

Dengue-A Re-emerging Infectious Disease in Singapore

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Abstract

Despite its well-established integrated nationwide *Aedes* mosquito control programme which incorporates source reduction, public health education and law enforcement, Singapore has not been spared from the regional resurgence of dengue. The disease incidence has been increasing from 9.3 per 100 000 in 1988 to 102.7 per 100 000 in 1996 at the time when the *Aedes* house index (HI) has dropped to around 1% from >25% in the 1960s. Majority of the cases reported from 1990 to 1996 were dengue fever (DF); dengue haemorrhagic fever (DHF) constituted only 6.7%. The case-fatality rate was 0.1% with 13 (81.3%) of 16 serologically confirmed deaths above 19 years of age. The median age has shifted from 14 years in 1973 to 27 years in 1996. The proportion of primary infections also increased from about one-third in 1990 to nearly half in 1996. All four dengue serotypes have been detected from infected persons with dengue 2 predominating in 1990, 1991 and 1993, dengue 3 in 1992 and 1994 and dengue 1 in 1995 and 1996. The disease incidence was significantly correlated with *Aedes aegypti* HI and residents of compound houses had a significantly higher rate of infection as well as a higher morbidity rate compared with dwellers of high-rise public housing estates. Seroprevalence surveys confirmed the low level of dengue transmission. The immunity level of the general population has been declining with only 6.4% of children and young adults below 25 years of age possessing haemagglutination-inhibition antibody to dengue 2. It would appear that the successful vector control programme over the last two decades has brought about a paradoxical situation in that outbreaks tend to occur more frequently and with even greater intensity because of the low herd immunity of the population. Until the dengue vaccine is commercially available for mass immunisation of the population, community-based integrated control of *Aedes aegypti* remains the key to the prevention and control of DF/DHF.

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Introduction

Dengue fever (DF) had been endemic in Singapore with the first epidemic reported in 1901.^{1,2} The haemorrhagic form of the disease, dengue haemorrhagic fever (DHF), was documented in 1960 when a total of 70 hospitalised cases were reported between June and October.³ The disease became an important public health problem with large epidemics occurring almost annually from 1961 to 1964 and 1966 to 1968. Of the four circulating dengue serotypes, type 1 and type 2 predominated.^{4,5} It was reported that 20% of the hospitalised cases of DHF developed dengue shock syndrome with a case-fatality of 10%.⁶⁻⁸

In June 1966, a Vector Control Unit was set up to carry out surveillance and research on the two dengue vectors, *Aedes aegypti* and *Aedes albopictus*. A pilot survey conducted at the Geylang-Tanjong Rhu area showed that it was possible to reduce the *Aedes* house index (HI) (percentage of houses positive for *Aedes* breeding) from 16% to 2% in just three months, or three rounds of house inspections for elimination of *Aedes* breeding habitats and health education.⁹ The study was extended to vari-

ous parts of the city to determine the ecology and bionomics of *Aedes aegypti* and *Aedes albopictus*.¹⁰⁻¹⁴

DHF was made administratively notifiable on 18 October 1966, based on clinical diagnosis without waiting for laboratory confirmation. On 1 August 1977, both DF and DHF became legally notifiable under the Infectious Diseases Act, 1976.¹⁵ Legislation to control the breeding of *Aedes* mosquitoes was enacted under the Destruction of Disease-Bearing Insects Act (DDBIA), 1968. A national health campaign on "Keep Singapore clean and mosquito free" was launched in October 1969 before the DDBIA was enforced countrywide.¹⁶

The nationwide *Aedes* mosquito control programme which incorporated source reduction, public health education and law enforcement was successfully implemented. The overall *Aedes* HI dropped markedly from >25 to around 5 in 1972 and corresponded with the sharp decline in disease incidence rate from 42.2 per 100 000 population in 1968 to between 3 and 10 per 100 000 from 1969 to 1972. However, an epidemic of 1187 cases of DF/DHF with 27 deaths occurred in 1973 when the *Aedes* HI just exceeded 5%.¹⁷ With further intensification of *Aedes*

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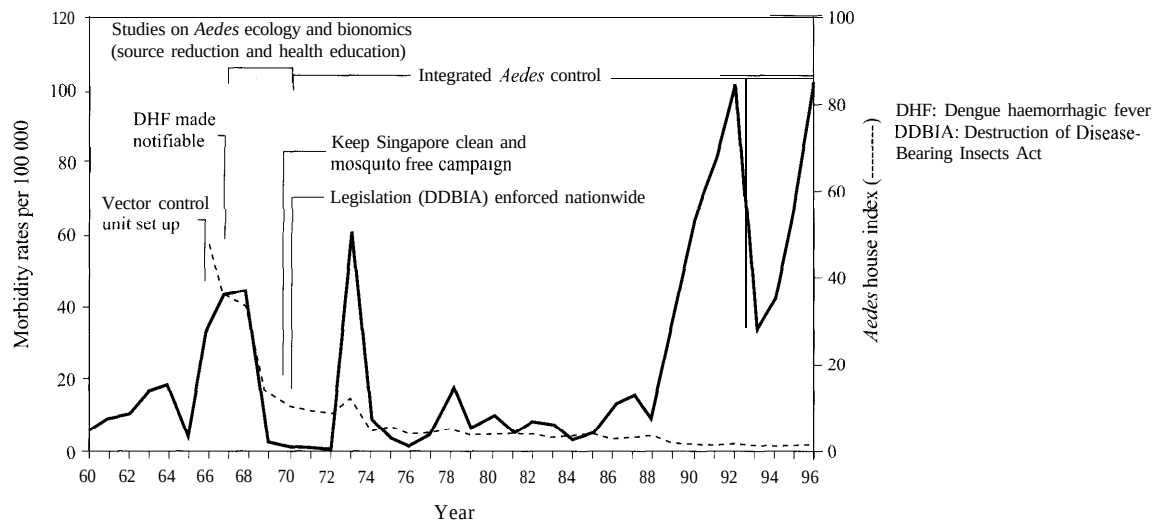


Fig. 1. Reported morbidity rate of DF/DHF and its relationship to *Aedes* house index in Singapore, 1960 to 1996.

control, the HI was reduced to 3, but this could not prevent the reappearance of another epidemic of 384 cases with two deaths in 1978.¹⁶

The whole strategy of *Aedes* surveillance and control was reviewed and the overall *Aedes* HI was brought to 2 in 1983 and to a record low level of 1 in 1985. In spite of this, nationwide outbreaks occurred with even greater frequency and intensity in subsequent years: 1986 (354 cases with one death);¹⁸ 1987 (436 cases with two deaths);¹⁹ 1989 (944 cases with two deaths);²⁰ 1990 (1733 cases with three deaths);^{21,22} 1991 (2179 cases with six deaths);²³ 1992 (2878 cases with six deaths);²⁴ 1993 (946 cases with no death);²⁵ 1994 (1239 cases with one death);²⁶ 1995 (2008 cases with one death);²⁷ and 1996 (3128 cases with three deaths)²⁸ (Fig. 1).

Epidemiology

A total of 14 111 cases of DF/DHF were reported to the Quarantine & Epidemiology Department, Ministry of the Environment, from 1990 to 1996. Of these, 1158 (8.2%) were classified as imported. The mean annual morbidity rate of reported indigenous cases was 69.3 per 100 000 population. DHF constituted between 0.8% and 16.7% of the reported cases. There were 20 deaths from dengue shock syndrome, giving a case-fatality rate of 0.1%. Of the 16 serologically confirmed deaths, 13 (81.3%) were above 19 years of age.

All age-groups were affected with the highest age-specific morbidity rate among teenagers and young adults between 15 and 24 years of age. There was a slight male predominance with a male to female ratio of 1.5:1 (Fig. 2). Among the three major ethnic groups, the mean annual ethnic-specific morbidity rate was highest in Chinese (63.5 per 100 000), followed by Indians (42.1 per 100 000) and Malays (27.6 per 100 000). Of the reported

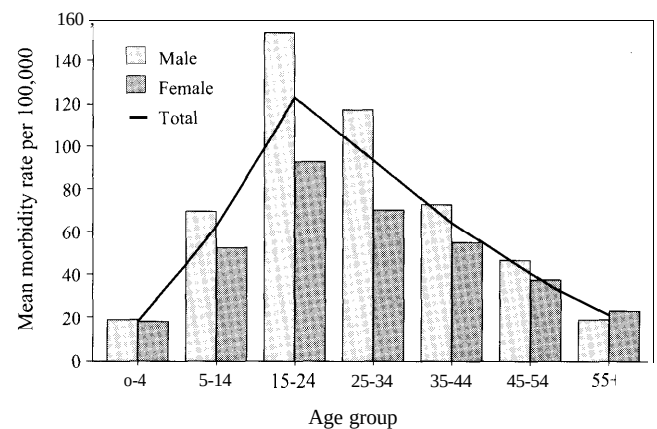


Fig. 2 Age-sex-specific morbidity rates of reported DF/DHF cases in Singapore, 1990 to 1996.

cases, 17.5% were foreign workers who acquired the infection at the place of work, in particular, construction sites. Residents of compound houses had a morbidity rate 5.6 times and 2.9 times higher than that of dwellers of high-rise public housing estates and private condominiums, respectively (Table I).

Most of the cases were reported during the second half

TABLE 1: MEAN ANNUAL MORBIDITY RATE OF REPORTED DF/DHF BY MAIN TYPE OF RESIDENTIAL PREMISES, 1990 TO 1996

	Cases	Mean annual rate per 100 000*
Housing & Development Board flat	6884	39.7
Compound house	4888	223.2
Private condominium apartment	789	76.6

* Based on 1990 census population (Department of Statistics, Singapore)

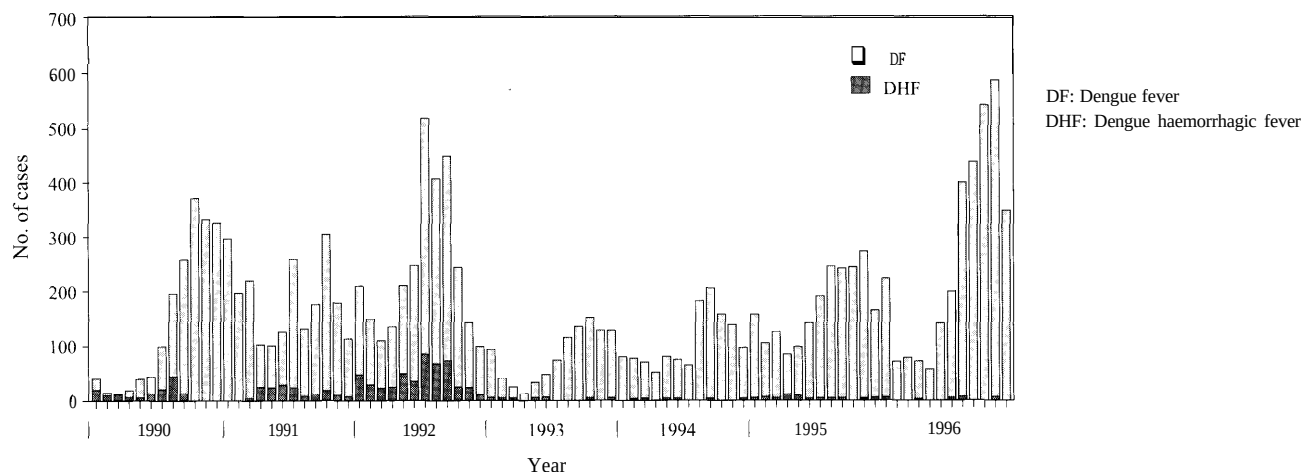


Fig. 3. Monthly incidence of reported DF/DHF in Singapore, 1990 to 1996.

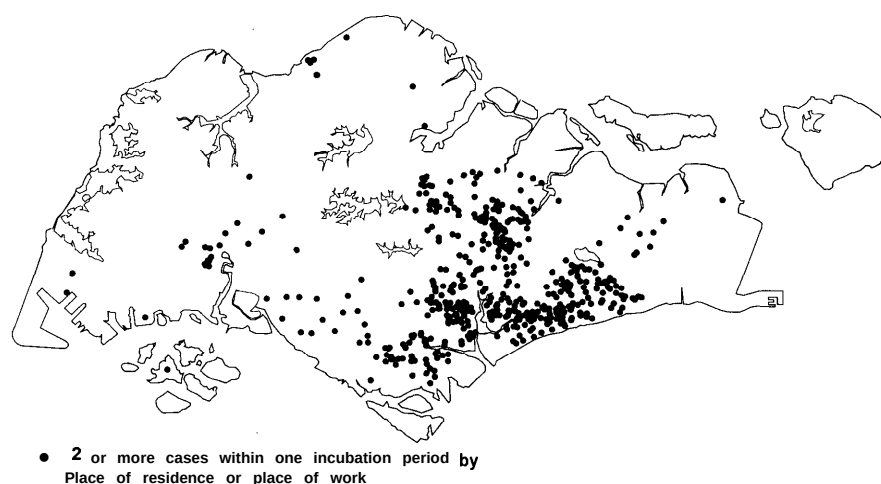


Fig. 4. Foci of dengue transmission in Singapore, 1990 to 1996.

of the year with peak incidences occurring around September to November in 1990, July to September in 1991, July to August in 1992, September to October in 1993, August to October in 1994, August to November in 1995 and August to November in 1996 (Fig. 3). Cases were mainly concentrated in the eastern (24.9%), north-eastern (22.1%) and south-eastern (22.1%) parts of Singapore. Majority of the cases occurred singly and sporadically. Between 15.6% and 38% of the cases could be epidemiologically-linked to one another at various foci of transmission (Fig. 4).

Ninety-four per cent of the reported cases were serologically confirmed by the presence of dengue-specific IgM antibody (IgM-capture enzyme-linked immunosorbent assay,^{29,30} dengue-specific IgG antibody (dengue blot assay),³¹ or a four-fold increase in haemagglutination-inhibition (HI) antibody titres.³² Based on a subsample, 46.2% of the cases were due to secondary infection. The mean age of those with secondary infection (35.5 years) was 10 years, higher than those with

primary infection (26.5 years).

All four dengue virus serotypes were detected from blood samples of infected persons, with dengue 2 predominating in 1990, 1991 and 1993, dengue 3 in 1992 and 1994 and dengue 1 in 1995 and 1996 (Table II).

Seroprevalence Surveys

Periodic serological surveys showed that the immunity level of the general population to dengue virus infection continued to decline.^{33,34} It dropped from an overall prevalence rate of 46% in 1982-1984³⁵ to 39% in 1993, with only 6.4% of children and young adults below 25 years of age possessing HI antibody to dengue 2.³⁶ However, the seroprevalence among the residents in two localities in the south-eastern part of Singapore where most of the cases were clustered, was found to be between 65.6% and 68.8% with children living there acquiring dengue infection earlier than those in other parts of Singapore (Fig. 5).³⁷ The annual rate of acquisition of dengue virus infection among the residents was

TABLE II: ISOLATION OF DENGUE VIRUS SEROTYPES FROM BLOOD SAMPLES OF HOSPITALISED PATIENTS IN SINGAPORE, 1992 TO 1996

Year	No. tested	No. positive (%)	% positive for				
			Dengue 1	Dengue 2	Dengue 3	Dengue 4	Untyped
1992	154	24 (15.6)	4.2	8.3	83.3	0	4.2
1993	257	21 (8.2)	4.8	66.7	19.0	0	9.5
1994	309	45 (14.6)	17.8	35.6	44.4	0	2.2
1995	257	47 (18.3)	42.6	17.0	36.2	4.3	0
1996	234	17 (7.3)	52.9	29.4	11.8	5.9	0

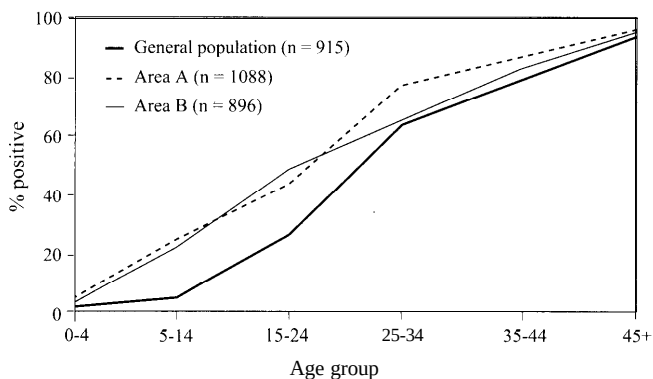


Fig. 5. Age-specific prevalence of HI antibody to dengue 2 virus in the general population (1993) and residents of two highly endemic areas (1994).

5.6%; the rate being highest in adults between 25 and 34 years of age.³⁸ Residents of compound houses had a significantly higher risk than those staying in high-rise public housing estates. The survey also showed that a very high proportion (97.5%) of the recently infected residents did not seek medical treatment as they, were either asymptomatic or had mild non-specific symptoms.

Among six-year-old school children living in the area, the seroprevalence was 13.6%.³⁹ Follow-up of the same cohort of children over a two-year period showed that the annual rate of acquisition of dengue virus infection was 2.2%. All these infections were asymptomatic or subclinical.⁴⁰

Aedes Surveillance

The primary vector is *Aedes aegypti*, an indoor breeder, while *Aedes albopictus*, an outdoor breeder, plays a secondary role in the transmission of dengue in Singapore.¹⁷ The common breeding habitats for both *Aedes aegypti* and *Aedes albopictus* detected during routine vector surveillance were discarded receptacles (including cups, plastic bags and drinks cans thrown in public places), domestic containers, ornamental containers, puddles/uneven ground depressions, canvas/plastic sheets used to cover stored items, roof gutters, unused toilet bowls/cisterns, choked drains, infrequently used gully traps and ponds/swimming pools. The proportion of compound houses breeding *Aedes aegypti*

and *Aedes albopictus* was significantly higher than that of high-rise public housing estates.²¹⁻²⁸ This could have accounted for the differences in the rate of acquisition of dengue infection and morbidity rate between these two groups of residents. Although the *Aedes* population was low with an overall *Aedes* HI of around 1 and 2, the incidence of DF/DHF was significantly correlated with *Aedes aegypti* HI, but not with *Aedes albopictus* HI. On the other hand, *Aedes albopictus* population was more closely correlated with rainfall than *Aedes aegypti*. However, there was no correlation between disease incidence and rainfall.⁴¹

Prevention and Control

A high degree of vigilance is maintained over the disease situation through the well-established epidemiological surveillance system whereby every suspected and confirmed case of DF/DHF is promptly reported and investigated.¹⁶ As soon as a focus of dengue transmission is detected, intensive "search and destroy" operations against *Aedes* mosquitoes are implemented to prevent further spread.

The main thrust of the *Aedes* surveillance and control programme is to prevent any area with high *Aedes* population from developing into a focus of dengue transmission. The goal is to maintain the *Aedes* HI in every part of the country at between 1 and 2. It is difficult to achieve a zero HI because breeding habitats in premises are constantly available at replacement level; i.e. habitats are created as quickly as they are eliminated by routine source reduction control measures. Priority is given to construction sites where unsatisfactory house-keeping and vector control have resulted in localised build-ups of *Aedes* population and dengue transmission among construction workers and residents living in the vicinity. Where *Aedes* breeding habitats are created due to structural designs in premises, these are being rectified through permanent control measures; eg. installation of mosquito-proof roof-top water tanks, retrofitting gully traps with an anti-mosquito valve.

The public is constantly reminded to keep their homes mosquito free by adopting a routine system of checks for *Aedes* breeding habitats within and around their homes

and by applying insecticide sand granules in water-containing receptacles. Residents of compound houses are advised to repair or remove defective roof gutters and to apply insecticide paint on roof gutters and flower pot plates. Health education and publicity through all possible channels, including the use of videos, are continued throughout the year and stepped up whenever there are signs of an impending outbreak. Neighbourhood sprucing up projects incorporating educational talks and exhibitions are regularly conducted with the assistance of grassroots organisations, such as residents' committees and town councils, schools and other agencies. Pamphlets in Tagalog and other foreign languages are used to spread the dengue message to foreign maids and construction workers.

Discussion

The epidemiological pattern of DF/DHF in Singapore has shifted from one with high *Aedes* population and high dengue transmission in the 1960s to one with low *Aedes* population and low dengue transmission.⁴² The majority of the cases are DF involving teenagers and young adults. Serological surveys confirmed the higher rate of acquisition of dengue virus infection in adults between 25 and 34 years of age. The median age has shifted from 14 years in 1973 to 27 years in 1996, while the proportion of cases with secondary infections declined from about two-thirds in 1990 to less than half in 1996. More than 80% of the serologically confirmed fatal cases reported during the period from 1990 to 1996 were young adults above 19 years of age. Deaths from DHF are no longer confined to the childhood population.⁴³

The effectiveness of the *Aedes* control programme since the early 1970s was confirmed by the 1993 national serological survey which showed that virtually all the children and young adults below 25 years of age did not possess HI antibody to dengue 2 virus. A mathematical model developed by the US Centers for Disease Control and Prevention demonstrated that the *Aedes* mosquito becomes much more efficient in dengue transmission when the herd immunity of the human population is low. When the immune status of the human population is high, epidemic transmission would not occur even in the presence of high *Aedes* population.^{44,45} It would appear that the comprehensive vector surveillance and control programme implemented during the past two decades has brought about a paradoxical situation in that dengue outbreaks tend to occur more frequently and with even greater intensity because of the declining herd immunity of the human population.⁴⁶

There are three other factors which could have contributed to the re-emergence of dengue in Singapore. First, as the country is situated in a dengue endemic region where there is a resurgence of the disease,⁴⁷⁻⁵² it is vulnerable to the introduction of dengue viruses by the

large influx of visitors into the country. The number of imported cases has been increasing from 39 in 1989 to 251 in 1996. Molecular epidemiological studies using nucleic acid sequence analysis confirmed that dengue virus strains isolated from different areas in the region are genetically related.⁵³ Secondly, although the overall *Aedes* HI was very low, the annual increase in disease incidence was preceded by localised build-ups of *Aedes* population in construction sites and in landed properties in several dengue-receptive areas where *Aedes* HI as high as 10% to 20% had been recorded. Thirdly, although it is not clear to what extent the changing disease trend could be accounted for by the prevailing dengue serotypes in circulation,⁵⁴ routine virological surveillance seemed to indicate that each of the outbreaks could be due to the re-emergence of a predominant serotype; e.g. dengue 1 in 1995 and 1996. It is not known if the recent strains circulating in the Southeast Asian region have greater epidemic potential or virulence.⁵⁵

Control of dengue outbreaks based on reported cases is not entirely satisfactory as the notified cases only represent about 5% of the actual extent of infection.⁵⁶⁻⁵⁸ The recently infected but apparently healthy persons could provide an important virus reservoir for further transmission of infection, especially in areas where the *Aedes* population is high. The efficacy of insecticide spraying in controlling outbreaks has also been questioned.^{44,45}

From the entomological aspects, although the mere presence of *Aedes* mosquitoes is not sufficient in itself to create a potential condition for an outbreak, the critical level the *Aedes* population should be reduced so that it would not sustain virus transmission epidemiologically in a susceptible population has not been determined. As there is a lack of precise relationship between the magnitude of various *Aedes* density parameters monitored in the country and the incidence of the disease during both epidemic and endemic period, reliance still has to be based on the *Aedes* HI until a better entomological indicator has been found. A computerised geographical mapping system is being used to monitor *Aedes* population trends spatially for forewarning dengue outbreaks, while virological surveillance based on detection and typing of dengue virus serotypes in adult *Aedes* mosquitoes is already in existence.

A safe and immunogenic tetravalent, live-attenuated vaccine has been developed in Thailand, but efficacy studies in human volunteers have still not been initiated.⁵⁹ Until the vaccine is commercially available for mass immunisation, the key to the prevention of dengue epidemics is community-based integrated *Aedes* control.⁶⁰⁻⁶³ While surveys showed that the extensive dengue health education programme has a definite impact in raising the level of awareness of the public on the danger of *Aedes* mosquitoes, there has been no substantial change

in attitude and behaviour modification, as reflected by the high recurrence of *Aedes* breeding in some residential areas.⁶⁴ This is not unexpected, as the public generally considers dengue control as the government's responsibility.

Current strategies in the prevention and control of dengue have proven to be largely ineffective, even with Singapore's well-established public health infrastructure, sound environmental management, close interagency collaboration and organised concerted efforts to deal with this complex urban problem. Without sustained active community participation, the war against dengue cannot be won and outbreaks will continue to occur. The dengue situation is unlikely to improve as factors contributing to the resurgence have remained largely unchanged. The problem of dengue has to be tackled on a regional basis. This initiative should include regular exchange of surveillance and research data and coordination in applied field research to contain this re-emerging public health problem.⁶⁵

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