



Review article

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Changing pattern of symptoms in dengue patients over the years: A review and meta-analysis

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ABSTRACT

Objective: To describe the pattern of vomiting, diarrhoea and abdominal pain among dengue patients over the years in different age groups.

Methods: Electronic databases were used to include studies that reported symptoms of vomiting, diarrhoea or/and abdominal pain. Confirmation of dengue was conducted by laboratory diagnosis. The exclusion criteria were case reports and studies which only described specific settings, focused only on dengue haemorrhagic fever or severe dengue and co-infection. Meta-analysis was performed on the overall prevalence of vomiting, diarrhoea and abdominal pain which was then stratified according to years and different age groups.

Results: Out of the 2002 studies, 32 studies were included. All studies were conducted between 1995 and 2014. The studies were conducted in 18 countries with a total sample size of 69466. The predominant symptom was abdominal pain before 2004 but became vomiting thereafter. The prevalence of vomiting was constant throughout the years (20%–40%), but the prevalence of abdominal pain reduced from 30%–50% to 20%–30%. The prevalence of diarrhoea increased steadily from 5% to 30%. Abdominal pain was the predominant symptom in children (75.03%) [95% confidence interval (CI): 64.89%–85.17%], while diarrhoea was predominant in adults (32.42%) (95% CI: 23.96%–40.88%). For studies which included all ages, the predominant symptom was vomiting (45.18%) (95% CI: 33.87%–56.49%).

Conclusions: The knowledge of symptomatic pattern change could assist clinicians in diagnosing and managing dengue patients. Future studies could address the occurrence of this change and the difference in symptoms between children and adults.

1. Introduction

The global burden of dengue is estimated to be 390 million infections per year[1]. Dengue is a mosquito-borne virus which can lead to various symptoms such as headache, rashes, vomiting, diarrhoea and abdominal pain. These symptoms were often confused with other infectious diseases in clinical practice. This has led to a list of differential diagnoses to be excluded which in turn, could delay the treatment of dengue infection. Furthermore, excluding other diseases would increase the cost of laboratory investigation[2].

If the predominant symptom generally remains the same for many decades, it is always easy to keep dengue infection as one of the

differential diagnoses whenever patients presented with symptoms mimicking acute gastroenteritis or other infectious diseases. If the predominant symptom changes over the years, this could confuse clinicians when diagnosing dengue.

A constant update of the common symptoms throughout the years especially vomiting, diarrhoea and abdominal pain is necessary. To our knowledge, no review has yet been found to describe the pattern of symptoms. Thus, this review sought to describe the pattern of vomiting, diarrhoea and abdominal pain over the years. The analysis of the review was also stratified according to different age groups to address the prevalence differences in the three symptoms.

2. Materials and methods

This was a review which included studies that reported symptoms (vomiting, diarrhoea or/and abdominal pain) of confirmed dengue patients. Confirmation of dengue was conducted by laboratory diagnosis such as dengue immunoglobulin M, serotyping by RT-PCR or with non-structural 1 antigen. Laboratory confirmation was necessary because suspected dengue cases could lead to false

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prevalence estimation of the symptoms. The exclusion criteria were case reports and studies which only described specific settings such as emergency or intensive care unit patients and focused only on dengue haemorrhagic fever, severe dengue or co-infection with other diseases which could lead to different clinical manifestations. Studies which only described specific settings of dengue patients or specific subgroup of dengue could also lead to false prevalence estimation of the symptoms.

These symptoms including vomiting, diarrhoea and abdominal pain were chosen because they were not as non-specific as other viral symptoms such as headache, body ache and rashes. Ideally, features of bleeding, signs of liver enlargement and fluid accumulation should also be reviewed. Unfortunately, during the piloting of data extraction for this review, many studies did not report these clinical features adequately, thus, making data extraction inefficient and meta-analysis could not be performed.

2.1. Search methods for identification of studies

Electronic search was performed using the bibliographic databases which provided searches relevant to the type of the studies in this review. The searches were conducted via Ovid SP. No language restriction was imposed. Databases were searched via Ovid SP: Biosis Previews (1995 to 2016 week 31); EMBASE (1975 to 2016 July 1); Epub Ahead of Print, In-Process and Other Non-Indexed Citations, Ovid MEDLINE(R) Daily Ovid MEDLINE(R) (1946 to July 3); EBM Reviews – Cochrane Database of Systematic Reviews (2005 to June 29, 2016); ACP Journal Club (1991 to June 2016); Database of Abstracts of Reviews of Effects (1st Quarter 2016); Cochrane Central Register of Controlled Trials (May 2016); Cochrane Methodology Register (3rd Quarter 2012); Health Technology Assessment (2nd Quarter 2016) and NHS Economic Evaluation Database (1st Quarter 2016).

2.2. Search strategy

Key words were used in the advance search of Ovid SP with appropriate truncation (*): symptom*, clinical presentation, sign*, warning sign*, h*emorrhag* fever, fever, severe dengue, shock syndrome, shock and bleed*. All the searched results were then combined using Boolean operator 'OR'. Subsequently, this was again combined by using Boolean operator 'AND' with 'dengue', in which the term 'dengue' appeared only in the title of articles and was limited to 'human' only. The searches were further refined by using Boolean operator 'NOT' on terms such as vaccine, test*, antibod*, aedes, gene*, season*, climate, spatial, mosquito, knowledge, HIV, transfus*, malaria, chikungunya, leptospirosis, survey, control, salmonella and replicat*.

2.3. Data collection and analysis

Titles and abstracts were screened by a single reviewer. Duplicate papers were filtered out manually after identifying similar titles, abstracts and authors. Subsequently, full-texts of selected papers

were retrieved for full review. Authors were contacted if full texts were not available. A pre-piloted data extraction form was used to extract the data.

2.4. Statistical analysis and data synthesis

The narrative synthesis was performed for all the studies included. The age was grouped according to children, adults or both. However, some studies used different age cut-offs for children. In this review, the cut-off for children was defined as below of any age but not more than 18 years old. Similarly, cut-off for adult was defined as above of any age but not less than 12 years old.

Meta-analysis was performed on the overall prevalence of vomiting, diarrhoea and abdominal pain. The prevalence was defined as the number of patients reported the symptoms over the total number of confirmed dengue cases. The prevalence of the symptoms was then stratified by years. For studies which were conducted over a period of more than a year, the prevalence of each symptom was assumed to be the same for all the years. The prevalence of the symptoms was also stratified according to age groups: children, adult and all ages. Inverse variance and random effect were used in all meta-analysis models in Review Manager (RevMan) version 5.3.5.

3. Results

A total of 2002 studies were identified through various databases. Out of the 2002 studies, 59 were included for full-text review. However, 32 studies were eventually selected to be included into this review after excluding the rest with various reasons (Figure 1).

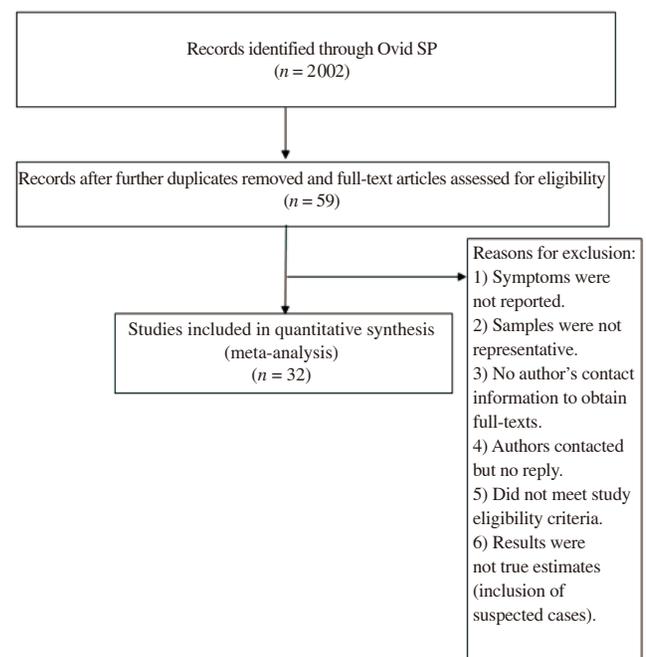


Figure 1. Flow diagram of the search.

All studies were conducted between 1995 and 2014. The majority of the studies were conducted for a duration less than five years but three studies were conducted for ten years or more[3-5]. The studies were conducted in 18 countries with the most studies conducted in Brazil[3,6-9]. Fifteen (46.9%) studies included all ages, six (18.8%)

studies included only children and seven (21.9%) studies included only adults. Four (12.5%) studies did not specify the age group. The total sample size of all studies included was 69 466. The characteristics of the included studies were tabulated (Table 1).

Table 1

The characteristics of the included studies.

| Studies | Year | Study duration | Sample size | Country | Age group | References |
|---------|------------------|----------------|-------------|------------------|-----------|------------|
| 1 | 2010 | 1 | 81 | Sudan | All | [10] |
| 2 | 2006 | 1 | 39 | Pakistan | Children | [11] |
| 3 | 2006–2010 | 5 | 323 | Thailand | NA | [12] |
| 4 | 2005 | 1 | 52 | India | Children | [13] |
| 5 | 2007 | 1 | 151 | Vietnam | Adult | [14] |
| 6 | 2007–2009 | 3 | 62 | Philippines | Children | [15] |
| 7 | 2011 | 1 | 102 | Brazil | All | [6] |
| 8 | 2004–2007 | 4 | 201 | Vietnam | Children | [16] |
| 9 | 1995–2006 | 12 | 48 768 | Brazil | All | [3] |
| 10 | 1996–1997 | 2 | 196 | French Polynesia | All | [17] |
| 11 | 2002–2011 | 10 | 51 | Peru | All | [4] |
| 12 | 1998 | 1 | 614 | Nicaragua | All | [18] |
| 13 | 2001–2002 | 2 | 183 | Sri Lanka | All | [19] |
| 14 | 2002 | 1 | 644 | Taiwan | All | [20] |
| 15 | 2014 | 1 | 1 700 | Malaysia | All | [21] |
| 16 | 2007, 2008, 2010 | 3 | 267 | Brazil | Children | [7] |
| 17 | 2011–2013 | 3 | 296 | Malaysia | NA | [22] |
| 18 | 2002–2005 | 4 | 61 | Spain | Adult | [23] |
| 19 | 2001–2002 | 2 | 453 | Brazil | All | [8] |
| 20 | 2000–2002 | 3 | 390 | Bangladesh | Adult | [24] |
| 21 | 2011–2012 | 2 | 299 | Pakistan | All | [25] |
| 22 | 2012 | 1 | 1 226 | India | NA | [26] |
| 23 | 2011 | 1 | 41 | Peru | All | [27] |
| 24 | 2010–2011 | 2 | 5 686 | Brazil | All | [9] |
| 25 | 2004–2005 | 2 | 183 | Malaysia | NA | [28] |
| 26 | 2004, 2007, 2008 | 3 | 1 507 | Singapore | Adult | [29] |
| 27 | 2004–2013 | 10 | 132 | Czech travellers | Adult | [5] |
| 28 | 2001–2003 | 3 | 173 | Indonesia | Children | [30] |
| 29 | 2005–2006 | 2 | 90 | Philippines | All | [31] |
| 30 | 2002 | 1 | 661 | Taiwan | All | [32] |
| 31 | 2005–2008 | 4 | 4 383 | Singapore | Adult | [33] |
| 32 | 2005–2011 | 7 | 451 | Singapore | Adult | [34] |

NA: Not available.

The predominant symptom was abdominal pain before 2004 but became vomiting thereafter. The prevalence of vomiting was constant throughout the years with 20%–40% but the prevalence of abdominal pain reduced from 30%–50% to 20%–30%. The prevalence of diarrhoea has been increasing steadily from 5% to 30%. The comparison among the symptoms between 1995 and 2014 was presented in Figure 2.

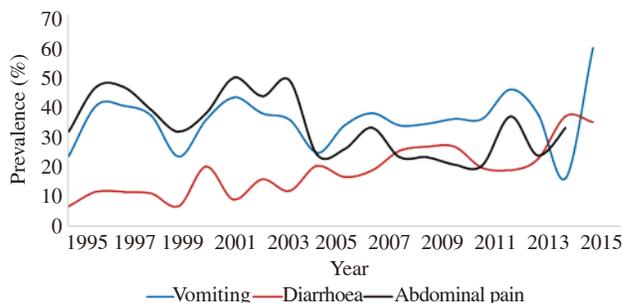


Figure 2. Meta-analysis of the prevalences of vomiting, diarrhoea and abdominal pain stratified by years from 1995 to 2014.

Single study was used to represent 1995, 1999, 2013 and 2014 in vomiting and diarrhoea, and 1995 and 1999 in abdominal pain.

The overall prevalence of vomiting was the highest (42.56%) (95% confidence interval (CI): 34.89%–50.23%), followed by abdominal pain (39.97%) (95% CI: 29.61%–50.33%) and diarrhoea (17.80%) (95% CI: 13.21%–22.39%). Upon stratification to different age groups, the predominant symptom in children was abdominal pain (75.03%) (95% CI: 64.89%–85.17%) and in adults was diarrhoea (32.42%) (95% CI: 23.96%–40.88%). Studies which included all ages has predominant symptom of vomiting (45.18%) (95% CI: 33.87%–56.49%) (Table 2).

Table 2

Meta-analysis of the prevalence of vomiting, diarrhoea and abdominal pain.

| Meta-analysis model | Prevalence of vomiting (95% CI) (%) | I ² (%) |
|------------------------|-------------------------------------|--------------------|
| Overall prevalence | | |
| Vomiting | 42.56 (34.89–50.23) | 99 |
| Diarrhoea | 17.80 (13.21–22.39) | 93 |
| Abdominal pain | 39.97 (29.61–50.33) | 97 |
| Prevalence in children | | |
| Vomiting | 46.31 (27.48–65.14) | 91 |
| Diarrhoea | 8.86 (–0.54–18.26) | 75 |
| Abdominal pain | 75.03 (64.89–85.17) | 42 |
| Prevalence in adult | | |
| Vomiting | 29.71 (11.65–47.77) | 93 |
| Diarrhoea | 32.42 (23.96–40.88) | 0 |
| Abdominal pain | 28.31 (10.99–45.64) | 90 |
| Prevalence in all ages | | |
| Vomiting | 45.18 (33.87–56.49) | 89 |
| Diarrhoea | 15.80 (9.15–22.45) | 86 |
| Abdominal pain | 39.74 (25.15–54.33) | 92 |

4. Discussion

A change in pattern involving the three symptoms was observed between 1995 and 2014. There was a difference in the predominant symptoms between children and adults. Studies which included all ages showed that the cases predominated by vomiting and diarrhoea had the lowest prevalence. This result could be explained by the low prevalence of diarrhoea among children. Thus, when studies included all ages, the prevalence of diarrhoea was ‘diluted’.

The prevalence of vomiting was static throughout the years. It is interesting to note that diarrhoea increased in prevalence after 2014. This has implication to the clinical diagnosis of dengue. Patient could present with diarrhoea alone but clinicians might misdiagnose such cases as other similar diseases such as acute gastroenteritis or food poisoning. The delay in treatment of dengue when patients are misdiagnosed could lead to severe complications and even death. Abdominal pain was once the most predominant symptom before 2004 until vomiting predominated thereafter. Clinicians should be aware of such changing pattern and, more importantly, future pattern changes. Fortunately, most clinicians who are in practice were well aware of these changes in pattern due to their experience in managing dengue cases. However, to acquire such experience, doctors should have managed a lot of dengue cases especially in dengue endemic countries[1]. Therefore, clinicians who are not in these endemic countries would need advice or information from scientific literature if they ever suspect a case of dengue especially in travellers returning from tropical countries[35,36]. Thus, it is

important to constantly update the pattern of dengue symptoms in order to provide information that could assist clinicians around the world.

The changing pattern of symptoms in dengue could also lead to some postulation about dengue virus. The change in the predominant symptom can be attributed to the mutation of dengue virus or the different serotypes circulating at different points in time. There are a few other possible factors such as environmental changes, changes in the vector transmitting the disease or changes in host immunity. The epidemiological triad should be examined closely to provide answers to these postulations.

Diarrhoea is the predominant symptom in adults as opposed to children. The occurrence of diarrhoea has yet to be explained in the pathophysiology of dengue infection. One study postulated that it could be due to the increased vascular permeability in the gut, thereby leading to osmotic diarrhoea[37]. However, this does not explain the difference in the prevalence of diarrhoea between adults and children. Abdominal pain could be possibly due to dengue hepatitis and is perhaps more commonly seen in children[38,39]. Vomiting in dengue might be explained by dengue hepatitis. To our knowledge, the pathophysiology of vomiting in dengue has not been described in literature. The knowledge on the differences in the predominant symptom may help doctors who are working in primary care or emergency departments in diagnosing patients. However, all three gastrointestinal symptoms could also be present in a patient with dengue infection.

Several limitations to this review could also affect the interpretation of the meta-analysis results. Ideally, this review should adhere to the systematic review recommendation such as Joanna Briggs Institute reviewers' manual and Cochrane handbook for systematic reviews of interventions[40,41]. To avoid bias in screening and full-text review, a second reviewer is necessary with or without a third reviewer to resolve any dispute between the first two reviewers. Risk of bias assessment for all included studies should be performed by two reviewers to evaluate and exclude any potential high risk studies which could affect the meta-analysis result.

Many studies screened did not provide the author's contact information and even if contact information were provided, they were not responsive to the requests for abstract and full-text. This could drastically reduce the potential studies to be included into this review which in turn affects the generalisability of the results across the world.

Future clinical epidemiological studies on dengue symptoms should update and improve this review by eliminating some of the limitation mentioned. The knowledge of symptomatic pattern change could assist clinicians in diagnosing and managing dengue patients. The findings of this study have also generated more hypotheses to be investigated for the changing pattern of symptoms over the years and for the difference in symptoms between children and adults.

Conflict of interest statement

I declare that I have no conflict of interest.

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