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Review

Systematic review of seroepidemiological studies on Japanese encephalitis in the Republic of Korea☆

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ABSTRACT

Background: Countries with strong vaccination programmes, including the Republic of Korea, have experienced changes in the epidemiology of Japanese encephalitis (JE), with an increase in cases seen among adults. However, the reasons for this increase are not clearly understood. This study describes the change in age-specific JE virus (JEV) seroprevalence over time in Korea, with a view to understanding this transition.

Methods: A search of Embase, MEDLINE, PubMed, KoreaMed, Korea Education and Research Information Service, National Library of Korea, and the Seoul National University Medical Library was conducted using the keywords 'Japanese encephalitis' combined with 'Korea', 'seroprevalence', 'seropositivity', 'seroepidemiology', 'serosurvey', 'immunity', and 'antibody'.

Results: Eighteen studies published between 1946 and 2012 were retrieved. In 1946, seropositivity was 51% in the 1–10 years age group, 79% in those aged 11–20 years, and 94% in those ≥61 years of age. In the 1970s, seropositivity in children and adolescents was low (10–59%); seropositivity in this group increased to 90–92% in 1984–1985, and increased further to 98% in 2012. Seropositivity among adults aged 41–50 years and 51–60 years in the 2010s ranged between 83.1% and 97.9% and between 77.5% and 98.3%, respectively.

Conclusions: The implementation of the universal JE vaccination programme in the 1980s has increased the seroprevalence of JEV in Korea, especially in children who are targeted for vaccination.

Contents

Introduction

Japanese encephalitis virus (JEV) is an important cause of encephalitis in Southeast Asia and the Western Pacific region. JEV is primarily transmitted by the vector mosquito *Culex tritaeniorhynchus*, and is maintained through zoonotic cycles between pigs and wild birds, with humans as incidental dead-

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end hosts. The virus may cause a symptomatic disease that frequently results in neurological complications, with a reported mortality rate in patients ranging from 10% to 70% (Monath, 1988). However, most cases of JEV transmission result in an asymptomatic infection, which induces an antibody response but lacks clinical symptoms requiring a medical consultation (Campbell et al., 2011).

In Japanese encephalitis (JE) endemic countries without a vaccination programme, the majority of cases occur in childhood, and the long-term burden of disease can be substantial. In JE high incidence areas with no vaccination programme, the incidence rate in children <15 years of age has been estimated to be 10.6 per 100 000 and in adults to be 3.7 per 100 000 (Campbell et al., 2011). About 30–70% of the population in high endemic countries are JEV seropositive, indicating at least one previous infection (Hiscox et al., 2010; Chatterjee et al., 2004; Fox et al., 2014). Conversely, in countries with strong JE vaccination programmes, the overall incidence has decreased dramatically since the introduction of the vaccine. In Japan, the incidence dropped from over 1000 cases annually in the 1960s to less than 10 cases annually in the 2000s (Arai et al., 2008). The introduction of a vaccination programme in Taiwan in 1968 resulted in a drop in incidence from 2.05 per 100 000 reported in 1967 to 0.03 per 100 000 in 1997 (Chang et al., 2017). In such countries with a historically high incidence and long-standing vaccination programmes, the incidence in children and adults is very low, estimated at 0.003 per 100 000 (Campbell et al., 2011). In Japan, seroprevalence data for 2004 showed that the JEV antibody-positive population was >70% for ages 4–24 years and 65–69 years, and between 20% and 70% for those aged 25–64 and ≥70 years (Arai et al., 2008). The majority of cases occurred in the adult and elderly populations, with the peak incidence in the 60–69 years age group.

The Republic of Korea is a JE endemic country that experiences seasonal outbreaks. The epidemic season usually begins in August, and the majority of cases are usually reported from southern parts of the country (Sohn, 2000). The JE vaccine was first licensed for distribution in Korea in 1967 and it has been part of the routine universal vaccination schedule for all children aged 1–15 years, with full government funding, since 1983 (Wu et al., 1999). The incidence rate has since decreased from more than 1000 cases per year in the 1960s to less than 20 cases annually in the 2000s (Sohn, 2000; Umenai et al., 1985). However, increased numbers of JE cases

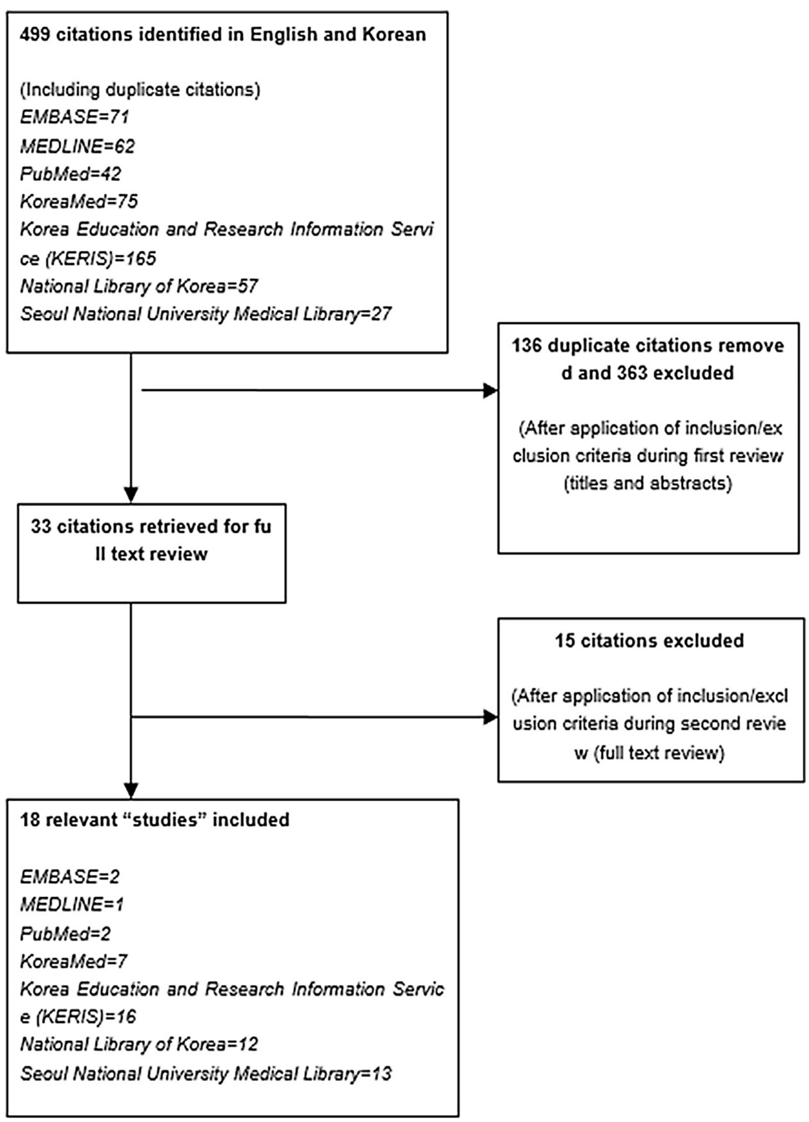

Figure 1. Results of the literature search and evaluation of identified studies, according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

in adults have been described since 2010, predominantly affecting unvaccinated adults >40 years of age (Lee et al., 2012; Sunwoo et al., 2016).

Examining JEV seroprevalence by age categories can provide a population profile of JEV immunity and susceptibility, describe populations or age-strata at elevated disease risk, and therefore inform vaccination programmes and other prevention and control measures. The aim of this study was to determine the change in age-specific JEV seroprevalence over time in the Republic of Korea.

Methods

A systematic search was conducted to identify studies reporting JEV seroprevalence in Korea. The literature search and evaluation were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. Embase, MEDLINE, PubMed, KoreaMed, Korea Education and Research Information Service (KERIS), National Library of Korea, and the Seoul National University Medical Library were searched using the following keywords in English for the international databases; translated into Korean as required for the local databases: 'Japanese encephalitis' combined with 'Korea'; 'seroprevalence'; 'seropositivity'; 'seroepidemiology'; 'serosurvey'; 'immunity'; and 'antibody'.

The title, abstract, and full length text were screened for all suitable articles written in English or Korean. Only original articles published in journals or dissertation papers were included. Duplicate articles or data (i.e., the same data published in journals and theses), review articles, clinical JE studies (i.e., serostatus in patients with confirmed JE), interventional vaccine trials, and non-human seroprevalence studies (pigs, horses, birds, chickens, or mosquitoes) were excluded. For each study included, data on the sampling location, year, month, population, age, setting, test method, and test threshold were extracted and recorded. Reported seropositivity rates were extracted from each study identified.

Data were presented as a narrative summary with graphs and tables. For consistent presentation, seroprevalence data were stratified into 10-year age categories: (for example, ages 1–10, 11–20, 21–30, and 31–40 years). If the reported age range overlapped two categories, the median age was used to allocate the seroprevalence data. Where the reported age range overlapped more than two age categories, the corresponding seroprevalence data were allocated to all age categories that contained ≥5 years of age data. Data were presented in graphs to provide a visual summary of the changing seroprevalence by age over time.

Results

Eighteen studies met the eligibility criteria (Figure 1). Fifteen studies were in Korean and three were in English. Twelve studies were conducted in Seoul and six elsewhere in the country (Figure 2). Two studies (study codes 1 and 6) presented data stratified by geographic region; data were extracted separately for each region for the analysis.

Study references, population characteristics, JEV seroprevalence, and related data extracted from the selected studies are summarized in Table 1. The first study was conducted by the US military in 1946 (Deuel et al., 1950). Following this, four studies were conducted in the 1960s (Lee et al., 1963; Chang et al., 1965; Kim et al., 1965; Chay, 1971), six studies in the 1970s (Kim, 1974; Kim et al., 1976; Lee and Lee, 1976; Lee and Lee, 1977; Lee and Ko, 1979; Lee et al., 1980), two studies in the 1980s (Lee and Youm, 1985; Lee et al., 1989), three studies in the 1990s (Cho et al., 1992; Kim et al., 1996; Choi, 1995), and two studies in the 2010s (Lee et al., 2016; Hong et al., 2013). The timing and seasons of blood sample collection varied across the studies. The haemagglutination

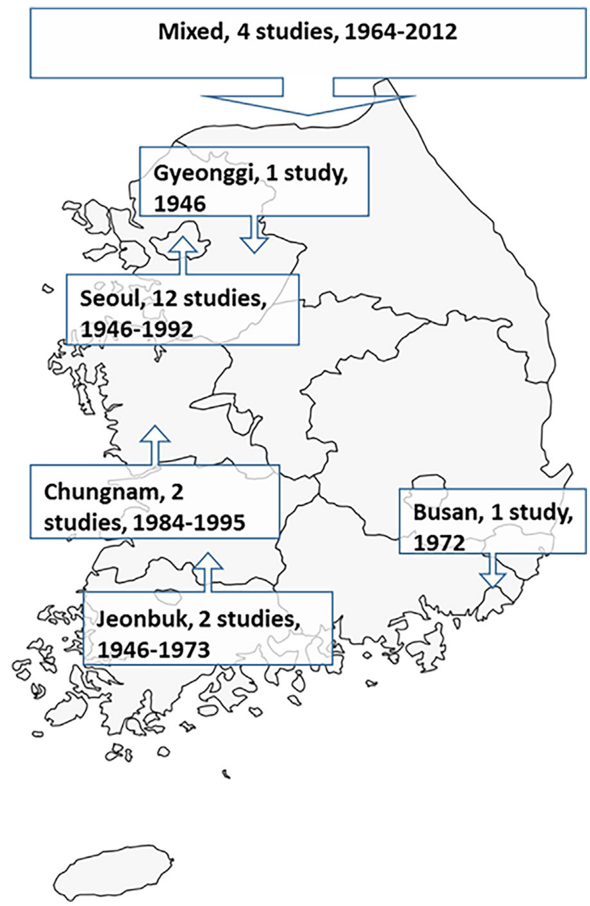

Figure 2. Map of the study sites and years.

inhibition (HI) test was used in most studies (15/18), while the two most recent studies used the plaque reduction neutralization test (PRNT) and the pseudotype virus assay to profile neutralizing antibody responses (Lee et al., 2016; Hong et al., 2013). The threshold cut-off value for the HI test was ≥1:10 in 13 studies, ≥1:20 in one study (Kim et al., 1996), and ≥1:50 in one study (Chang et al., 1965).

Figure 3 summarizes the age-stratified seropositivity rate of the 18 studies by study year. In 1946, seropositivity was 51% in the 1–10 years age group, 79% in those aged 11–20 years, and 94% in those ≥61 years of age. In the 1970s, seropositivity in children and adolescents was low (10–59%); seropositivity in this group increased to 90–92% in 1984–1985, and increased further to 98% in 2012. Seropositivity among adults aged 41–50 years and 51–60 years in the 2010s ranged between 83.1% and 97.9% and between 77.5% and 98.3%, respectively. For the 51–60 years age group in 1964, only two individuals were tested for seroprevalence, and both were JEV seronegative.

Discussion

Over the past seven decades, there have been noticeable changes in the patterns of JEV seroprevalence in the Korean population. Overall, seropositivity has increased, particularly in the younger age groups. More importantly, starting in the 1980s, the seropositivity rate in children became higher than that in adults. Aligned with this immunological trend, among 45 JE cases identified in South Korea between 2007 and 2010, 44 (97.8%) involved adults >20 years of age (Lee et al., 2012). The trend extended to 2015, with 129 JE cases reported between 2010 and

Table 1
Details of the included studies.

Geographic coverage	Code	Year	Season	Age groups included (years)	Median age/age group	Sample size	Population source	Assay[a]	Threshold	Seroprevalence (%)
Seoul, Gyeonggi, Jeonbuk	1	1946	Oct–Nov	1–4, 5–9, 10–14, 15–19, 20–39, 40–59, 60+	40–59	210	Community	NTAb	≥50	76.3
Seoul	2	1961	Jun–Oct	22–29	22–29	247	Community	HI test	≥10	34.5
Seoul	3	1963	Yearly	0–1, 2–4, 5–9, 10–14, 15–19, 20–59, 60+	2–4	638	Community + hospital	HI test	≥50	12.5
Mixed	4	1964	Yearly	0–4, 5–9, 10–14, 15–19, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60+	25–29, 30–34	1656	Community	HI test	≥10	19.0
Seoul	5	1969–1970	Yearly	18–19, 20–24, 25–29, 30–34, 45–39, 39+	30–34	2111	Hospital	HI test	≥10	40.7
Seoul, Busan, Jeonbuk	6	1972	Nov–Jun	0–4, 5–9, 10–14, 15+	N/A	414	Community	HI test	≥1:10	29.6
Seoul	7	1973–1974	Oct–Mar	1–10, 11–20, 21–30, 31–40, 41–50, 51–60, 60+	41–50	498	Hospital	HI test	≥1:10	9.4
Seoul	8	1975	Jul–Nov	0–10, 11–20, 21–30, 31–40, 41–50, 51–60, 61+	11–20	594	Hospital	HI test	≥1:10	53.3
Seoul	9	1976	Yearly	0–10, 11–20, 21–30, 31–40, 41–50, 51–60, 61+	11–20	1204	Hospital	HI test	≥1:10	55.4
Seoul	10	1977–1978	Yearly	0–10, 11–20, 21–30, 31–40, 41–50, 51–60, 61+	51–60	3164	Hospital	HI test	≥1:10	61.2
Seoul	11	1979	Jun–Dec	0–10, 11–20, 21–30, 31–40, 41–50, 51–60, 61+	31–40	568	Hospital	HI test	≥1:10	55.1
Chungnam	12	1984–1985	Yearly	0–10, 11–20, 21–30, 31–40, 41–50, 51–60, 61–70, 71+	11–20	889	Hospital	HI test	≥1:10	94.2
Seoul	13	1987	Yearly	11–20, 21–30, 31–40, 41–50, 51–60	41–50	600	Hospital	HI test	≥1:10	59.2
Mixed	14	1991	Apr–Dec	0–9, 10–19, 20–29, 30–39, 40–49, 50–59, 60+	41–50	1532	Community + hospital	HI test PRNT	≥1:10 ≥80%	58.8
Seoul	15	1992	May–Jun	4–6, 7–9, 10–12, 13–15	10–12	862	Hospital	HI test	≥1:20	40.7
Chungnam	16	1995	Yearly	0–9, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69	51–60	600	Hospital	HI test	≥1:10 ≥80%	58.3
Mixed	17	2010	N/A	30–39, 40–49, 50–59, 60–69	51–60	945	Community	PRNT ELISA	≥50%	98.1
Mixed	18	2012	Yearly	15, 16, 17, 18, 19, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–65, 65–69, 70+	25–29, 30–34	1603	Hospital	NTAb	≥1:50	87.4

N/A, Not applicable.
[a] NTAb, neutralizing antibody; HI, haemagglutination inhibition; PRNT, plaque reduction neutralization test; ELISA, enzyme-linked immunosorbent assay.

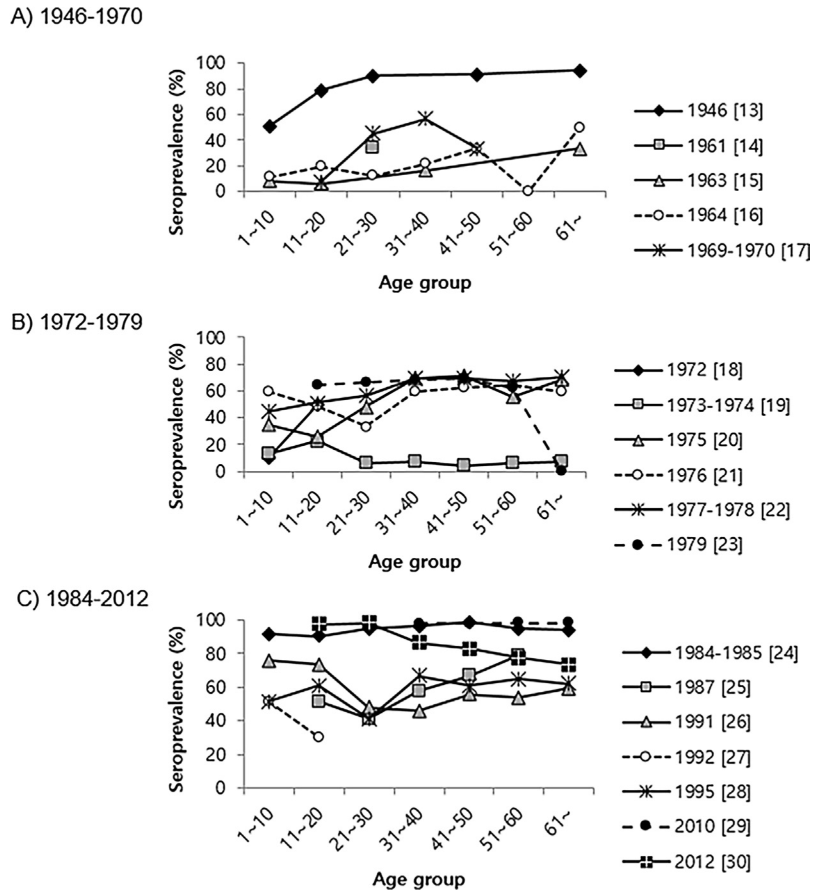

Figure 3. Reported age-stratified seroprevalence of Japanese encephalitis virus in the Republic of Korea by time period. Each line refers to one study. The number in parenthesis indicates the study code.

2015 (Sunwoo et al., 2016); the median age of these cases was 53 years, and those <19 years of age accounted for only 3.1% of cases.

Although the JE vaccine was first introduced in Korea in the 1960s, vaccination coverage was initially low at 1–5% in the 1970s (Kim, 1972). Following a nationwide outbreak of JE in 1982 that resulted in 1197 cases and 40 deaths, the JE vaccine was included in the national immunization programme provided to all children aged 1–15 years (Lee and Oh, 1987). JE vaccination has been included as a routine vaccine since then, and vaccination coverage increased to 80–95% in the 1980s (Hong, 2008). Some of the immunological observations described in this review are likely attributable to this programme, which has resulted in a gradual increase in vaccine-induced JE seropositivity since the 1980s and a decrease in JE cases in the paediatric target population.

During the pre-vaccination era from 1955 to 1966, the highest incidence rate of symptomatic JE disease was in the 0–9 years age group; 88% were susceptible, as evidenced by a lack of protective antibodies (Wu et al., 1999; Umenai et al., 1985). In the 2010s, with sustained high vaccination coverage among children, the JE incidence rate in adults >20 years of age was low at 0.9 per 100 000, but was nonetheless significantly higher than in children (Lee et al., 2012; Sunwoo et al., 2016). As a consequence of both vaccination and, presumably, natural infection, only 10% of adults remained susceptible to JE infection by 2010–2016. However, this is higher than in those aged 10–19 years, the vast majority of whom will have been vaccinated in childhood. Similar changes have been observed in nearby countries: in Japan in 2004, those aged 25–64 years had a seropositivity rate between 20% and 70% (Arai et al., 2008); however, prior to that, from 1982 to 2004, 78% of the total cases in Japan involved adults aged ≥40 years. In Taiwan, where a shift in JE cases from young children to adults has also occurred, a similar pattern of low JE seroprevalence among adults and higher incidence compared to children has been described (Hsu et al., 2014).

Other environmental factors may have contributed to the change in JE seroprevalence and epidemiology in Korea. Economic growth in the 1960s and 1970s resulted in rapid urbanization. In 1955, only 28.5% of Koreans were urban dwellers, a proportion that had increased to 88.3% by 1999 (Rii and Ahn, 2001). This massive population migration, with a greater distance between residences and the main ecological sources of the mosquito vector (i.e., flooded rice paddy fields), along with improved sanitary conditions, may have resulted in a lower overall number of natural infections in humans. A comparison between the 1984–1985 study (Lee and Youm, 1985), which took place in Chungnam, a rural area of the country, and the 1992 study (Kim et al., 1996), which was conducted in metropolitan Seoul, indicated that the variation in seroprevalence may be attributable to the geographic risk of JE transmission. The geographic variation in vaccination coverage may also have contributed to the difference in seroprevalence. The 1991 study used residual serum from all over the country (Seoul, Gangwon, Jeonbuk, Jeonnam, Jeju), but most of the paediatric samples were from Seoul, where there was better access to medical care and vaccination (0–9 year olds, Seoul/total = 126/298, 42.3%) (Cho et al., 1992). The 1995 study used residual serum from outpatient clinic visits at Dankook University Hospital (located in Chungnam Province) from January 1995 to December 1995; that study included 43 children aged 0–9 years (Choi, 1995).

There are limitations to the results of this study. Due to the limited information presented in the studies included, other important factors such as the location of residence and individual vaccination status, which may have influenced seroprevalence, could not be taken into account. It was not possible to perform a meta-analysis, nor was it possible to exclude sampling or selection bias in the overall compilation of the results, partly because risk factors for JEV infection are relatively poorly understood. In addition, the data included in this review were derived from various serological assays with differing cut-off thresholds. This heterogeneity may have affected the comparisons between seroprevalence studies and interpretation of the longitudinal changes.

Despite these limitations, the data compiled highlight consistent changes in JEV susceptibility and may aid in the identification of vulnerable populations in Korea. This study indicates that protective immunity remains high in adults vaccinated during childhood, up until the age of at least 30 years (Sunwoo et al., 2017). This may be a reflection of the duration of protection of the vaccines, or a consequence of natural boosting in these vaccinated individuals. These effects may be synergistic and consequently provide a significant level of protection throughout childhood and early adulthood. JE vaccination has clearly reduced susceptibility among the paediatric segment of the population, and this study confirms the significant impact of the universal childhood vaccination programme in reducing susceptibility in children. This finding may be useful in informing countries that plan to implement JE vaccination in their public health programmes in the future.

Data from previously published studies on the seroprevalence of JEV in the Korean population suggest that individuals are likely to be protected by the universal vaccination programme introduced in the 1980s. Population immunity data over time suggest that the recent level of protection against JEV is high in children, whereas susceptible individuals are found in the adult population among those who were not vaccinated or exposed to natural infection in childhood.

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Conflict of interest

YJC, AFT, JN, HSS, and HSK are employed by Sanofi Pasteur.

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