


# BMJ Open National database study of trends in bacteraemia aetiology among children and adults in Japan: a longitudinal observational study

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## ABSTRACT

**Objectives** Domestic epidemiological studies are needed to ascertain the disease burden of bacteraemia in individual countries. This study aimed to evaluate the domestic trends in paediatric and adult bacteraemia in Japan.

**Setting** Laboratory-based surveillance was used to obtain data from 592 hospitals located throughout Japan.

**Participants** The study was conducted using the results of 827 780 and 3 512 524 blood culture tests obtained from children and adults, respectively, between January 2010 and December 2016.

**Outcome measures** We analysed the temporal trends in specific bacterial species (*Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Salmonella enterica*, *Haemophilus influenzae*, *Listeria monocytogenes* and *Neisseria meningitidis*) detected from the blood cultures of children and adults. For children aged ≤2 years, the data were analysed for each year of age. The proportions of bacteraemia-positive results among the patients were also evaluated.

**Results** The number of bacteraemia-positive samples over the study period was 47,125/827,855 (5.7%) in children and 959,765/3,513,885 (27.3%) in adults. *S. pneumoniae* was the most frequent cause of bacteraemia in children in 2010. However, after 2011, *S. aureus* bacteraemia was the most frequent, followed by *S. pneumoniae* and *E. coli*. *E. coli* bacteraemia showed significant increases in both children and adults. In children, *S. pneumoniae* and *H. influenzae* bacteraemia decreased from 2010 to 2013. However, *S. pneumoniae* bacteraemia case numbers stabilised from 2013, whereas *H. influenzae* bacteraemia cases continued to decrease until 2016.

**Conclusion** The results suggest that the introduction of the 13-valent pneumococcal conjugate vaccine did not substantially affect disease occurrence. In contrast to the decreasing trends in *H. influenzae* and *S. pneumoniae* bacteraemia, *S. aureus*, *E. coli* and *S. agalactiae* bacteraemia showed increasing trends. These findings shed light on recent temporal trends in bacteraemia in both children and adults in Japan.

## Strengths and limitations of this study

- This is the first study to document the aetiological changes in bacteraemia in Japan following the widespread dissemination of immunisation.
- The study data were obtained from Japan's largest government-operated microbiological surveillance system, which increases the findings' national generalisability.
- The separate evaluation of bacteraemia in children and adults due to their aetiological differences simplifies the interpretation of the results.
- The data lacked important patient-level information, such as inpatient or outpatient statuses, patient background and prognoses.
- Causative pathogen subtypes, such as capsule types and serotypes, could not be analysed due to database limitations.

## INTRODUCTION

Bacteraemia continues to impose a considerable disease burden in both lower-income and higher-income countries.<sup>1,2</sup> Due to international differences in the distribution of causative bacteria (eg, meningococci and non-typhoidal salmonella),<sup>3,4</sup> individual countries need to conduct domestic epidemiological studies to ascertain disease burden and inform the development of targeted strategies to improve public health. Studies from various countries have examined the changes in paediatric bacteraemia following the spread of immunisation and improvements in sanitation.<sup>5–7</sup> For example, the implementation of a universal pneumococcal immunisation programme in a US integrated managed care consortium substantially reduced the morbidity of bacteraemia in young children, with contaminants more frequently recovered from samples than true pathogens.<sup>5</sup> Furthermore, these vaccinations shifted the burden of paediatric bacteraemia

in the USA from pneumococcal infections to those by *Staphylococcus aureus*, *Salmonella* spp, and *Escherichia coli*.<sup>5</sup> Other studies have also documented the epidemiological changes in bacteraemia in adult populations.<sup>8,9</sup>

In Japan, the *Haemophilus influenzae* type b vaccine and 7-valent pneumococcal conjugate vaccine were introduced as 'optional' vaccines in December 2008 and February 2010, respectively. The early dissemination of these vaccines may have been stifled as optional vaccines require patient out-of-pocket payments under Japan's healthcare system. However, the Ministry of Health, Labour and Welfare (MHLW) implemented an extensive immunisation promotion programme in November 2010 and approved these two vaccines as 'mandatory' (removing the need for out-of-pocket payments) in April 2013, thereby increasing vaccine utilisation. In November 2013, the 7-valent pneumococcal conjugate vaccine was replaced by the 13-valent version. Despite these changes in vaccine availability and coverage, their effects on the epidemiology of paediatric bacteraemia in Japan remain unclear. Ubukata *et al* analysed patients with invasive pneumococcal diseases between 2010 and 2017 using a laboratory-based surveillance system, and reported that the causative pathogens demonstrated serotype changes over time.<sup>10</sup> However, their surveillance system was not government-operated and participation was voluntary, and their findings may be susceptible to selection bias. In addition, little is known about the epidemiological changes in non-pneumococcal bacteraemia in Japan.

Through an analysis of data from the largest government-operated microbiological surveillance system in Japan, this study aimed to evaluate domestic trends in paediatric and adult bacteraemia, including the epidemiological changes in *H. influenzae* and pneumococcal bacteraemia.

## METHODS

### Data source

We conducted the observational database study. We acquired information on the results of blood culture tests conducted between January 2010 and December 2016 from a database provided by the MHLW's Japan Nosocomial Infections Surveillance (JANIS) Clinical Laboratory Division, which routinely collects microbiological test results from approximately 2000 hospitals located throughout the country. In 2019, 24.8% of all hospitals (2,075/8372). Participation was high among those with >500 beds (82.8%, 338/408), while it was relatively low among hospitals containing between 200 and 499 (46.9%, 1019/2174) and <200 beds (12.4%, 718/5790).<sup>11</sup> To eliminate the effects caused by temporal changes in the number of participating hospitals on the number of blood culture samples, we only included data from facilities that continuously participated in JANIS throughout the study period. Because JANIS aims to provide microbiological information from a diverse range of hospitals (including smaller, resource-limited hospitals), the programme only collects basic information to encourage

sustainable participation. Thus, the database did not include detailed information on causative pathogen subtypes (eg, *H. influenzae* capsule types or *Streptococcus pneumoniae* serotypes).

### Data processing

We compiled the blood culture results as 'sets' for each patient, which included the combination of aerobic and anaerobic cultures if both samples were obtained. To eliminate data duplication from simultaneously obtained blood cultures (ie, multiple sets) and blood cultures obtained to confirm microbiological cure (ie, follow-up cultures), we only examined the first positive result in patients who had  $\geq 2$  blood cultures in a year. If all the blood cultures obtained from a patient in a year were negative, we only included the first negative result.

### Outcomes

We first evaluated the proportions of bacteraemia-positive results from blood cultures in children and adults. For this study, age was provided in 5-year increments. As a consequence, children were defined as individuals aged <20 years, which differs from the definition (<18 years) used by the United Nations.<sup>12</sup> Adults were defined as individuals aged  $\geq 20$  years.

Next, we analysed the temporal trends in bacterial species detected from the blood cultures of children and adults. This analysis included the following bacteria, which are known to cause bloodstream infections in healthy individuals: *S. aureus*, *S. pneumoniae*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *E. coli*, *Klebsiella pneumoniae*, *Salmonella enterica*, *H. influenzae*, *Listeria monocytogenes* and *Neisseria meningitidis*. We excluded bacteria that generally cause bloodstream infections in immunocompromised patients or are regarded as culture contaminants, such as *Pseudomonas aeruginosa*, *Bacillus* spp, and coagulase-negative staphylococci. For children aged  $\leq 2$  years, the data were analysed for each year of age due to the higher risk of bloodstream infections.<sup>5</sup>

### Statistical analysis

To evaluate the bacteria-specific temporal changes in bacteraemia over the study period, we examined the trends in the proportions of bacteria-specific bacteraemia to the total number of tested blood cultures using the Cochran-Armitage trend test. All data management and statistical analyses were conducted using R V.4.0.2 (R Foundation for Statistical Computing, Vienna, Austria). Two-tailed p values <0.05 were considered statistically significant.

### Patient and public involvement

No patients or members of the public were involved in the development or conduct of the study.

The board waived the need for informed consent as the data were anonymised before being received by the authors.

**Table 1** Annual numbers of bacteraemia cases according to causative bacteria in children and adults

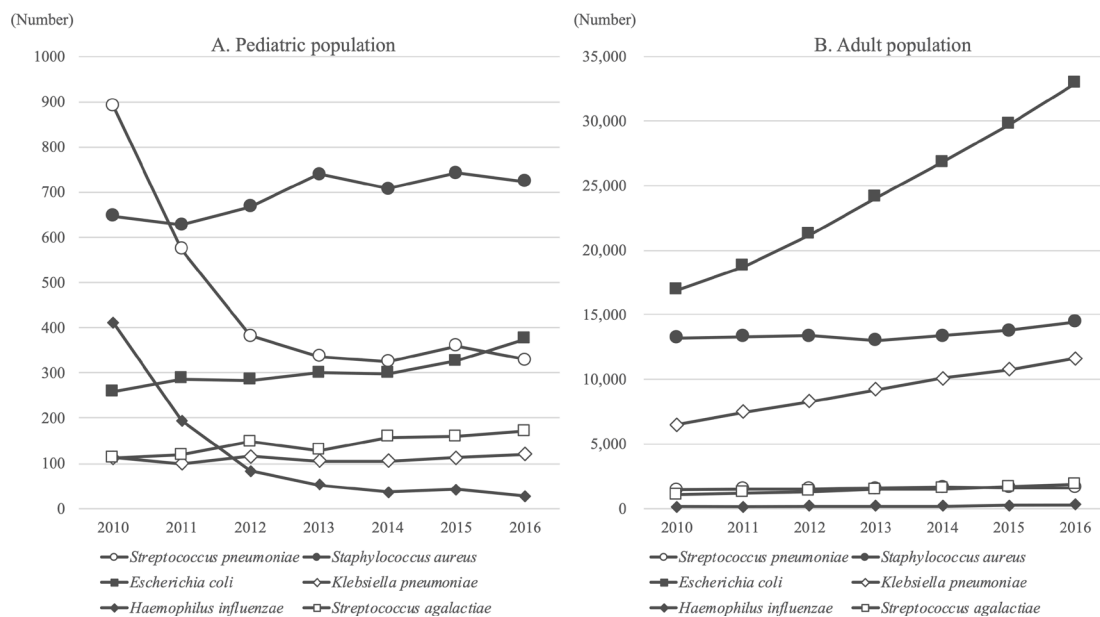
Paediatric population	No of bacteraemia cases/year							Cochran-Armitage test (p value)
	2010	2011	2012	2013	2014	2015	2016	
<i>Streptococcus pneumoniae</i>	891	574	382	337	325	360	330	<0.0001
<i>Staphylococcus aureus</i>	648	628	668	740	708	743	724	<0.0001
<i>Escherichia coli</i>	259	287	284	300	299	326	375	<0.0001
<i>Klebsiella pneumoniae</i>	112	99	116	105	105	112	120	0.0152
<i>Salmonella enterica</i>	27	23	33	33	59	70	56	<0.0001
<i>Haemophilus influenzae</i>	412	195	84	53	36	43	28	<0.0001
<i>Streptococcus pyogenes</i>	20	36	20	34	22	54	39	<0.0001
<i>Streptococcus agalactiae</i>	112	119	148	129	158	160	172	<0.0001
<i>Listeria monocytogenes</i>	3	5	6	4	8	7	9	0.0281
<i>Neisseria meningitidis</i>	0	4	0	3	0	2	2	0.6182
Others	5.904	4984	4631	4279	4265	4948	4725	–
Total	8388	6954	6372	6017	5989	6825	6580	–
Adult population	2010	2011	2012	2013	2014	2015	2016	Cochran-Armitage test (P value)
<i>S. pneumoniae</i>	1470	1553	1551	1584	1682	1654	1626	<0.0001
<i>S. aureus</i>	13239	13334	13390	13011	13377	13783	14444	<0.0001
<i>E. coli</i>	16906	18764	21238	24113	26819	29728	32935	<0.0001
<i>K. pneumoniae</i>	6517	7496	8305	9229	10103	10746	11646	<0.0001
<i>S. enterica</i>	179	130	157	151	181	168	196	0.0601
<i>H. influenzae</i>	166	160	182	202	222	233	283	0.0131
<i>S. pyogenes</i>	315	454	484	462	503	559	650	0.0005
<i>S. agalactiae</i>	1085	1206	1306	1461	1534	1665	1893	<0.0001
<i>L. monocytogenes</i>	88	105	139	181	185	205	211	<0.0001
<i>N. meningitidis</i>	7	2	4	7	14	13	13	0.0219
Others	77596	75992	78732	84333	89131	94793	101584	
Total	117568	119196	125488	134734	143751	153547	165481	

## RESULTS

Data were obtained from 592 hospitals. In children, we obtained blood culture results from 98 295 samples in 2010, 109 611 samples in 2011, 115 172 samples in 2012, 115 172 samples in 2013, 120 561 samples in 2014, 131 297 samples in 2015 and 138 452 samples in 2016. In adults, we obtained blood culture results from 390 796 samples in 2010, 428 529 samples in 2011, 462 153 samples in 2012, 497 143 samples in 2013, 530 399 samples in 2014, 579 195 samples in 2015, and 625 670 samples in 2016. Overall, the number of bacteraemia-positive samples was 47 125 (5.7%) in children and 959 765 (27.3%) in adults.

Table 1 shows the annual numbers of bacteraemia cases according to causative bacteria, and figure 1 shows the temporal trends in the number of bacteraemia cases for six major pathogens (*S. pneumoniae*, *S. aureus*, *E. coli*, *K. pneumoniae*, *H. influenzae* and *S. agalactiae*). *S. pneumoniae* was the most frequent cause of bacteraemia in children in 2010. However, after 2011, *S. aureus* bacteraemia was the

most frequent in children, followed by *S. pneumoniae* and *E. coli*. In 2016, *E. coli* bacteraemia became more common than *S. pneumoniae* bacteraemia. In contrast, *E. coli* bacteraemia was the most frequent in adults, followed by *S. aureus* and *K. pneumoniae*, consistently. *E. coli* bacteraemia significantly increased in both children and adults. An increase in *S. enterica* bacteraemia was observed in children, but not adults, during the study period. *S. agalactiae* bacteraemia increased in both children and adults. *L. monocytogenes* was rarely detected in children, but accounted for more than 100 bacteraemia cases in adults in all years except 2010; in addition, *L. monocytogenes* bacteraemia increased throughout the study period in adults. In contrast, *N. meningitidis* was rarely detected in both children and adults. In children, both *S. pneumoniae* and *H. influenzae* bacteraemia decreased from 2010 to 2013. However, *S. pneumoniae* bacteraemia cases were relatively consistent from 2013, whereas *H. influenzae* bacteraemia cases continued to decrease and were almost eliminated by 2016.



**Figure 1** Temporal trends in the number of bacteraemia cases according to causative bacteria. (A) paediatric population. (B) adult population.

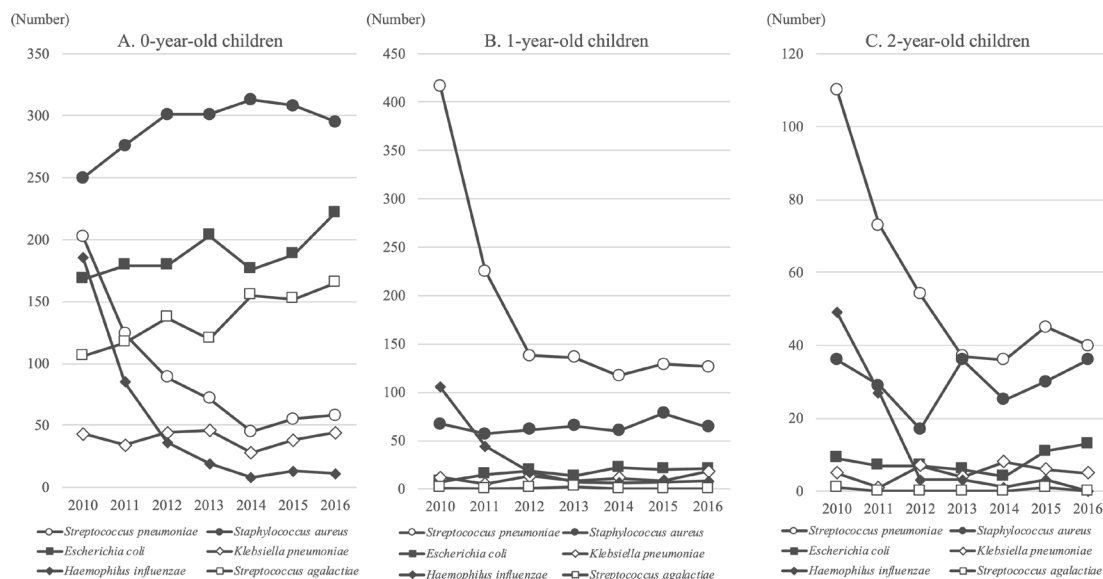
The breakdown of bacteria-specific bacteraemia trends in children aged 0, 1 and 2 years is shown in figure 2. Although the number of *S. aureus* bacteraemia cases was highest in 0-year-old children, numerous cases were also observed in 1-year-old and 2-year-old children. A decrease in the number of *S. pneumoniae* bacteraemia cases from 2010 to 2013 was observed in all three age groups; however, these cases became relatively stable in 0-year-old and 1-year-old children, but increased in 2-year-old children.

## DISCUSSION

To the best of our knowledge, this is the largest study that evaluates the trends and aetiology of bacteraemia in children and adults in Japan. Because the data were

obtained from the country's largest government-operated microbiological surveillance system, our findings may be regarded as having a high degree of generalisability to the Japanese population.

Our analysis revealed reductions in *S. pneumoniae* and *H. influenzae* bacteraemia over the study period, but increases in *S. aureus*, *E. coli*, and *S. agalactiae* bacteraemia. In particular, *E. coli* bacteraemia increased in both children and adults, with the number of adult cases doubling over the 6-year study period. Similar increases in *E. coli* bacteraemia have also been reported in the UK, Europe and the USA.<sup>8 9 13</sup> Although the reasons remain unclear, *E. coli* bacteraemia frequently originates from urinary tract infections.<sup>14 15</sup> Other reports have found



**Figure 2** Temporal trends in the number of bacteraemia cases according to causative bacteria in children aged 0–2 years. (A) 0-year-old children. (B) 1-year-old children. (C) 2-year-old children.

that community-onset cases account for a greater proportion of *E. coli* bacteraemia than hospital-onset cases and antimicrobial-resistant strains are increasing.<sup>8 15</sup> While population ageing is a possible factor for these increases in adults,<sup>16</sup> it does not explain the rise in paediatric cases. Although there is currently no definitive evidence, it has been postulated that the emergence of antimicrobial resistance is a bacterial factor that contributed to the increase in *E. coli* bacteraemia within the community.<sup>8 15</sup> Similarly, a study reported that the rise in a pandemic *E. coli* strain was associated with an increase in infant urinary tract infections.<sup>17</sup> Further investigations are needed to elucidate these issues.

*S. aureus* was a major cause of bacteraemia among both adults and children in our study population. Studies from other countries have also reported that *S. aureus* bacteraemia is likely to occur in the hospital setting and in infants.<sup>18 19</sup> Therefore, the high incidence of *S. aureus* bacteraemia in our subjects may be explained by the focus on hospitalised patients (including those in neonatal intensive care units). Similar results have also been reported in a metropolitan hospital in Australia.<sup>20</sup> There may be a need for programmes to promote hospital infection control and prevention measures, such as compliance with hand hygiene guidelines, to halt the increase in paediatric *S. aureus* bacteraemia. Although studies have also reported increases in community-onset *S. aureus* bacteraemia,<sup>18 21</sup> it was unclear as to whether our cases originated in the community or healthcare setting as our data did not specify the location of onset. Our observed increases in *S. agalactiae* bacteraemia were corroborated by previous studies that reported increases in late-onset infections.<sup>22 23</sup>

Immunisations using the *H. influenzae* type b vaccine and pneumococcal conjugate vaccine have increased rapidly in Japan, with almost all eligible children receiving these inoculations since 2013 (online supplemental table 1). *H. influenzae* bacteraemia cases continued to decline over the study period, but the decline in *S. pneumoniae* bacteraemia cases ceased in 2013. Among 1-year-old children (who are most eligible for these immunisations), both bacteraemia types decreased sharply until 2012, whereupon the decrease in pneumococcal bacteraemia stopped. Numerous studies in other countries have demonstrated the efficacy of the 13-valent pneumococcal conjugate vaccine against pneumococcal bacteraemia,<sup>5 24–26</sup> but the impact of this vaccine (introduced in November 2013) was not apparent in Japan. We posit that this may have been affected by the higher rate of serotype replacements in pneumococcal bacteraemia in Japan relative to other high-income countries.<sup>10</sup> Hence, 13-valent vaccine possibly suppressed the increase in bacteraemia causes by 7-valent vaccine-uncovered pneumococcal serotypes. Additionally, *S. pneumoniae* serotype 12F has caused domestic outbreaks of invasive pneumococcal diseases in Japan since 2016, and our observed increase in pneumococcal bacteraemia cases in 2016 may be associated with these outbreaks.<sup>27 28</sup>

*L. monocytogenes* bacteraemia was observed to be more common in adults than in children among our subjects. Similar findings were reported in the USA, which raised questions about the necessity of *L. monocytogenes* coverage in empiric antibiotic therapy for infants.<sup>6</sup> However, we observed a consistent—although low—level of *L. monocytogenes* bacteraemia in Japanese children every year, and the removal of *L. monocytogenes* coverage would require careful consideration. In contrast, the rarity of *N. meningitidis* bacteraemia in both children and adults suggests that there is currently no need for a mandatory meningococcal vaccine programme in Japan.<sup>29</sup>

Recent years have seen an increased understanding in physicians of the importance of obtaining and testing blood culture samples in Japan, and this was reflected in the rising number of samples taken from both children and adults throughout the study period (online supplemental figure 1). In children, the proportion of bacteraemia-positive cases had gradually declined over time due to the increase in the number of bacteraemia-negative samples; the latest proportion of bacteraemia-positive cases in 2016 was 4.75%. The proportion of bacteraemia-positive cases due to our target pathogens (ie, bacteria that can cause bacteraemia in healthy children) was 1.30%, which is generally higher than those of other high-income countries.<sup>5 30 31</sup> This disparity may be partially affected by our focus on more severe cases that require hospitalisation. Unfortunately, our database did not include information on the ward in which each positive blood culture was obtained, and we could not identify and exclude patients in intensive care units. Also, increases in the actual number of bacteraemia-positive cases were observed in adults, but not in children. This may have been influenced by the epidemiologic changes in paediatric bacteraemia over the study period.

## LIMITATIONS

Our study has several limitations. First, the JANIS data did not include patient and clinical information such as inpatient or outpatient statuses, patient background and prognoses. As a result, the identification of bacteraemia-positive samples lacked context for interpretation. Second, we attempted to minimise the possible statistical issues stemming from the voluntary nature of the surveillance programme through the exclusion of multiple-set and follow-up blood cultures, but could not address the bias arising from the increasing emphasis on obtaining blood cultures. Third, we assessed the epidemiology of *H. influenzae* and *S. pneumoniae* bacteraemia, but could not analyse their respective capsule types or serotypes. Further studies are, therefore, needed to evaluate the epidemiological differences, if any, among these various strains. Finally, the relatively high proportion of bacteraemia cases attributed to ‘other’ bacterial species may be due to blood culture contaminants (eg, skin commensals). However, we were unable to distinguish between contaminants and true pathogens from the laboratory

data alone. Therefore, the prevalences of *E. coli* and *S. aureus* bacteraemia cases would be higher if the contaminants could be accurately identified and excluded.

## CONCLUSION

This study described the domestic trends in bacteraemia in Japan from 2010 to 2016. *H. influenzae* bacteraemia cases continued to decline over the study period, whereas *S. pneumoniae* bacteraemia cases declined until 2013. These findings suggest that the introduction of the 13-valent pneumococcal conjugate vaccine did not have a substantial impact on disease occurrence. In contrast to the decreasing trends in *H. influenzae* and *S. pneumoniae* bacteraemia, the analysis found increasing trends in *S. aureus*, *E. coli* and *S. agalactiae* bacteraemia. Continued epidemiological monitoring is needed to ascertain the changes in the domestic burden of bacteraemia in Japan.

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**Contributors** YK is responsible for the study conceptualisation, design, investigation and drafting of the manuscript. KI contributed to the study design, manuscript review and editing and supervision. HF contributed to the study design, data acquisition, formal analysis and supervision. NM contributed to the study design and supervision. NO contributed to the study conceptualisation, funding acquisition and supervision. All authors read and approved the final manuscript.

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**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** The study was approved by the Kyushu University Institutional Review Board for Clinical Research (approval number: 2019-180).

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data may be obtained from a third party and are not publicly available. For the JANIS data, the Ministry of Health, Labour and Welfare of Japan has placed strict legal restrictions on the release or sharing of these data. As a result, these data are not publicly available. However, the same data may be obtained from a third party through a formal application.

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## Supplementary table 1.

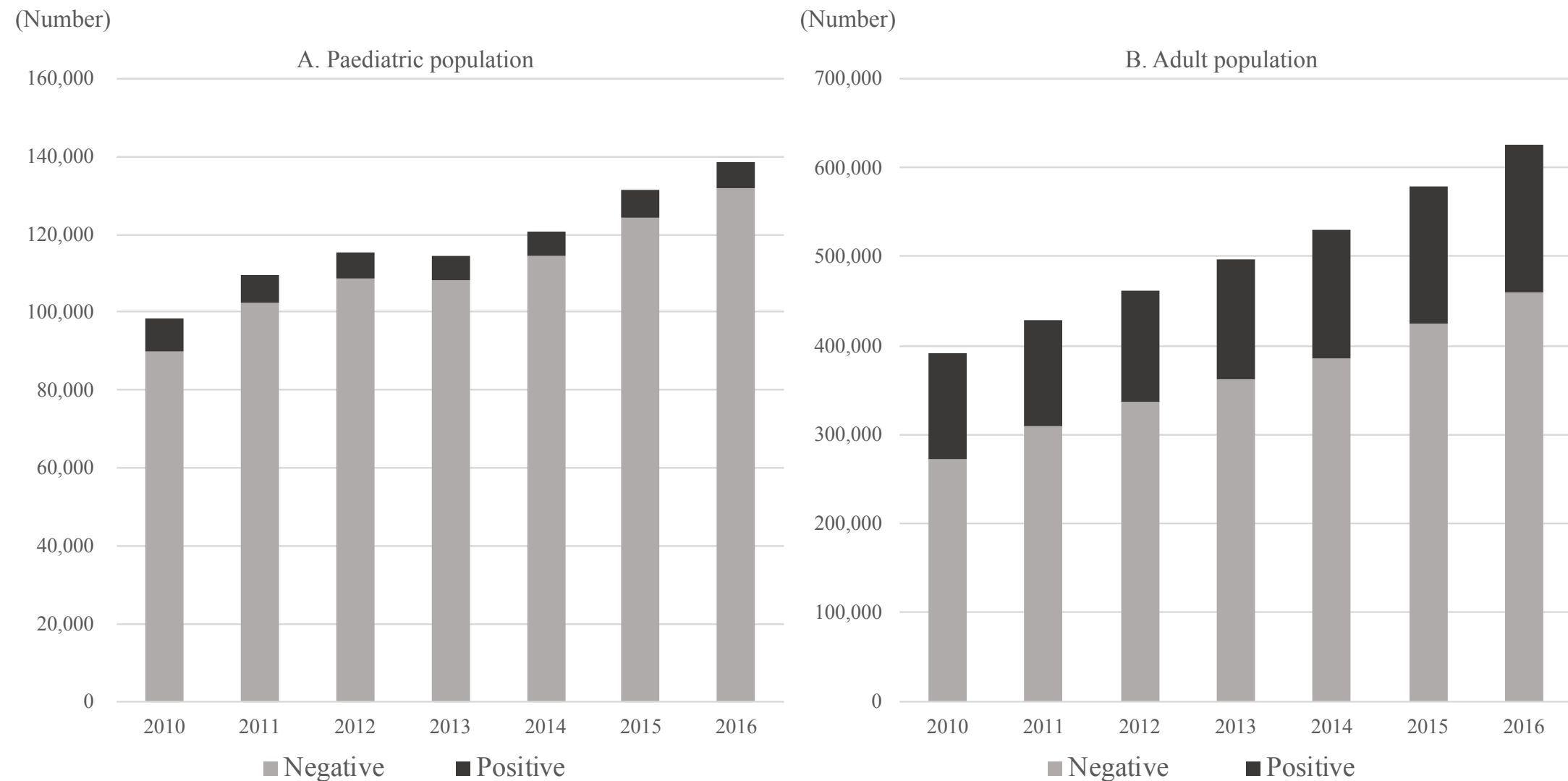
Proportion of vaccine coverages in *Haemophilus influenzae* type b and Pneumococcal conjugate vaccine in Japan

Vaccine	Dose	2010	2011	2012	2013	2014	2015	2016
<i>Haemophilus influenzae</i> type b vaccine (%)	First Dose	NA	NA	NA	113.8	102.4	105.9	98.7
	Second Dose	NA	NA	NA	102.5	98.8	105.0	98.2
	Third Dose	NA	NA	NA	105.2	102.8	106.2	99.6
	Booster	NA	NA	NA	107.2	96.8	100.0	103.4
Pneumococcal conjugate vaccine (%)	First Dose	NA	NA	NA	115.6	103.2	106.2	98.9
	Second Dose	NA	NA	NA	104.6	99.8	105.4	98.5
	Third Dose	NA	NA	NA	103.4	102.5	106.5	99.9
	Booster	NA	NA	NA	90.6	93.7	100.7	103.3

Numbers are obtained from webpage of Ministry of Health, Labour and Welfare (<https://www.mhlw.go.jp/topics/bcg/other/5.html>). Proportion of vaccine coverages were obtained by dividing the number of inoculated vaccines by that of target population. The number of target population was estimated by the population data, thus the proportion of vaccine coverages are possible to be recorded higher than 100%. Data from 2010 to 2012 is not available because survey was not performed (these vaccines were not mandatory during the period).



## Supplementary Fig 1. Temporal trends in the total number and bacteraemia-positive number of blood culture samples



(A) Paediatric population. (B) Adult population. The grey bars and black bars represent the number of bacteraemia-negative and bacteraemia-positive blood culture samples, respectively.