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Clinical and laboratory features that distinguish dengue from other febrile illnesses in endemic populations

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Summary

OBJECTIVE—Clinicians in resource-poor countries need to identify patients with dengue using readily-available data. The objective of this systematic review was to identify clinical and laboratory features that differentiate dengue fever (DF) and/or dengue hemorrhagic fever (DHF) from other febrile illnesses (OFI) in dengue-endemic populations.

METHODS—Systematic review of the literature from 1990-Oct. 30, 2007 including English publications comparing dengue and OFI.

RESULTS—Among 49 studies reviewed, 34 did not meet our criteria for inclusion. Of the 15 studies included, 10 were prospective cohort studies and five were case-control studies. Seven studies assessed all ages, four assessed children only, and four assessed adults only. Patients with dengue had significantly lower platelet, white blood cell (WBC) and neutrophil counts, and a higher frequency of petechiae than OFI patients. Higher frequencies of myalgia, rash, hemorrhagic signs, lethargy/prostration, and arthralgia/joint pain and higher hematocrits were reported in adult patients with dengue but not in children. Most multivariable models included platelet count, WBC, rash, and signs of liver damage; however, none had high statistical validity and none considered changes in clinical features over the course of illness.

CONCLUSIONS—Several individual clinical and laboratory variables distinguish dengue from OFI; however, some variables may be dependent on age. No published multivariable model has been validated. Study design, populations, diagnostic criteria, and data collection methods differed widely across studies, and the majority of studies did not identify specific etiologies of OFIs. More prospective studies are needed to construct a valid and generalizable algorithm to guide the differential diagnosis of dengue in endemic countries.

Introduction

Classical dengue fever (DF) is a viral illness transmitted through the bite of an infected mosquito, usually *Aedes aegypti* or *Aedes albopictus* (Halstead, 1988). This illness is endemic in tropical regions and affects between 50-100 million people worldwide annually (Gibbons & Vaughn, 2002). Dengue illness can range from a nonspecific febrile illness, as in DF, to a more severe illness with bleeding tendency, thrombocytopenia, and plasma leakage (dengue hemorrhagic fever, DHF). The dengue virus (DENV) complex consists of four distinct serotypes. Primary infection with one serotype provides lifelong immunity to the infecting serotype only but increases the risk of severe dengue illness, DHF, upon secondary infection with a different serotype (Rothman, 2003; Solomon & Mallewa, 2001).

Most developing countries have epidemics of febrile illnesses, including measles, typhoid fever, leptospirosis, and severe acute respiratory syndrome (SARS) that can be confused with DF (Dietz *et al*., 1992; Flannery *et al*., 2001; Karande *et al*., 2005; Watt *et al*., 2003; Wilder-Smith *et al*., 2004). At presentation, DF and other febrile illnesses may share similar clinical features, including headache, myalgia, and rash. Clinical features of DHF, such as bleeding

and plasma leakage, are seen after the initial febrile phase is subsiding, typically after the third or fourth day of fever. Patients are classified with DHF according to WHO guidelines based on all of the following four signs: fever, thrombocytopenia (platelet count <100,000/μL), bleeding tendency (positive tourniquet test or spontaneous bleeding), and plasma leakage (evidence of pleural effusion, ascites or ≥20% hemoconcentration) (World Health Organization, 1997); however, these findings may not appear until the patient is already critically ill. Patients suspected of having dengue, who include patients with other febrile illnesses, are sometimes hospitalized unnecessarily for observation to ensure that characteristics of DHF do not develop. Hospitalization of patients with suspected dengue has been shown to be a significant financial burden in developing countries (Clark *et al*., 2005; Suaya *et al*., 2007). Ideally, only severe DF and DHF cases should be hospitalized. Confirming a dengue diagnosis by serologic tests may take several days and evidence of plasma leakage may be difficult to measure (Schwartz *et al*., 2000). Furthermore, expensive laboratory tests may not be available in resource-poor countries.

Populations that do not have access to sophisticated laboratory tools need early clinical and/or simple laboratory indicators that can provide a reliable diagnosis of dengue prior to hospitalization. Early distinction between dengue and OFI could help clinicians to identify patients who should be closely monitored for signs of DHF. Differences in clinical and laboratory features between dengue and other febrile illnesses have been reported; however, published studies can vary considerably in terms of duration of symptoms, age of patients, and quality of the study which could impact the clinical applicability of these differences. The objective of this systematic review was to identify clinical and laboratory features that differentiate DF and/or DHF from other febrile illnesses and to identify gaps in current knowledge.

Methods

Search strategy

An electronic search of PubMed and Global Health databases using combinations of Medical Subject Headings (MeSH) and text words was conducted. Search terms were grouped as follows: (indicators OR “Dengue/diagnosis” OR clinical aspects OR clinical features OR clinical manifestations OR clinical characteristics OR clinical presentations OR physical signs OR physical symptoms) AND (dengue OR dengue fever OR dengue hemorrhagic fever OR dengue haemorrhagic fever). Articles were obtained electronically or in paper form.

Selection criteria

Studies were included if they met the following criteria: published between 1990 and October 2007, in English, and included comparisons between patients with DF and/or DHF and OFI patients in the abstract. We excluded studies prior to 1990 to improve the reliability of laboratory confirmation and to reflect the changed global distribution of dengue and DHF; this exclusion also helped limit the number of papers required to be reviewed. Studies were excluded if they used “travel” or “travelers” as MeSH terms to assess only populations in dengue-endemic areas. An assessment of titles and abstracts was done to exclude non-human studies, studies that assessed only molecular detection methods, and studies that did not compare patients with dengue and those with OFI.

Study assessment and data extraction

The quality of selected studies was assessed using a modified version of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (von Elm *et al*., 2007). The STROBE is a quality assessment checklist for observational studies that consists of 22 items. The STROBE was modified by adding questions about the serologic method used

to confirm dengue diagnosis, use of viral isolation, and whether the study was based on a single dengue outbreak or transmission season. Use of viral isolation increased the score whereas single outbreak studies received no additional points. The quality score was the number of items from the STROBE checklist addressed as a percentage of the total number of items applicable (minimum of 23 and maximum of 25). Studies with a quality assessment below 50% were excluded. Each selected article was characterized for study design, study location, type of patients (outpatients or inpatients), age of patients, type of dengue illness (primary or secondary; DF or DHF), method to confirm dengue (viral isolation, ELISA), duration of illness, and clinical and laboratory features.

Results

Search

The initial search retrieved 1575 articles/abstracts (Figure 1). We excluded 182 studies because they included “travel” or “travelers”, 293 published prior to 1990, 112 non-English studies, 147 duplicates, and 790 based on title/abstract assessment. A total of 51 articles were selected for data abstraction. Among these, two were unavailable for review (Ali *et al*., 2006;Zahur ur *et al*., 2001). Forty-nine articles were reviewed and an additional 34 (Supplemental Table 1) were excluded for the following reasons: 18 lacked statistical comparison between dengue and OFI, 9 lacked an OFI comparison group, 4 had a quality assessment <50%, one had a limited number of dengue cases (nine), one compared environmental factors only, and one was a short report lacking necessary abstraction data. A total of 15 published articles were included in this review.

Characteristics of included studies

The characteristics of the included studies are listed in Table 1. There was substantial heterogeneity in study design and inclusion criteria. Among these, 10 were prospective cohort studies and five were case-control studies; 9/15 (60%) were single outbreak studies or concluded within one year. The majority of studies were carried out in dengue-endemic regions of Southeast Asia/Pacific except for three studies from the Americas (Brazil, Nicaragua, and Puerto Rico) and one study from Australia. The included studies had quality assessment ratings ranging from 63% to 88%. One study assessed outpatients only and one study gave no information on the type of patients included. Four studies assessed adults only (defined as >14 years old), four studies assessed children only (defined as >11 months and <14 years old), and seven studies assessed all age groups (including infants).

The sample sizes of laboratory-confirmed dengue patients ranged from 13 to 2108 and the sample sizes of OFI patients ranged from 37 to 1065. All studies used hemagglutination inhibition and/or ELISA assays for serological confirmation of DENV infection; seven studies also used viral isolation for laboratory confirmation of infection. Six studies relied on a single blood sample for serology. For studies with convalescent samples, the shortest time between acute and convalescent samples was three days (Low *et al*., 2006); however, this study obtained an additional sample at 3-4 weeks. Five studies used duration of fever prior to enrollment as part of their selection criteria (Kalayanarooj *et al*., 1997; Low *et al*., 2006; C. X. Phuong *et al*., 2004; H. L. Phuong *et al*., 2006; Suwandono *et al*., 2006), four studies mentioned duration of fever prior to enrollment but did not use it as an enrollment criteria (Chadwick *et al*., 2006; Deparis *et al*., 1998; Sawasdivorn *et al*., 2001; Wilder-Smith *et al*., 2004) and six studies didn’t mention duration of fever prior to enrollment (Bruce *et al*., 2005; Buchy *et al*., 2005; Hammond *et al*., 2005; Karande *et al*., 2005; McBride *et al*., 1998; Nunes-Araujo *et al*., 2003). The mean duration of illness during the study period, noted in nine of the 15 studies, ranged from 3.3 to 10.5 days. Only two studies analyzed clinical and laboratory symptoms according to day of illness (Deparis *et al*., 1998; Kalayanarooj *et al*., 1997). The percentage of

DHF cases was determined in eight studies and ranged from 0% (Nunes-Araujo *et al*., 2003) to 47% (Kalayanarooj et al., 1997). The percentage of secondary infections was determined in seven studies and ranged from 43% (Low et al., 2006) to 93% (Kalayanarooj et al., 1997). No study statistically compared patients with DHF and patients with OFI; however, Kalayanarooj et al (1997) listed the frequencies of symptoms separately for DHF and OFI. Only two studies separated primary and secondary infections in the analysis; neither found any significant differences in signs or symptoms between patients with primary and secondary infections (Low et al., 2006; H. L. Phuong et al., 2006). Two studies used a distinct serologically identified comparison group- either SARS (Wilder-Smith *et al*., 2004) or leptospirosis (Bruce et al., 2005); three additional studies provided information about the specific diagnoses in the OFI group (Chadwick *et al*., 2006; Karande *et al*., 2005; C. X. Phuong *et al*., 2004) Seven of the 15 studies used data collected at presentation to make comparisons (Bruce *et al*., 2005; Chadwick *et al*., 2006; Kalayanarooj *et al*., 1997; Low *et al*., 2006; C. X. Phuong *et al*., 2004; H. L. Phuong *et al*., 2006; Wilder-Smith *et al*., 2004); the other 8 studies did not clearly define which data were used for statistical comparisons (maximum, minimum, mean, median).

Indicators of dengue illness

Table 2 indicates the direction of association for clinical and laboratory features that were reported in at least two studies where one (or more) found a significant difference between dengue and OFI patients. Bruce et al (2005),Deparis et al (1998),Hammond et al (2005),Karande et al (2005),Low et al (2006),Nunes-Araujo et al (2003), and Phuong et al (2006) showed significant increases/decreases in mean likelihood of dengue versus OFI as relative risks or odds ratios. All other studies reported independent associations as differences in proportions (for categorical variables) or means (for continuous variables) between patients with dengue and OFI. For clinical and laboratory features reported in at least two prospective and two retrospective studies, the directions of association were similar except for gender and headache/retro-orbital pain. The consistency score is an evaluation of the direction of association for each variable across all the studies that measured that variable, weighted by the quality assessment percentage of each study.

Demographic indicators—No consistent associations were observed between age and occurrence of dengue across all studies or within age-grouped studies. Two retrospective studies showed a significantly higher frequency of dengue among males (Bruce *et al*., 2005; Wilder-Smith *et al*., 2004).

Clinical findings—Among studies that assessed adults only, consistently higher frequencies of rash and hemorrhagic signs were reported in patients with dengue when compared to patients with OFI (Chadwick *et al*., 2006; McBride *et al*., 1998; Wilder-Smith *et al*., 2004); however, the frequency of hemorrhagic signs showed no differences between dengue and OFI in the four studies that assessed children only (Deparis *et al*., 1998; Hammond *et al*., 2005; Nunes-Araujo *et al*., 2003; H. L. Phuong *et al*., 2006). Hammond et al (2005) reported hemorrhagic signs in specific categories; the frequencies of melena and hematemesis were higher in children with dengue but not in adults. In four of seven studies assessing all age groups, the frequency of rash was also higher in patients with dengue (Deparis *et al*., 1998; Hammond *et al*., 2005; Nunes-Araujo *et al*., 2003); however, two studies assessing children only found no significant association with rash (Karande *et al*., 2005; Sawasdivorn *et al*., 2001). Three studies that assessed children only found a higher frequency of petechiae among patients with dengue and one study that measured petechiae in adults only also found a positive association (Chadwick *et al*., 2006; Kalayanarooj *et al*., 1997; C. X. Phuong *et al*., 2004; Sawasdivorn *et al*., 2001). A greater percentage of patients with dengue reported lethargy/prostration and arthralgia/joint pain in two studies assessing adults only (McBride *et al*., 1998); however, lethargy/prostration was not reported in studies assessing children only and the patterns of arthralgia/joint pain were

inconsistent in all other studies (children or all ages). In two studies that only included children, the frequency of anorexia was higher among patients with dengue (Kalayanarooj et al., 1997; C. X. Phuong et al., 2004). Taste alteration and skin sensitivity were more frequently reported in patients with dengue in two studies assessing adults only. Nonspecific symptoms, such as headache/retro-orbital pain, abdominal pain, diarrhea, vomiting, itching/pruritis, and nausea showed inconsistent or non-significant associations. Duration of fever prior to or during the study period showed inconsistent or non-significant associations with the occurrence of dengue versus OFI.

Laboratory indicators—Neutrophil and lymphocyte counts were significantly lower in patients with dengue when compared to patients with OFI among studies that measured these variables (Chadwick *et al*., 2006; Deparis *et al*., 1998; Hammond *et al*., 2005; Kalayanarooj *et al*., 1997; Karande *et al*., 2005; Low *et al*., 2006; C. X. Phuong *et al*., 2004; Wilder-Smith *et al*., 2004). All studies measuring WBC found a lower WBC count among patients with dengue, except for one retrospective study by Sawasdivorn et al (2001), which showed no association. Nine of 11 studies found lower platelet counts among patients with dengue compared to OFI patients. Two of three studies that measured prothrombin time found significantly lower values among patients with dengue (Chadwick *et al*., 2006; Wilder-Smith *et al*., 2004). Bruce et al (2005) and Chadwick et al (2006) found lower creatinine levels and a lower percentage of jaundice among patients with dengue. Higher levels of hepatic transaminases (AST/ALT) were found in patients with dengue in three of four studies (Chadwick *et al*., 2006; Kalayanarooj *et al*., 1997; Wilder-Smith *et al*., 2004). Increased hematocrit and hemoglobin levels were observed among patients with dengue in two adult-only studies (Chadwick *et al*., 2006; Wilder-Smith *et al*., 2004); however, hematocrit showed inconsistent associations in three children-only studies. Other laboratory measures, such as total protein, APTT, and urea, also showed inconsistent patterns with the occurrence of dengue (Chadwick *et al*., 2006; Wilder-Smith *et al*., 2004). Kalayanarooj et al (1997) and Hammond et al (2005) were the only studies to measure pleural effusion or ascites. Kalayanarooj et al (1997) reported a higher frequency of pleural effusion in patients with DHF compared to DF or OFI. Hammond et al (2005) found an increased odds of having pleural effusion and ascites among children and adults with dengue.

Other indicators—Table 3 lists additional symptoms that showed associations between dengue and OFI but were reported in only one of the 15 studies reviewed. Table 4 lists symptoms that were measured in only one study and had no statistical association between dengue and OFI. Other common laboratory tests- sodium, potassium, glucose, alkaline phosphatase, and lactate dehydrogenase-measured in Chadwick et al (2006) and Wilder-Smith et al (2004) showed no differences between dengue and OFI.

Combined clinical and laboratory indicators—Seven studies (Chadwick *et al*., 2006; Deparis *et al*., 1998; Karande *et al*., 2005; McBride *et al*., 1998; C. X. Phuong *et al*., 2004; Sawasdivorn *et al*., 2001; Wilder-Smith *et al*., 2004) carried out multivariable regression analysis in an attempt to distinguish patients with dengue from those with OFI (Tables 5 and 6). Among these seven studies, all studies that measured WBC included this variable in their final model and showed a reduced WBC count in patients with dengue compared to patients with OFI. Three of these seven studies included some measure of liver function in the final model. Wilder-Smith et al found that increased AST resulted in an increased odds of dengue. Phuong et al found that hepatomegaly resulted in an increased adjusted odds of dengue. On the other hand, Chadwick et al found that lower bilirubin values resulted in increased adjusted odds of dengue. Chadwick et al (2006) was the only one of these studies that reported platelet count and did not include this variable in the final model. Three studies included signs of bleeding such as petechiae, hematocrit, and positive tourniquet test in their final model and

showed that positive signs of bleeding increased the odds of having dengue (McBride *et al*., 1998; C. X. Phuong *et al*., 2004; Sawasdivorn *et al*., 2001). Three studies also showed a higher frequency of rash among dengue patients in their final model (Chadwick *et al*., 2006; Deparis *et al*., 1998; McBride *et al*., 1998). The final model in Karande et al (2005) had a negative predictive value (NPV) of 45% and was the only study to report a NPV with the final model's positive predictive value (PPV).

Discussion

The findings of our review suggest that several clinical and laboratory measures could potentially distinguish patients with dengue from those with OFI. Low platelet count and decreases in WBC and neutrophils were independently associated with the presence of dengue, when compared to patients with OFI, in both adults and children. These variables, as well as signs of rash and liver damage, were also used in multivariable models to distinguish patients with dengue from those with OFI. However, it is unlikely that any single indicator will be useful in clinical practice because these signs and symptoms are present in other diseases, such as viral hepatitis and leptospirosis, which are also endemic in areas with a high prevalence of dengue.

Low platelet count is currently used as a criterion for the diagnosis of DHF (World Health Organization, 1997). The cause of thrombocytopenia in dengue is unknown; however, decreased production of platelets in DF and increased destruction of platelets in DHF have been described (Cardier *et al*., 2005). Kalayanarooj et al (1997) attributed the reduction in WBC to bone marrow suppression by dengue virus (La Russa & Innis, 1995); however, Deparis et al argued that these laboratory measures are not dengue-specific in the early stages of the disease (Deparis *et al*., 1998).

Alterations in the microvascular endothelium in patients with dengue are thought to lead to a higher likelihood of hemorrhage (Bandyopadhyay *et al*., 2006; Cardier *et al*., 2005). In this review, an increased frequency of hemorrhage was observed in adults with dengue but was not associated with dengue in studies that only included children; however, Hammond et al demonstrated that some types of hemorrhage (e.g., hematemesis and melena) were associated with dengue in children, suggesting that the types of hemorrhagic manifestations seen in dengue may depend on the age of the patient.

Signs of rash and indicators of liver damage, in combination with other variables such as age, myalgia, WBC count, and platelet counts, may help to establish a diagnostic algorithm to distinguish dengue from OFI patients. Several studies used multivariable regression models to discriminate dengue from OFI; however, most published models had lingering statistical questions. Wilder-Smith *et al* (2004) presented a model with very large odds ratios; however, the confidence intervals for their model were also large and questions of over-fitting and co-linearity were not discussed. Deparis *et al* (1998) presented a model with an unusually small odds ratio for a categorical variable (low platelet count), which may not be applicable in a clinical setting. None of the regression models was validated using a training and testing dataset approach. Furthermore, the generalizability of these models is questionable since most were derived from single outbreak studies. For example, Karande *et al* (2005) was a single outbreak study and presented a model with 100% PPV, but they only had 13 patients with dengue in the model. Since the authors selected the variables for analysis, our review is unable to determine whether a specific value versus an increase (or decrease) in a particular variable is most useful.

Any algorithm to identify patients with dengue would need to be applied early in the illness in order to be useful in reducing unneeded hospitalizations. This review highlights a weakness in the literature as few studies indicated which day of illness clinical and laboratory measures

were assessed. Only Kalayanarooj et al (1997) and Deparis et al (1998) separately analyzed clinical and laboratory measures according to day of illness. Kalayanarooj et al (1997) showed that positive and negative predictive values for individual variables differed depending on the stage of illness. Deparis et al (1998) showed that the frequency of clinical and laboratory symptoms varied according to day of illness.

Five of the included studies were case-control studies that relied on review of medical records or patient recall, which could bias the findings of these studies. Furthermore, two of the case-control studies did not use a standardized data collection form. Six studies relied on serologic testing of a single blood sample, which could increase the risk of misclassification of patients with dengue. Only two studies serologically confirmed all diagnoses in the OFI group, and differences found between patients with dengue and patients with OFI depended on the specific comparison febrile illness. Bruce et al (2005) used a leptospirosis comparison group and was the only study that found no differences in platelet count or AST/ALT. Illnesses with similar characteristics, such as dengue and leptospirosis, will clearly be more difficult to discriminate on the basis of any clinical algorithm.

Duration of illness prior to study enrollment did not distinguish patients with dengue from those with OFI in four out of five studies. Duration of illness prior to presentation may be more applicable in distinguishing patients with DHF from patients with DF. On average, patients with DHF have a more severe illness and may require hospitalization for a more extended period of time after defervescence in comparison to DF. No study in this review prospectively compared clinical signs and symptoms in patients with DHF to patients with DF or OFI. We are, therefore, unable to make any conclusions from this review of which signs and symptoms, if any, can prospectively distinguish patients with DHF from patients with DF or OFI. It is perhaps surprising that 4/9 (44%) of studies that measured hematocrit found no significant differences between dengue and OFI. However, hemoconcentration is a feature of DHF and not of DF, and is defined based on comparison to a patient's baseline hematocrit rather than a single measurement.

This review has several limitations. There were no inter-rater or intra-rater reliability of quality assessment ratings and the STROBE is mainly a score of reporting and may impact the ability to extract information rather than quality of the study itself. There is a lack of established quality assessment rating scales for evaluating observational studies. The STROBE gives merit to a study for addressing its limitations, which may explain why the retrospective studies had the highest quality assessment ratings. Not all studies had robust statistical methods. Both the dengue and OFI groups were heterogeneous, the former including both milder and more severe disease and the latter including a wide variety of possible etiologies. Some studies failed to include duration of fever or illness in their analysis, which could affect the interpretation of time-dependent variables. Also, most dengue outbreaks occur in countries where English is not the primary language. Thus, the restriction to English-language studies may have affected the findings of this review. Finally, many studies did not note what day of illness the clinical and laboratory data were measured, which makes it impossible to determine whether these data can distinguish dengue from OFI early in the course of illness.

Until low-cost, rapid, and sensitive laboratory assays are widely available for diagnosis of dengue, diagnostic algorithms will continue to have an important place in clinical management. Additional prospective studies are needed to establish an algorithm that can be validated and generalized to distinguish dengue from OFI and DF from DHF in the early stages of illness. Furthermore, longitudinal studies that routinely document clinical and laboratory signs and symptoms throughout each patients' course of illness would provide much needed data to develop a predictive model that can distinguish patients with dengue who will require

hospitalization from patients with OFI. An easily applicable clinical algorithm could have a favorable impact on the economies of dengue-endemic developing countries.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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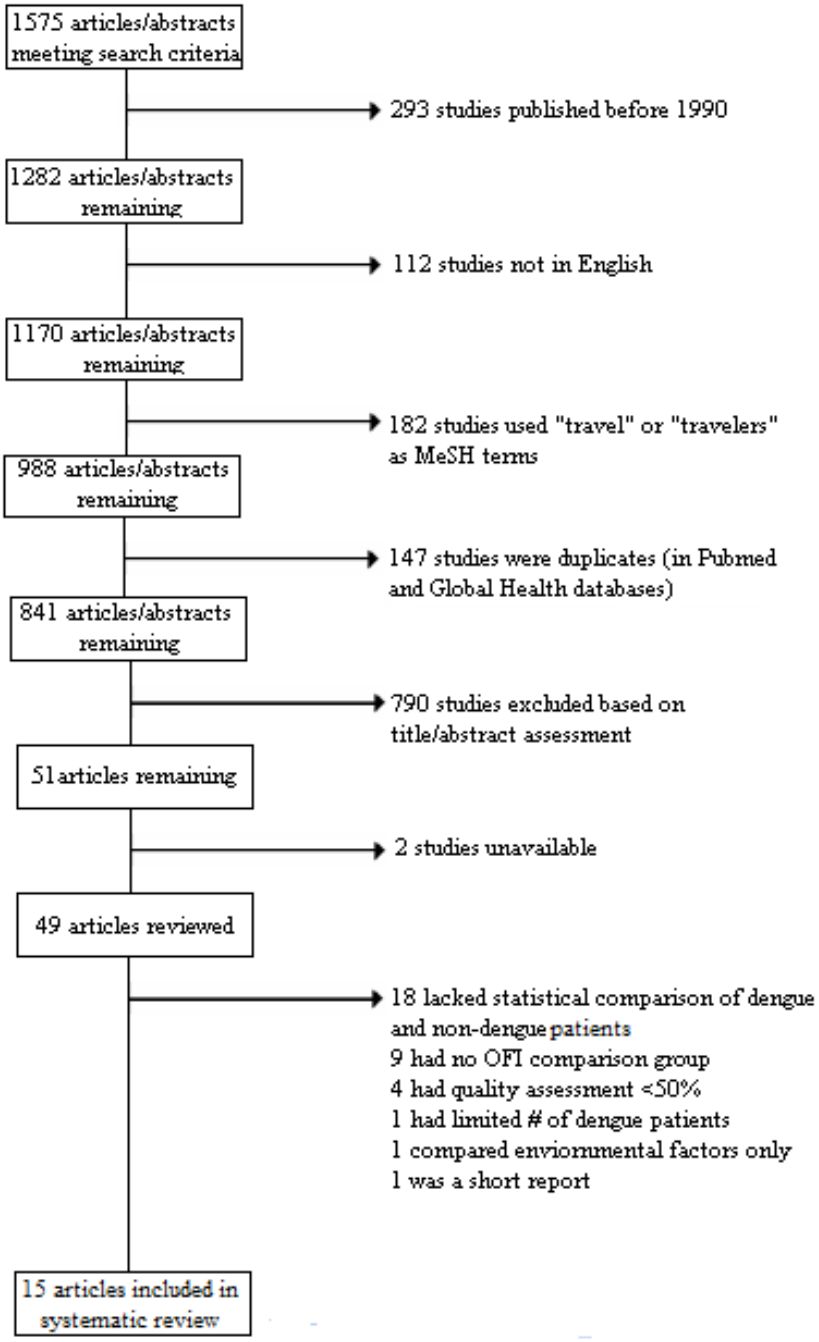

Figure 1.
Flow-chart of review process

Table 1

Characteristics of included studies

First Author	Study design	Study Year(s)	Location	Patients	Age	Sample Size		Viral isolation	Duration of fever prior to enrollment (days)	Duration of illness during study period (days)	Modified STROBE QA (%)
						Dengue[A]	OFI[B]				
Low (2006)	Prospective cohort	2005	Singapore	Mixed	Adults	133 (3%)*	321	Yes	<3	Mean 10.5	84%
Phuong (2004)	Prospective cohort	1996-1998	Vietnam	Inpatients	Children	712 (45%)	85[C]	No	<7	N/A	84%
Chadwick (2006)	Prospective cohort	1998-2000	Singapore	Inpatients	Adults	148 (23%)	233[D]	No	Mean 5.2	N/A	80%
Kalayanarooj (1997)	Prospective cohort	1994	Thailand	Inpatients	Children	60 (47%)	112	Yes	<3	Mean 4.0	80%
Phuong (2006)	Prospective cohort	2001-2002	Vietnam	Mixed	All ages	234 (N/A)	463	No	<14	Median 5	79%
Deparis (1998)	Prospective cohort	1996-1997	French Polynesia	N/A	All ages	196 (3%)	102	Yes	Median 2.5	N/A	76%
Hammond (2005)	Prospective cohort	1999-2001	Nicaragua	Inpatients	All ages	2108 (N/A)**	1065	Yes	N/A	Infants 6.4 Children 6.0 Adults 5.2	76%
Karande (2005)	Prospective cohort	2002	India	N/A	Children	13 (38%)	37[E]	No	N/A	Mean 5.5	68%
Buchy (2005)	Prospective cohort	2001-2002	Vietnam	Inpatients	All ages	108 (4%)*	17	Yes	N/A	Median 3.9	64%
Suwandono (2006)	Prospective cohort	2004	Indonesia	Inpatients	All ages	180 (27%)	92	Yes	<7	N/A	63%
Wilder-Smith (2004)	Retrospective case-control	2003; 1997-2000	Singapore	Inpatients	Adults	147 (N/A)	55[F]	No	Median 4	Median 4	88%
Bruce (2005)	Retrospective case-control	1996-1997	Puerto Rico	Mixed	All ages	84 (N/A)	42[G]	No	N/A	Median 10	83%
Nunes-Araujo (2003)	Retrospective case-control	1993-1998	Brazil	N/A	All ages	495 (0%)	650	No	N/A	N/A	78%
Sawasdivorn (2001)	Retrospective case-control	1998-1999	Thailand	Inpatients	Children	45 (53%)***	38	Yes	Mean 3.71	Mean 3.37	76%
McBride (1998)	Retrospective case-control	1995	Australia	Mixed	Adults	399 (N/A)	600	No	N/A	N/A	67%

List of included studies indicating: first author, study design, year the study was performed, location of the study (country), type of patients (“inpatients”, “outpatients”, or “mixed” which includes both inpatients and outpatients), sample size (“dengue” is the number of confirmed dengue patients, and “OFI” is the number of other febrile illness patients), viral isolation, duration of fever prior to enrollment (among the dengue patients enrolled), duration of fever during study period, and modified STROBE quality assessment rating (shown as a percentage)

[A] % of patients with DHF is in parenthesis

* notes only hospitalized cases of DHF

** it is unclear as to the total percentage of dengue patients that had DHF

*** There were 93 patients with DHF; however, comparisons were made using only 45 patients with DF

[B] All OFIs were unidentified unless otherwise noted

[C] 6 had typhoid fever, 1 had P. falciparum malaria, 1 had measles-like rash, and the remainder had no specific alternate diagnosis

[D] 84 were undiagnosed; 77 had malaria; 29 had typhus; 14 had mumps; 11 had pneumonia; 6 had enteric fever; 5 had gastroenteritis; 4 had measles/rubella; 3 had viral hepatitis

[E] OFIs were identified as malaria, leptospirosis, enteric fever, viral hepatitis, pneumonia, pyogneic meningitis, septicaemia, urinary tract infection, and undiagnosised; however, the dengue (-) group consisted of only 37 out of a possible 74 and it is not clear which of the OFIs listed made up the dengue (-) group

[F] All OFI were SARS

[G] All OFI were leptospirosis

Table 2

Symptoms and laboratory measures assessed in at least two studies where one study showed an association with dengue

Symptoms	Consistency Score	All ages						
		Phuong (2006)[A]	Deparis (1998)[A]	Hammond (2005)[A]	Nunes-Araujo (2003)[A]	Buchy (2005)	Bruce (2005)[A]	Suwandono (2006)
DEMOGRAPHICS								
Age	↑ 25%	↓	0	0	↑	0	-	-
Males	Males 9%	0	0	0	0	0	↑	-
CLINICAL INDICATORS								
Taste alteration	↑ 100%	-	-	-	-	-	-	-
Skin sensitivity	↑ 100%	-	-	-	-	-	-	-
Petechiae (scattered, spontaneous bleeding)/ positive tourniquet test	↑ 75%	0	-	-	↑	0		↑
Liver size >1cm/hepatomegaly	↑ 74%	0	-	↑	-	-		-
Anorexia	↑ 74%	0	-	-	-	-		-
Lethary/Prostration	↑ 74%	-	↑	-	0	-		-
Rash (including macular rash)	↑ 65%	0	↑	↑	↑	0	↑	-
Arthralgia/joint pain	↑ 50%	↑	0	-	0	-		-
*** Hemorrhagic signs	↑ 49%	0	↑	↑	0	0		-
Itching/Pruritis	↑ 46%	-	-	-	-	-		-
Cough/rhinitis/breathlessness/coryza/runny nose	↓ 44%	↓	0	-	-	0		-
Vomiting	↑ 42%	0	0	-	-	0		0
Abdominal pain/abdominal tenderness/stomach ache	↑ 32%	↑	0	↑	-	0		0
Nausea	↑ 31%	0	-	-	0	0		0
Myalgia/muscle pain/backache	↑ 30%	↑	-	-	0	0	0	0
Sore throat/red pharynx	↑ 21%	0	-	-	-	-		0
Duration of fever[B]	↑ 20%	0	-	-	-	-		-
Headache/retro-orbital pain	↑ 16%	↓	0	-	↑	0	0	0
Diarrhea	↓ 16%	↓	0	-	-	-		-
Splenomegaly	0	0	0	-	-	-		-
LABORATORY INDICATORS								
Neutrophils/neutropenia	↓ 100%	-	↓	-	-	-		-

Symptoms	**Consistency Score**	**All ages**						
		Phuong (2006)[A]	**Deparis (1998)[A]**	**Hammond (2005)[A]**	**Nunes-Araujo (2003)[A]**	**Buchy (2005)**	**Bruce (2005)[A]**	**Suwandono (2006)**
Hemoglobin	↑ 100%	-	-	-	-	-		-
Lymphocytes/lymphopenia	↓ 100%	-	↓	-	-	-		-
WBC/Leukocytosis/Leukopenia	↓ 89%	-	↓	↓	-	-	↓	↓
Platelets/Thrombocytopenia	↓ 83%	-	↓	↓	-	0	0	↓
AST/ALT	↑ 75%	-	-	-	-	-	0	-
PT	↓ 67%	-	-	-	-	-	0	-
Creatinine	↓ 65%	-	-	-	-	-	↓	-
Hematocrit	↑ 55%	-	0	-	-	0		↑
Total Protein	↓ 52%	-	-	-	-	-		-
Albumin	↑ 50%	-	-	-	-	-		-
Jaundice/Icterus/Bilirubin[§]	↓ 43%	0	-	-	-	-	↓	-
APTT	↑ 32%	-	-	-	-	-	0	-
Urea	0	-	-	-	-	-	0	-
Symptoms		Children				Adults			
		Phuong (2004)	[*]Kalayanarooj (1997)	Karande (2005)[A]	Sawasdivorn (2001)	Chadwick (2006)	Wilder-Smith (2004)	McBride (1998)	Low (2006)[A]
DEMOGRAPHICS									
Age		↑	↑	0	0	0	0	-	↑
Males		0	0	0	0	0	↑	-	0
CLINICAL INDICATORS									
Taste alteration		-	-	-	-	-	-	↑	↑
Skin sensitivity		-	-	-	-	-	-	↑	↑
Petechiae (scattered, spontaneous bleeding)/ positive tourniquet test		↑	↑	-	↑	↑	-	-	
Liver size >1cm/hepatomegaly		↑	-	-	-	↑	-	-	
Anorexia		↑	↑	-	-	-	-	-	↑
Lethary/Prostration		-	-	-	-	-	-	↑	↑
Rash (including macular rash)		-	-	0	0	↑	-	↑	↑
Arthralgia/joint pain		0	-	↑	0	-	-	↑	↑
[***] Hemorrhagic signs		0	0	0	0	↑	-	↑	↑
Itching/Pruritis		-	-	-	-	0	-	↑	

Symptoms	Consistency Score	All ages						
		Phuong (2006)[A]	Deparis (1998)[A]	Hammond (2005)[A]	Nunes-Araujo (2003)[A]	Buchy (2005)	Bruce (2005)[A]	Suwandono (2006)
Cough/rhinitis/breathlessness/coryza/runny nose	↓	-	0	-	0	-	↓	
Vomiting	↑	↑	0	-	0	-	↑	↑
Abdominal pain/abdominal tenderness/stomach ache	↑	0	0	-	0	-	0	-
Nausea	-	↑	-	-	0	-	-	↑
Myalgia/muscle pain/backache	0	-	-	0	↑	-	↑	0
Sore throat/red pharynx	↑	-	-	-	0	-	0	
Duration of fever[B]	↑	0	0	0	-	-	-	↑
Headache/retro-orbital pain	0	0	0	-	0	-	↑	↑
Diarrhea	0	-	0	-	0	-	0	0
Splenomegaly	↓	-	-	-	↑	-	-	
LABORATORY INDICATORS								
Neutrophils/neutropenia	-	↓	-	-	↓	↓	-	↓
Hemoglobin	-	-	-	-	↑	↑	-	
Lymphocytes/lymphopenia	-	-	-	-	↓	↓	-	↓
WBC/Leukocytosis/Leukopenia	-	↓	-	0	↓	↓	-	↓
Platelets/Thrombocytopenia	↓	↓	↓	-	↓	↓	-	↓
AST/ALT	-	↑	-	-	↑	↑	-	
PT	-	-	-	-	↓	↓	-	
Creatinine	-	-	-	-	↓	0	-	
Hematocrit	↑	0	↑	-	↑	↑	-	0
Total Protein	-	-	-	-	0	↓	-	
Albumin	-	0	-	-	↑	-	-	
Jaundice/Icterus/Bilirubin[§]	-	-	0	-	↓	0	-	
APTT	-	-	-	-	↑	0	-	
Urea	-	-	-	-	↓	↑	-	

[*] Only analysis performed on day of presentation is shown

[**] Consistency score= ![Σ(quality assessment %)(+1/-1/0)]/[Σ(quality assessment % of studies measuring this variable)]!, for example, anorexia: ![(.84)(0) + (.79)(1) + (.80)(1) + (.84)(1)]/[(.84) + (.79) + (.80) + (.84)]!=↑74%

[***] Hemorrhagic signs: other than petechiae (bleeding gums, gingival bleeding, mucosal bleeding, vaginal bleeding, hematemesis, reported bleeding, bleeding manifestations, melena)

[§]=bilirubin is a laboratory measure that correlates with clinical measures of jaundice/icterus

↑= indicates positive association with dengue positive patients compared to patients with OFI

↓= indicates negative association with dengue positive patients compared to patients with OFI

0= indicates no significant association

-= not measured

[A]=Reported associations as relative risks or odds ratios

[B]=prior to enrollment except for Karande and Low which is during illness

Table 3

Signs, symptoms, and additional indicators reported in only one study but which showed a significant association between dengue and OFI

Study	Symptoms	Direction of association
McBride (1998)	Days of work lost Visited the doctor Hospitalized	↑
Chadwick (2006)	Pulse Temperature	↓
Chadwick (2006)	Skin flushing Islands of sparing	↑
Hammond (2005)	Chills	↑
Karande (2005)	Edema	↓
Phuong (2006)	Pallor	↑
Kalayanarooj (1997)	Absolute monocyte counts	↓
Bruce (2005)	Skin abrasions	↓
Low (2006)	Red eyes	↑

Table 4

Non-significant signs, symptoms, and additional indicators reported in one or more studies

Study	Symptoms
Phuong (2006)	Tender muscles on palpation Arthritis Dehydration Tender liver Constipation Altered consciousness Bruises Lymphadenitis Eschar Vesicles
Bruce (2005)	Red eyes Eye irritation Eye pain Nuchal rigidity
Karande (2005)	Polyserositis Altered sensorium Convulsions Oliguria Respiratory rate Hepatosplenomegaly
Deparis (1998)	Acute respiratory distress
Chadwick (2006)	Respiratory rate
Buchy (2005)	Conjunctival injection
Low (2006)	Swollen glands

Table 5

Studies with multivariable predictor models presented as odds ratios

Study	Predictors	OR (95% CI)
Wilder-Smith (2004)	Platelet count (10^9 platelets/L) <140	456 (37, 5917)
	AST (IU/L) >34	68 (6, 719)
	WBC (10^9 cells/L) <5	47 (4, 518)
Phuong (2004)	Petechiae	4.82 (2.71, 8.58)
	Hepatomegaly >1 cm	2.93 (1.14, 7.53)
	Admission after >3 days of illness	2.47 (1.38, 4.42)
	Hematocrit	1.13 (1.05, 1.22)
	Coryza	0.36 (0.16, 0.81)
	Sore throat	0.33 (0.14, 0.76)
Deparis (1998)	Macular rash	2.07 (1.53, 2.62)
	Pruritis	2.55 (2.31, 2.79)
	Low Platelet Count	1.002 (1.001, 1.005)
	Leukopenia	1.2 (1.06, 1.37)
Chadwick (2006)	Rash (patient reported)	9.13 (2.14, 38.94)
	Hemoglobin	1.52 (1.11, 2.06)
	WBC	0.43 (0.31, 0.59)
	Creatinine	0.73 (0.57, 0.93)
	Bilirubin	0.74 (0.59, 0.94)
	Prothrombin Time	0.44 (0.30, 0.65)

Table 6

Studies with multivariable models presented as positive predictive values

Study	Predictors	Positive Predictive Value
Sawasdivorn (2001)	Fever + Positive Tourniquet Test + Leukopenia	73%
McBride (1998)	Rash + Bleeding (gums, nose, vagina) + bone pain + Taste Alteration	73%
Karande (2005)	Arthralgia + Thrombocytopenia	100%