samples are negative for HBsAg
- cut-off index > or equal to 1.0 are reactive.
- If qualitative value of HBsAg was ≥2.0, the sample was classified as positive.

Anti- HBsAg test*:* The tests were performed using Elecsys Anti-HBS kit from Cobas. If the concentration of HBsAb in the sample was > 10mIU /mL, the sample was considered sero-positive.

Anti-HBc: The cut-off index for a positive result for anti-HBC was < or equal 1.0, whereas the cut-off index for a negative result was >1.0

Measles IgG: The tests were performed using ELISA Measles IgG by Human (brand). A_{450} is the absorbance wavelength used to read the colour development of the samples after the test has been completed. A sample is interpreted as having a positive result if the A_{450} is more than or equal to the cut-off value (COV) +15% and a negative result if the A_{450} is less than the COV+15%. A result is said to be indeterminate if values fall between the positive and negative COVs.

Data analysis: Data was analysed using Epi-Info 11.0.

Follow-up action on results: Children who were found to be HBsAg positive had their parents contacted for counseling and contact tracing. A repeat blood test was done to confirm the result and if found to be negative, the previous results were discarded. The children were then referred to a paediatrician for further follow up and management. Children who were found to be HBsAg negative had their results sent to their children's respective schools in a sealed envelope to be given their parents. Parents of children who were bled but did not have a result due to either insuffi-

cient sample or missing results, were written to and given the opportunity to retest in their respective government health centres. The parents were left to decide when to bring their children for testing. However, any results from retesting these children would not be included in the study. Children who had tested negative for anti-HBS and for Measles IgG were given the option of immunisation if they had no evidence of previous vaccinations

RESULT

Response rate: All 179 schools (government and private) in Brunei Darussalam with Year 4 students participated in the study with a total population of 6,358 students invited. This number represented all of the Year 4 students in Brunei Darussalam. Out of this number 6,088 had returned their data and consent form with a response rate of 95.8%. However, 5,128 out of the total 6,358 (80.7%) students invited had both their parents and the child themselves agreed to be bled. Out of the total number of students who were bled, 4,671 blood samples were obtained (91.1%). Out of the 6,088 students who had returned their consent forms, 632 students did not have parental consent, 143 students refused to be bled and 185 students were absent during the school visit. There was no reason to believe that parents would refuse testing for their child due to known HBsAg positive status although there is a possibility that some may have refused testing as their children may have been screened previously from contact tracing.

Table 5: Ages of respondents.

Age	Numbers	Percentage
8	2,156	35.4
9	3,745	61.5
10	187	3.1
Total	6,088	100

Demographic of respondents: The ratio of male to female students were 1:1. These are shown in Tables 4 and 5.

Vaccination coverage of sampled population: From 6,088 respondents who returned their forms, 2,797 (45.9%) have no information on hepatitis B vaccination status and 2,838 (46.6%) have no information on MMR vaccination status. Information on vaccination was obtained from copies of the child's health cards which parents were asked to bring with them during the study visit. In many cases, the parents did not bring any copies of the cards. However, some cases had copies of

Table 6: Ethnicity of respondents and proportion who had blood test.

Ethnicity	Respondents		Bled		Percentage (%) bled by ethnicity
	Number	Percentage (%)	Number	Percentage (%)	
Malay	4,879	80.1	3,775	80.8	77
Chinese	568	9.3	378	8.1	67
Dusun	183	3.0	158	3.4	86
Murut	29	0.5	25	0.5	86
Iban	210	3.5	181	3.9	86
Indian	44	0.7	36	0.8	82
Others	156	2.6	105	2.2	67
Unknown/ Not specified	19	0.3	13	0.3	68
Total	6,088	100	4,671	100	77

Table 7: Completed vaccination status of respondents.

Immunisation status	Complete vaccination		Incomplete vaccination	
	n	%	n	%
Hepatitis B (n=3,291)	3,268	99.3	23	0.7
MMR (n = 3,250)	3,107	95.6	83	4.4

their vaccination cards held by the school. Completeness of hepatitis B and MMR vaccination status was verified through the respondents' Child Health Cards and the dates of the three doses hepatitis B vaccinations and two doses of MMR received.

HBsAg seroprevalence and HBsAb and Measles IgG seroconversion: Only five children were found to be HBsAg positive during the survey. However, one child had a false positive result and was found to be HBsAg negative on repeat testing. Therefore only a total of four children were found to be HBsAg positive (0.09%). Out of 4,671 students with a record of blood samples taken, results for 55 students were missing with an additional 103 students with insufficient blood for HBsAg testing (total of 4,513 valid test results). There was no clustering seen in the four children that had tested positive.

A total of eight students were positive for anti-HBC (0.18%). Out of 4,671 with a record of blood samples taken, results for 56 students were missing with an additional 88 students with insufficient blood taken for anti-HBC testing.

A total of 1,584 (35%) students were positive for HBsAb with seropositivity (>10 mIU/ml). Out of 4,671 students with a record of blood samples taken, results for 56 students were missing with an additional 92 students with insufficient blood for anti-HBS testing (total of 4,523 valid test results)

A total of 3,519 (78.7%) students were positive for Measles IgG. Out of 4,671 students with a record of blood sample taken, results for 63 students were missing with an additional 138 students with insufficient blood for Measles IgG testing and 358 students with indeterminate results (total of 4,469 valid test results).

DISCUSSION

Despite obtaining an overwhelming response rate from parents by returning the questionnaire, consent for blood sampling was slightly less encouraging. However, consent for blood sampling by both parents and children was still deemed positive with an overall consent rate of 80.7%. Although parents were informed to bring their child's health cards during the study visits, a big proportion of parents did not bring the cards and therefore total vaccination could not be ascertained. However, based on the information available, at least 99.3% and 95.6% of children who had received 1st doses of hepatitis B and MMR vac-

Table 8: Summary of valid blood test results.

	HBsAg	anti-HBC	Anti-HBS	Measles IgG
Valid Test results	4,513 (96.6%)	4,527 (96.9%)	4,523 (96.8%)	4,469 (95.6%)
Positive results	4 (0.09%)	8 (0.18%)	1,584 (35.0%)	3,519 (78.7%)

cinations respectively were noted to have completed their vaccination course.

Blood results for 56 students were missing for hepatitis panel and 63 students for measles IgG. Reasons for the results to be missing are unknown. Some samples may have been lost between bleeding the student and the laboratory or there may just have been insufficient blood in the tubes for testing.

The percentage of respondents do not correlate to the general population with a higher percentage of Malay students (80%) when compared to a general population percentage of 67% Malays. This may be attributed to the large numbers of expatriate workers in Brunei Darussalam and the possibility that many do not bring their dependents with them into the country leading to different ethnic percentages between the general population and the primary school population.

CONCLUSION

The prevalence of HBsAg among Year 4 school children in Brunei Darussalam who were supposed to have received hepatitis B vaccination was 0.09%. Despite an immunisation coverage of over 90% as recorded by the Ministry of Health in previous years, evidence of seroconversion by the time the children reached the age of 8-10 years old, were 35% and 78.7% for anti-HBs and Measles IgG respectively. Efforts need to be continued to ensure maximal coverage in order to reduce these infections.

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