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Global Epidemiology of Dengue: Health Systems in Disarray

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INTRODUCTION

In terms of their geographic scope, the dengue viruses rival malaria as the most widespread human mosquito-borne infection of the modern era. Because they are transmitted in cities and in densely populated areas, annual dengue virus infection rates are probably several times higher than those for malaria. In terms of total number of infections, total number of sick persons and total numbers of deaths, dengue is by far the most important human mosquito-borne viral pathogen. Further, dengue viruses are moving; they and their efficient mosquito vector, *Aedes aegypti*, have spread thousands of miles into new territories within the past decade. But, something much more sinister is afoot. Dengue viruses are emerging slowly, steadily as new and awesome human pathogens. All this inexorable spread and mysterious change finds modern societies unprepared and modern science in a state of disorder. The victories in this global invasion all belong to the microorganism.

Dengue: Epidemiological Challenges

I will ask my entomological colleagues to discuss strategies for the containment of the present dengue pandemic. Here, I will-discuss the epidemiological challenges posed by the dengue viruses and their mid-20th century clinical outcome, dengue hemorrhagic fever, dengue shock syndrome (DHF/DSS). I will focus on two sets of global data which document first, the spread of *Aedes aegypti* and dengue, and, somewhat more interestingly, the spread of DHF/DSS, and second, the variations in the incidence rates, the case fatality rates and other features in the epidemiology of DHF/DSS.

Figure 1 illustrates the remarkable control achieved by the American region's *Aedes aegypti* eradication campaigns by around 1960. *Aedes aegypti* had almost disappeared from a whole continent and except for a small dengue 3 epidemic in Puerto Rico, dengue and urban yellow fever were absent. Within three decades, the picture changed dramatically, with *Aedes aegypti* regaining most of its pre-1930 domain. But, because the population of Latin America has increased markedly since the end of World War II, many more persons are at risk to dengue infections than was the case in the first half of this century.

Figure 2 contrasts dengue viral transmission in the 1960's with that of the 1990's.

The situation on dengue transmission in Africa in the 1960's was not well known. Evidence of the transmission of dengue types 1 and 2 in the 1960's was obtained by a Rockefeller Foundation research group at Ibaden, Nigeria (1). But, they obtained little information about clinical disease. DHF/DSS, which was first recognized in the 1950's, by the end of the decade of the 1960's had been clinically or virologically documented in all the larger Southeast Asian countries. By the 1990's, DHF/DSS was highly endemic in all Southeast Asian countries. Epidemics had occurred on Hainan Island, and possibly in south China. DHF/DSS had been virologically and clinically documented in the Maldive

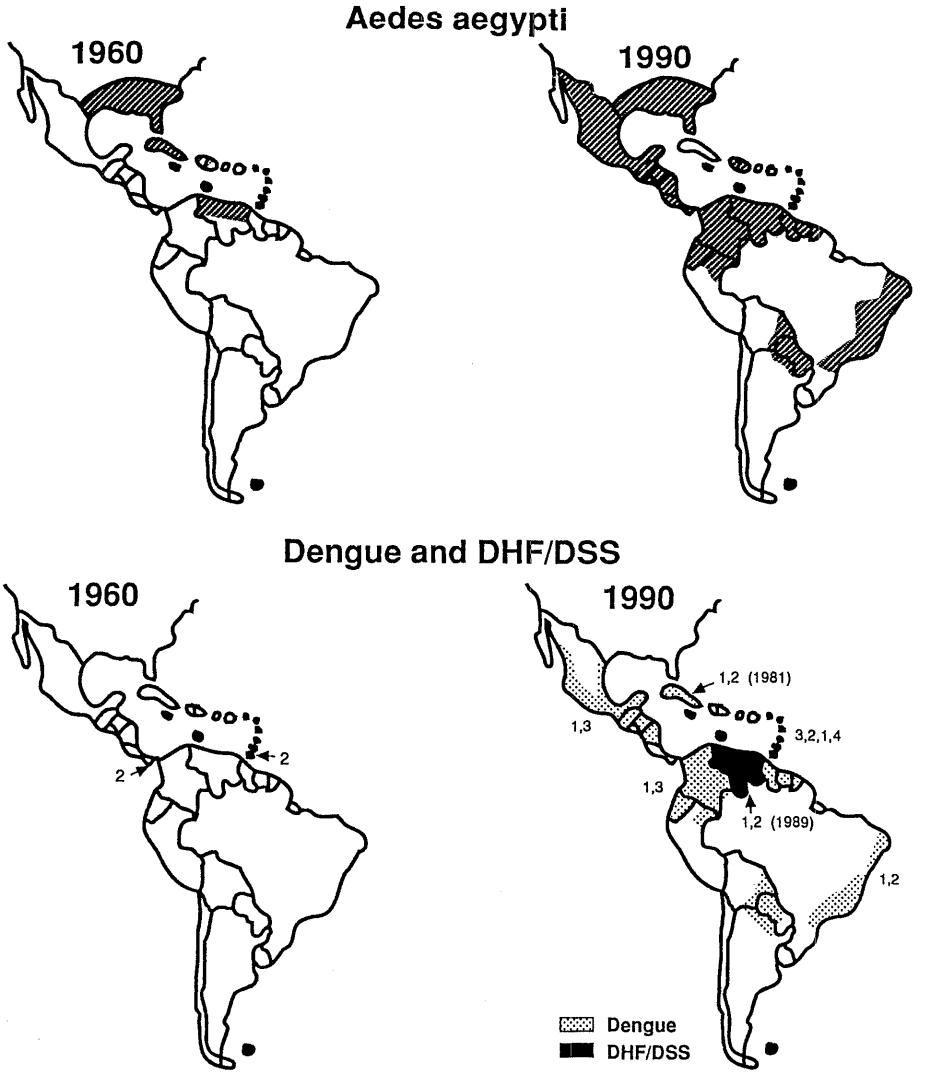

Fig. 1. Distribution of *Aedes aegypti* and dengue in the Americas, 1950-1990

Islands, Sri Lanka and India. DHF/DSS also made the gigantic leap to the Western Hemisphere where there were sharp outbreaks in Cuba in 1981, Venezuela in 1990 and Rio de Janeiro in 1991. Classical DHF/DSS was documented on Tahiti in 1991-92.

Table 1 summarizes global data annually for the period 1981-1992 and in aggregate for the period 1956-1980. Data are given for each country which has reported DHF/DSS

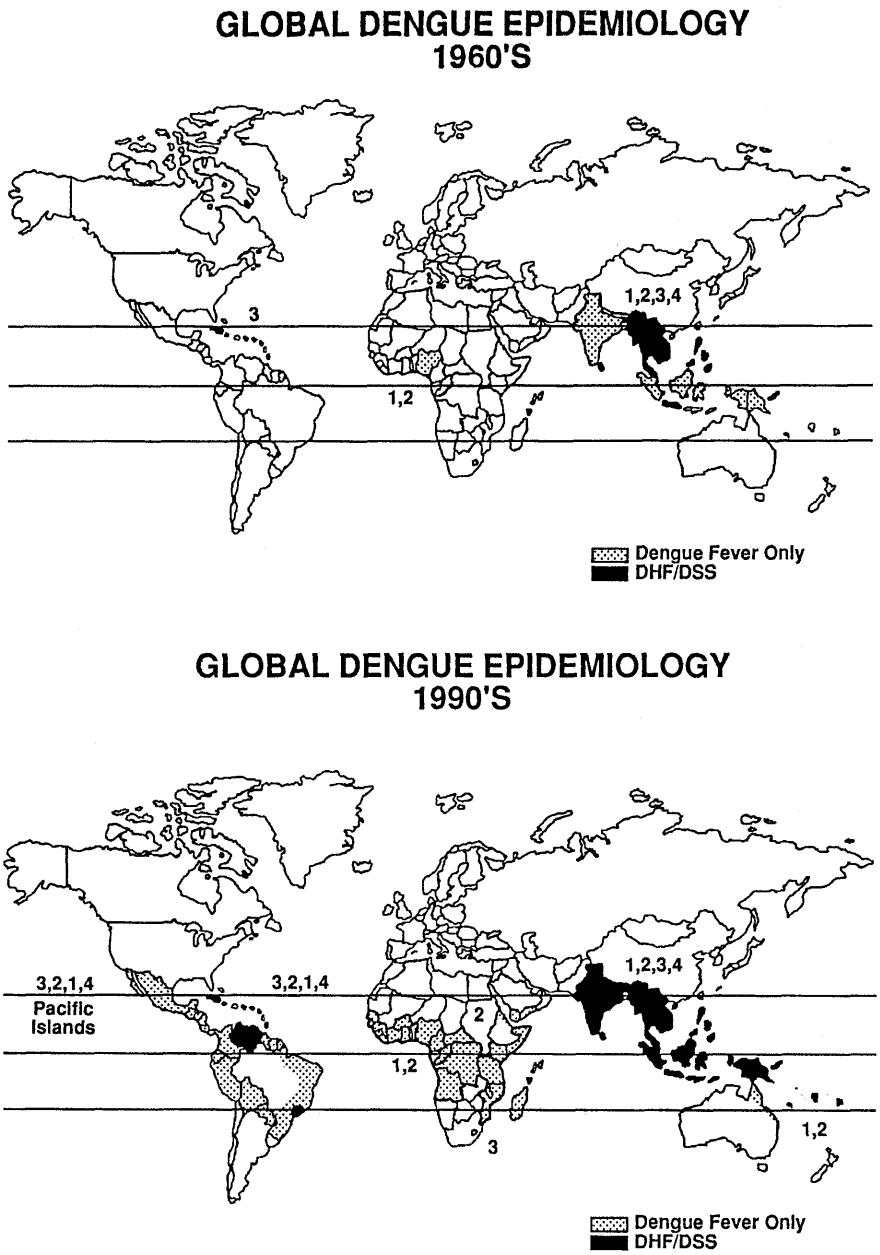

Fig. 2. Global dengue epidemiology

Table 1. Dengue hemorrhagic fever cases reported to World Health Organization regional officers, 1956 -1990. 10/6/93

YEAR	PHILIPPINES		VIETNAM		CHINA		THAILAND		LAOS		KAMPUCHEA		MYANMAR		MALAYSIA	
	C	D	C	D	C	D	C	D	C	D	C	D	C	D	C	D
1956-1980	25831	2124	325409	6268	36256	2455	236556	5926	37	0			30267	1342	4862	330
1981	123	8	35323	408			25641	194	0	0			1524	90	270	14
1982	305	31	39806	361			22250	159	0	0				49	860	36
1983	1684	130	149519	1798	85293	3032	30022	231	54	6			2856	83	215	10
1984	2545	89	30498	368			69597	451	22	14			2323	39	150	5
1985	2096	210	45107	399			80076	542	1759	15			2666	134	112	11
1986	687	30	46266	511			27837	236	365	43			2192	111	310	9
1987	859	27	354517	1566			174285	1007	5263	91			7292	222	304	9
1988	2922	68	85160	826	51510	1259	26926	179	1212	27			1181	65	233	3
1989	305	14	40205	289	37996	907	69204	280	n.a.	n.a.			1196	52	517	16
1990	588	27	37569	255	38062	2626	92005	14	60	3	7241	403	6318	182	645	21
1991	1865		94630	403			43782	119	249	7	1882	148	8055	305	741	39
1992			51040	271			36485	113			4800	172	1514	40	649	25
1981-1985	6753	468	300253	3334	85293	3032	227586	1577	1835	35			9369	395	16070	76
1986-1990	5361	166	563717	3447	127568	4792	390257	1716	6900	199	7241	403	18179	632	2009	58
1991-1992	1865	-	145670	674	-	-	80267	232	249	7	6682	320	9569	345	1390	64
TOTALS:	39810	2758	1335049	13723	249117	10279	934666	9451	9021	241	13923	723	67384	2714	24331	528

either to the regional offices of the World Health Organization, to the Dengue Newsletter or to the published literature. But, what is the authenticity of these reports and what do they mean?

Validity of Epidemiologic Data

Regarding authenticity, we are up against some stark facts. Despite the existence of a formal reporting system supplemented by an informal communications network, (e. g., the Dengue Newsletter of the South East Asia Regional Office of the World Health Organization, New Delhi, and the Dengue Surveillance Summary published by the Dengue Branch, Division of Vector-Borne Infectious Diseases, Centers for Disease Control, USA), reporting of DHF/DSS is both deficient and inaccurate. This is probably partly due to the fact that DHF/DSS is a "new" disease in some areas and not as clinically recognizable as cholera, for example. It also reflects serious deficiencies in outbreak investigation capa-

Table 1. page 2

YEAR	SINGAPORE		INDONESIA		INDIA		SRI LANKA		CUBA		VENEZUELA		PACIFIC ISLANDS	
	C	D	C	D	C	D	C	D	C	D	C	D	C	D
1956-1980	5240	51	48982	2676	1500	156	79	17						
1981	133	0	5978	231					116143	159				
1982	216	0	5451	255										
1983	205	2	13668	491										
1984	86	0	12710	382										
1985	126	2	13588	460										
1986	354	1	16529	608										
1987	436	2	23864	1105										
1988	245	0	47573	1527	128	28	10	0						
1989	944	2	10362	464	104	21	203	20			2665	40	213*	5*
1990	1733	3	22807	821			1121	61			3325	30	2421	19
1991	2179	6	21120	578			970	31					590	6
1992			13348	382	595	20								
1981-1985	766	4	51395	1819					116143	159				
1986-1990	3712	8	121135	4525	232	28	1334	81			5990	70	2634	24
1991-1992	2179	6	34468	960	595	49	970	31					590	6
TOTALS:	11897	69	255980	9980	2327	233	2383	129	116143	159	5990	70	3224	30

CASES: 3,071,245
DEATHS: 51,087

* French Polynesia

10/6/93

bilities, but, most importantly, the absence in many countries of sufficient or any dengue diagnostic laboratories. In short, DHF/DSS may not be recognized clinically, may not be reported or investigated or may not be identified etiologically. Each of these phenomena can contribute to underreporting. The most egregious examples are recent epidemics in India, where the incidence may be underestimated by tens or hundreds of thousands of cases.

But, DHF/DSS is also over-reported. The magnitude of over reporting is unknown. For example, sometime in the early 1980's the Division of Epidemiology of the Ministry of Public Health of Thailand began to count as notifiable cases of DHF/DSS, children who were only seen in out-patient facilities, but never hospitalized. In the Western Pacific Region, dengue fever and DHF/DSS are reported interchangeably. The dengue fever syndrome may occur in the absence of DHF/DSS, and where DHF/DSS is endemic, 50-200 dengue infections may accompany a single case of DHF/DSS (2). For these reasons, the mixed reporting of DF and DHF/DSS almost surely under-reports DF and says little about the relative magnitude of severe dengue as a clinical or epidemiological problem. With

the well-established ability of certain dengue viruses to produce serious bleeding phenomena in adults who otherwise experience only the dengue fever syndrome (3), the potential for serious over- or misdiagnosis of DHF/DSS is present. This is illustrated by the recent experience in Singapore where a successful *Aedes aegypti* control program had reduced dengue virus transmission significantly. The result was a cohort of young adults who are susceptible to dengue infection (4). From many studies we know that in adults, the ratio of clinical diseases to dengue infection is nearly one. With a sensitive surveillance system, this means that a few thousand dengue infections can produce a few thousand clinical cases of dengue fever. If some of these cases express bleeding phenomena, an "outbreak"of DHF may be diagnosed. This may explain at least some of the recent emergence of "DHF/DSS" in Singapore under conditions of very low endemicity.

There are many reasons why disease reporting should be accurate, for example, the planning and evaluation of control programs require complete and accurate disease incidence or prevalence data. But, with DHF/DSS, the most serious outcome of poor reporting may be to hopelessly confuse an epidemiological understanding of DHF/DSS.

Granting the caveat that at present DHF/DSS may be both under- and over-reported, what do the available data mean?

Significance of epidemiologic data : research question

So far as is known, DHF/DSS occurs only in the context of sequential infections or with the infection of infants circulating maternal dengue antibodies. Antibody-dependent infection enhancement still appears to be the central pathogenic mechanism which transforms the relatively benign dengue fever syndrome to the rapid-onset leaky capillary syndrome known as DHF/DSS. It is important to underscore that dengue infections with moderate or severe gastrointestinal hemorrhaging, even with fatal outcome may *not* be DHF/DSS. Good data suggest that dengue infections in individuals with underlying pathology, such as a peptic ulcer, may cause severe bleeding phenomena (3). This causes a background of DHF/DSS-like cases which occurs everywhere that dengue fever occurs. Strain variations may account for some of the inhomogeneities in "hemorrhagic dengue."

A glance at Figure 2 reveals certain unexplained phenomena - the absence until recently of DHF/DSS in India ; this, despite the circulation of multiple dengue serotypes (2, 5). The absence of DHF/DSS from much of the Caribbean and Latin America despite the circulation of multiple serotypes and the absence of DHF/DSS from Africa despite the circulation of multiple dengue serotypes.

These seemingly similar phenomena may have different underlying mechanisms. Genetic studies of dengue viruses associated with secondary infection DHF/DSS in Cuba, Venezuela and Brazil have shown these viruses to be Southeast Asian topotypes (6). An extremely important opportunity presented itself to make similar studies on viruses recovered from the newly emerged DHF/DSS of India and Sri Lanka. To date, these important studies have not been done ; and, it is not as clear as it could be that DHF/DSS is associated with a Southeast Asian "biotype."

Even more unfortunate has been the failure to test the Kliks hypothesis in India. In a longitudinal study in Thailand, Kliks et al. (7), observed that essentially all children who circulated enhancing antibodies in the absence of low levels of cross-reactive neutralizing antibodies were hospitalized during secondary dengue infections. This simple but powerful study should have been repeated in India where pre-outbreak monotypic dengue -immune sera could have been examined for low level neutralizing antibodies against the dengue strains recovered from the DHF/DSS outbreak. This test may be the most important predictor of risk of acquiring DHF/DSS during a secondary dengue infection. It might also help describe the different sets of viral epitopes which might be present on the sequential infecting virus pairs responsible for either enhanced or down-regulated secondary infections.

Data from the Cuban DHF/DSS outbreak suggest a remarkable, possibly unique, but certainly important phenomenon - a human dengue resistance gene found in blacks (8). It may be relevant that DHF/DSS has not been reported from Africa ; even dengue fever outbreaks have been reported infrequently.

Table 1 shows quite clearly the yearly variations observed in reported DHF/DSS cases over the past 12 years. Despite many claims to the contrary, no regular periodicity can be detected. Countries which are immediately adjacent to each other, Myanmar, Thailand, Laos and Vietnam were all involved simultaneously in the gigantic 1987 epidemic. Remarkably, Malaysia and Singapore seem not to have participated in the 1987 epidemic at all. By contrast, the 1987 epidemic arrived in 1988 in the island nations of Southeast Asia, the Philippines and Indonesia. Or so it seems.

But, the only available data on the 1987 outbreak are from Thailand and fragmentary data from Indonesia which showed unusual dengue 3 activity to be present in 1987 and 1988, respectively (9, 10). Otherwise, we know little about the virological events of 1987 and less about the antecedent events which may have been critical in determining 1987 DHF/DSS attack rates.

Of some interest in this connection are the studies of Lam and his group in Malaysia (10) who, in the relatively low incidence year of 1989, observed that dengue 1 viruses predominated in dengue fever cases, while in 1990 and 1991, years with relatively high deaths, dengue 2 virus isolations were prominent. These data are reminiscent of the 1980 Thailand experience where, on a background of dengue 1 infections, secondary dengue 2 caused DHF/DSS (11).

But, what about the mysterious extremely low incidence of DHF/DSS in the Philippines ? Comparative age-specific hospitalization rates are shown in Table 2. It has been suggested that the transition from *Aedes aegypti* to *Aedes albopictus* has never been completed in the Philippines as it was on mainland Southeast Asia. *Albopictus* is a vastly inferior transmission vector of dengue viruses. The fact is, we don't know why dengue disease is still such a small problem in the Philippines. No one has bothered to ask the question let alone find an answer.

A final mystery can be found in case fatality rates. Data for Thailand, Myanmar

Table 2. Average yearly DHF/DSS age-specific hospitalization rates for children <1-14 years-old, in five Southeast Asian countries, 1986 -1990.

COUNTRY	AVERAGE ANNUAL DHF/DSS HOSP. RATES, PER 100,000
Philippines	4.5
Vietnam	448.9
Thailand	429.0
Myanmar	25.2
Indonesia	63.1

Table 3. DHF cases, deaths and case-fatality rates in Indonesia, Myanmar and Thailand, 1986-1992

YEAR	INDONESIA			MYANMAR			THAILAND		
	NO. OF CASES	NO. OF DEATHS	CFR %	NO. OF CASES	NO. OF DEATHS	CFR %	NO. OF CASES	NO. OF DEATHS	CFR %
1986	16,529	608	3.65	2,192	111	5.06	27,837	236	0.84
1987	23,864	1,105	4.56	7,292	222	3.04	174,285	1,007	0.58
1988	47,573	1,527	3.20	1,181	65	5.50	26,926	179	0.66
1989	10,362	464	4.50	1,196	52	5.78	69,204	280	0.40
1990	22,807	821	3.60	6,318	182	2.8	92,005	414	0.45
1991	21,120	578	2.7	8,055	305	3.70	43,782	119	0.29
1992*	13,340	382	2.9	1,514	40	2.63	36,405	113	0.31

* Data available up to November 1992

and Indonesia are shown in Table 3. In countries with relatively high case fatality rates, the CFR shows an annual variation nearly 2-fold, but, with no obvious correlation to the total number of cases. In Thailand, where the CFR is about one tenth that in Myanmar and Indonesia, variations are less pronounced. Thai CFRs also do not fluctuate inversely with reported cases. Fluctuating CFRs were first noted in 1963 in Thailand (12). This appears to be real phenomenon and not an artefact of annual increases or decreases in the diagnoses of mild DHF cases.

CONCLUSIONS

Dengue has become a global problem of major proportions. DHF/DSS, is a frightening and often fatal disease, which affects otherwise healthy children. The major human health impact of DHF/DSS and it's remarkable accessibility to modern research facilities call out for greater resources to be mobilized to study and control this disease.

In this paper, I have noted that important genetic questions are posed by dengue. Understanding how the severity of secondary dengue infections may be controlled by human genes could shed light on viral pathogenetic mechanisms generally. A still larger challenge is to understand the viral mechanisms which operate to cause DHF/DSS. Is DHF/DSS the result simply of the sequential circulation of two dengue viruses which do *not* share neutralizing epitopes? Is this the secret of the Southeast Asian dengue topotypes which appear to cause epidemic DHF/DSS? Why do secondary dengue 1 infections *not* result in DHF/DSS? Or do they? What accounts for epidemic-specific severity differences reflected by varying case fatality rates?

It is doubtful that the answers to these questions can emerge from the fragmented and weak surveillance and research resources committed to dengue research at present. It is critically important that the global dengue epidemiological picture be monitored and that sufficient resources are committed to take advantage of novel twists in epidemiological expression of dengue infection. The introduction of DHF/DSS into India, for example, should never have gone unnoticed and unstudied. Affiliated with a regional or global surveillance mechanism should be several high quality prospective country studies, each designed so as to measure dengue infection in an open population of at-risk children. These studies should specifically test the hypothesis that children circulating enhancing but not neutralizing antibodies after their first dengue infection are at risk to DHF/DSS with dengue 2, 3 or 4 infections. The matching virus pairs should be studied appropriately. Ordinarily, the world would turn to WHO to provide regional leadership and funding for the research and control of public health problems. The time has come to admit candidly that other mechanisms and other funding must be found.

What seems hopelessly complicated in biology has often been found to be explained by simple underlying mechanisms. The DHF/DSS global pandemic has struck at a time when biomedical research possesses unique power and precise tools. Is it too much to ask that an appropriate allocation of research resources be committed to save the lives of children.

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