TECHNICAL HANDBOOK

Technical handbook for dengue surveillance, dengue outbreak prediction/detection and outbreak response ("model contingency plan")

World Health Organization

TDR For research on diseases of poverty
UNICEF • UNDP • World Bank • WHO

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FOREWORD

In 1999, given the rapidly increasing public health importance of dengue, the disease was incorporated into the portfolios of the Special Programme for Research and Training in Tropical Diseases (TDR), which is hosted at the World Health Organization (WHO) and co-sponsored by United Nations Children's Fund (UNICEF), the United Nations Development Programme (UNDP), the World Bank and the World Health Organization (WHO). Then, in 2002, a World Health Assembly (WHA) Resolution, WHA55.17, urged greater commitment to tackling dengue among Member States and WHO. Of particular significance is the 2005 revision of the International Health Regulations (IHR)[1] that includes dengue as an example of a disease that may constitute a public health emergency of international concern. It was against this background that the Scientific Working Group (SWG) on dengue comprising 60 experts from 20 countries was organized by TDR in October 2006. The aim was to review existing knowledge on dengue and establish priorities for future research. Priority dengue research areas were identified and organized around four major research streams intended to provide evidence and information for policy-makers and control programmes, and lead to more cost-effective strategies; those for dengue surveillance and outbreak response included the following recommendations (WHO/TDR, 2006).

- The development and utilization of early warning and response systems.
- The triggers that will allow effective response to incipient epidemics.
- Factors leading to the success or failure of national programmes.
- Decision-making that results in a declaration of state of emergency.
- Analysis of the context of dengue surveillance and outbreak management.

Since the publication of the updated edition of WHO's *Dengue: guidelines for diagnosis, treatment, prevention and control* (WHO/TDR, 2009), new developments in dengue warrant an interim analysis of progress so far. According to the WHO handbook for the development of guidelines (WHO 2012a), precise high-level evidence is needed to do so, including systematic reviews. This requirement for systematic reviews arises from developing public health policy that is based on available research, which includes implementation and operational research, linking research and practice. The need to fill this gap in high-level evidence is particularly relevant in the context of neglected tropical diseases (Nagpal et al. 2013). In an interview-based study, Francis et al. (2014) found that policy-makers need systematic reviews that are:

> *…policy relevant, rigorous, and translatable to their local context, actionable, timely and well communicated...(that the) question should rather focus on the relevance to policymakers than the current scientific literature,...suggestions of how to enhance the usefulness of reviews to the policy process included the improved collaboration and engagement between policymakers and review authors around the identification of review topics and scope…. and a greater focus on heterogeneity of interventions, contexts and effectiveness.*

1 WHA58.3.

This handbook was produced by TDR together with WHO's Neglected Tropical Diseases (NTD) Department and WHO regional offices in the context of a European Union-financed research programme, the International Research Consortium on Dengue Risk Assessment, Management and Surveillance (IDAMS), to develop an evidence-based handbook for the early outbreak detection and management of dengue fever outbreaks. The handbook targets public health providers, in particular those at national level. It is not an implementation guideline, but a framework for developing a national contingency plan with local adaptations that acknowledge micro-level programme components. Response planning requires contextual details encompassing the structure of the health and vector control services, the availability of infrastructure and budget, and human resources, and the willingness of staff to cooperate, among others.

The aim of this "model contingency plan" is to assist programme managers and planners in developing a national, context-specific, dengue outbreak response plan in order to: (a) detect a dengue outbreak at an early stage through clearly defined and validated alarm signals; (b) precisely define when a dengue outbreak has started; and (c) organize an early response to the alarm signals or an "emergency response" once an outbreak has started. A summary of this document is published under Runge-Ranzinger et al. 2016.

ACKNOWLEDGEMENTS

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The handbook was developed in the context of a dengue research programme supported by a grant from the European Commission (Grant Number m281803) to the International Research Consortium on Dengue Risk Assessment, Management and Surveillance (IDAMS) within the 7th Framework Programme of the European Commission, and by WHO and TDR.

ABBREVIATIONS

BCC	behaviour change communication
BI	Breteau index
°C	degree Celsius
CI	container index
COMBI	Communication for Behavioural Impact
DENV	Dengue virus
DENV-1	dengue virus serotype 1
DENV-2	dengue virus serotype 2
DENV-3	dengue virus serotype 3
DENV-4	dengue virus serotype 4
DF	dengue fever
DHF	dengue haemorrhagic fever
DSS	dengue shock syndrome
ELISA	enzyme-linked immunosorbent asssay
g	gram
HI	house Index
IEC	Information, education and communication
M&E	monitoring and evaluation
NGO	nongovernmental organization
NS	non-structural protein (NS-1)
PPP	pupae per person
PCR	polymerase chain reaction
PPV	positive predictive value
SD	standard deviation
SOP	standard operating procedure
TDR	Special Programme for Research and Training in Tropical Diseases of the WHO
WHO	World Health Organization

Chapter 1
Introduction and methodology

1.1 Introduction

Dengue, a mosquito-borne viral disease, is emerging as one of the world's most rapidly spreading and important infectious diseases of the 21st century (WHO, 2009; WHO, 2012b). A recent re-assessment of the dengue burden using novel modelling methods has shown that the dengue burden is about three times higher than estimated by WHO (Bhatt et al. 2013). Messina et al. (2014) showed the worldwide expansion of the serotypes of disease hyperendemicity, and the establishment of an increasingly important infectious disease of global public health significance. Other reviews of national epidemiological dengue data for Brazil, the Caribbean, Malaysia, Mexico, the Philippines and Thailand, sponsored by the World Health Organization (WHO) and the vaccine industry support these facts (Horstick & Morrison, 2014a). The increasing global threat of dengue outbreaks in both endemic and non-endemic regions of the world has focused attention on effective outbreak management.

Preparedness planning (used synonymously with outbreak response planning or contingency planning) has been described as a way in which to augment the engagement of partners, build capacity and develop infrastructure, providing operational links to ensure a structured and coordinated response. Preparedness planning starts in the inter-epidemic phase and its success depends on the combination of year-round routine activities usually established in national dengue control plans, preparedness planning during the inter-epidemic phase, up-scaling of routine interventions, and timely and systematically initiated additional measures during an epidemic.

The national contingency plan should be distributed during the inter-epidemic phase to all relevant stakeholders (see Chapter 3), and mechanisms to ensure its implementation should be established. Checklist 1 summarizes the main components to be considered when developing a contingency plan, and a framework is attached in Annex 1.

Dengue outbreak response has been defined as the sum of measures specifically addressing a dengue outbreak aimed at reducing case fatality rates, numbers of cases and entomological parameters (Pilger et al. 2010). Early detection of outbreaks is important for timely response and the alarm signals triggering the early response need to be established (Chapter 3).

Timely response is essential for mitigating the enormous social and economic costs of a dengue outbreak.[1] Stakeholder involvement as an important element in outbreak response is presented in detail in Chapter 3.

[1] Costs of outbreaks have been investigated by a literature review and cost evaluations in four countries revealing that only one paper (Baly et al. 2011) addresses the costs of outbreaks explicitly and methodologically accurately in a prospective study. Nevertheless, one review showed that the costs of dengue control interventions are much lower than actual outbreak costs if the outbreak is left uncontrolled. In the case study, the findings of the literature review have been confirmed: it is much cheaper to prevent dengue outbreaks than to pay for the consequences of an outbreak in terms of treatment costs and additional costs for vector control and information, education and communication (IEC) activities (Stahl et al. 2013).

CHECKLIST 1. **GENERAL RECOMMANDATIONS FOR NATIONAL PREPAREDNESS PLANNING**

Its is recommeded to:

1. Ensure a minimal documented accountability for each intervention ("who is responsible for what"), defining a person or units/agencies/institutions to be in charge of certain activities
2. Ensure that a dengue contingency plan contains detailed instructions
3. Distinguish between the routine interventions that should be performed in the inter-epidemic period (particularly in advance of the seasonal peak of cases), and outbreak interventions during the outbreak (that is, between the up-scaling of preventive interventions before the dengue season starts and specific outbreak procedures)
4. Ensure continuity between surveillance, outbreak alerts, outbreak confirmation, outbreak declaration and response
5. Ensure that governance during the response has the regulatory framework in place and the means to oversee activities and interventions
6. Highlight all stakeholders to be involved (refer to Table 6)
7. Include human-resource preparedness planning for all sectors
8. Ensure that instructions on training are included and implemented
9. Provide details on monitoring and evaluation (M&E) of preparedness activities and response
10. Ensure that the dengue contingency plan is sufficiently distributed and implemented

1.2 Methodology

In response to the research areas formulated by the 2006 TDR Scientific Working Group (SWG) around the development and utilization of early warning and response systems and triggers/factors that will allow effective response to incipient epidemics, several systematic literature reviews were undertaken by: Heintze, Garrido & Kroeger (2007); Erlanger, Keiser & Utzinger (2008); Runge-Ranzinger et al. (2008; 2014); Esu, Lenhart & Horstick (2010); Pilger et al. (2010); Horstick et al. (2010; 2014b); Boyce et al. (2013); Stahl et al. (2013); Bowman, Runge-Ranzinger & McCall (2014); George et al. (2015); Han et al. (2015), Lazaro et al. (2015); and Bowman, Donegan & McCall (2016a).

In a second step, factors were identified that lead to the success or failure of national programmes, and decision-making that results in a declaration of a state of emergency. Analyses were undertaken of stakeholders' perceptions in the context of dengue surveillance and outbreak management, practical application needs and the identification of additional knowledge gaps. These analyses were conducted in Bolivia, Brazil, Cambodia, Indonesia and Thailand (Rediguieri, 2009; Runge-Ranzinger, 2010; Yusadiredja, 2010), leading to additional systematic reviews as well as a comparative analysis of dengue contingency plans including a gap analysis (Harrington et al. 2013) to cover all relevant items for dengue contingency planning. Finally, a multi-country study was conducted assessing dengue contingency planning in 10 countries (Badurdeen et al. 2013) focused specifically on policy-makers' perceptions of outbreak management. The study included several meetings of experts and policy-makers to assure their involvement and capture their needs during the process. For the development of an alert algorithm for dengue outbreaks, an expert technical group identified potential alarm indicators from the literature and their experience, and agreed on the ones to incorporate into a phase of retrospective testing and model development.

In a third step, using epidemiological and alarm signals data from Brazil, the Dominican Republic, Malaysia, Mexico and Viet Nam (Bowman et al. 2016b), a retrospective analysis of those alarm indicators was undertaken and a model for outbreak alert developed. This model is currently e valuated in a prospective controlled trial in order to be piloted in a study over 18 months in three countries (Brazil, Malaysia and Mexico) to assess its feasibility and cost effectiveness. This trial is also focusing on the use of a 'staged response', where specific interventions (improved use of surveillance information, timely application of response activities as per national guidelines, vector control strategies) are activated or deployed in response to the presence of specific alarm signals. The overall results are summarized in this handbook as described above, in order to assist programme managers and planners in the development of best possible evidence-based dengue outbreak response planning in a specific context.

The lead writer chose a group of peer reviewers, not excluding any potential peer reviewer for a particular view. The peer reviewers were not paid for their work. Declarations of interest were obtained from all of them and no conflicting interests were declared.

For each chapter, the resolution of disputed issues arising from the reviewers' comments was achieved through discussion with the lead writer using electronic mail.

Examples are given in text boxes and the evidence from literature reviews in footnotes.

Chapter 2
Dengue surveillance

2.1 Passive disease surveillance[2]

2.1.1 Challenges of the routine surveillance system

Passive routine reporting of dengue cases as the backbone of epidemiological information monitors the spatial and temporal distribution of dengue in its different clinical expressions, determines the risk and priority areas for interventions, and serves as a trigger for outbreak alert. However severe underreporting, especially of non-hospitalized dengue cases (in addition to those not reported due to asymptomatic or mild disease not presenting to health services and/or non-users of the public health sector and others), is an issue. For an alert system to trigger actions, the surveillance system needs to be: (a) sensitive in predicting or detecting an outbreak in a timely manner; and (b) specific to avoid unnecessary false alerts. When the sensitivity of an alarm signal increases, the specificity decreases and vice versa, but the optimal level of sensitivity/specificity is unclear (Runge-Ranzinger et al. 2008; 2014).[3]

The following aspects are of importance in a national surveillance system:

- the use of a simplified and standardized case classification, available with the revised WHO case classification,[4] see Annex 2 (WHO/TDR, 2009; Horstick et al. 2014b);
- improved laboratory support through standardized and quality-controlled testing procedures (WHO/TDR, 2009);
- the addition of active/enhanced/syndromic surveillance components (Runge-Ranzinger et al. 2008; 2014; Brady et al. 2015).

[2] Passive surveillance relies on standardized reporting forms provided by the state or local health departments. These completed forms are returned to the health department when cases of disease are detected. Passive reporting systems are generally less costly than other reporting systems, and data collection is not burdensome to health officials, but the challenge is how to increase the reporting mentality of health providers and ensure standardized case classification (Thacker et al. 1986).

[3] It is not yet clear how sensitive the surveillance data need to be (level of underreporting accepted) in order to fulfil its purpose: (a) to reflect disease trends accurately; and (b) to serve as a baseline for early alert. However, it seems that to a certain extent, underreporting can be tolerated in high-endemic settings, as long as data are representative and, ideally, laboratory supported (Runge-Ranzinger et al. 2008; 2014).

[4] A systematic review of the published studies and an expert consensus based on regional research comparing the two classifications has been published (Horstick et al. 2014b; 2015). 12 studies were performed after the publication of the 2009 WHO case classification and most were performed in Asia with the exception of three studies – one that included 18 study sites worldwide (Barniol et al. 2011), one study from Nicaragua and one study from Peru. Ten expert opinion articles were used for discussion. The 2009 WHO case classification studies show: (1) that when determining severe dengue, sensitivity was measured between 59% and 98% (88% and 98% for the two prospective studies), and specificity was between 41% and 99%, (99% for the prospective study); when comparing the 1997 WHO classification with that of 2009, the sensitivity was lower between 24.8% and 89.9% (24.8% and 74% for the prospective studies); specificity for the 1997 WHO case classification was 25% and 100% (100% from the prospective study); (2) it is easy to apply the 2009 WHO case classification; (3) for (non-severe) dengue as defined in the 2009 WHO case classification, there may be a risk of monitoring increased dengue case numbers; and (4) studies are needed to further validate the warning signs.

CHAPTER 2
Dengue surveillance

Elements that were suggested to potentially improve the passive surveillance system are summarized in Checklist 2. It should be noted that harmonization with national surveillance guidelines is crucial.

CHECKLIST 2. **ELEMENTS AND CHARACTERISTICS OF AN ADEQUATE SURVEILLANCE SYSTEM**

1. Objectives of the surveillance system(s) should be clear to all stakeholders
2. Terminology of dengue surveillance should be described and consistent
3. Dengue notification should be mandatory
4. National guidelines for dengue/disease surveillance should be distributed
5. Both suspected and confirmed dengue cases should be reported
6. Timeliness of all reporting steps should be optimized (Flowchart 1)[a]
7. The sensitivity of disease surveillance for early alert can be increased by including the private sector, all health units including outpatient departments, all age groups and by adding enhancement strategies
8. Usage of easy to apply notification forms,[5] standardized data entry processes and electronic-based reporting
9. Clear data flow including timely information feedback, defined responsibilities and linkage to response should be in place
10. Continuous data analysis including the lowest possible level of the health system by a defined team of epidemiologists should be ensured
11. Serosurveys to calculate an expansion/correction factor should be considered in order to: (1) assess the level of underreporting; and (2) calculate the national burden of disease[b]
12. Regular internal and external evaluations of the routine surveillance system to improve quality standards should be organized, a possible format is given in CDC (2001)[c]
13. The specificity of dengue information can be improved by quality-controlled laboratory support. Laboratory networks are crucial
14. Laboratory confirmation of all dengue suspected cases, mainly with immunoglobulin M (IgM) and immunoglobulin G (IgG) enzyme-linked immunosorbent assay (ELISA) and increasingly with non-structural protein (NS-1) should be envisaged
15. During outbreaks, a small fraction of suspected cases should be tested (for example, 10–30%)
16. Regular training for epidemiologists, clinicians, laboratory staff and others should be ensured so that staff are knowledgeable about case definitions and case management
17. Alarm signals with a threshold level ('trigger') to initiate activities should be identified (example: excess of reported dengue cases >2 standard deviation (SD) of the five-year average),[6] see details in Chapter 3.

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[5] For example, see http://www.cve.saude.sp.gov.br/htm/outros/fichas/FICHA_DENGUE_ONLINE_2014.pdf (accessed 8 May 2016).

[6] The following indicators for detecting the deviation of reported dengue cases or laboratory results from 'average' (pattern recognition technique) have been tested: two or more epidemic months (i.e. months with reported dengue cases more than 1 SD above the monthly average) based on the retrospective analysis of dengue reporting (population based) in a passive surveillance system in Thailand (Barbazan, Yoksan & Gonzalez, 2002); an excess of reported cases of dengue notifications (population-based) >2 SD above the average in a routine surveillance system in Puerto Rico (Rigau-Pérez et al. 1999); and Viet Nam where the level of increase above average was not mentioned (Tien et al. 1999).

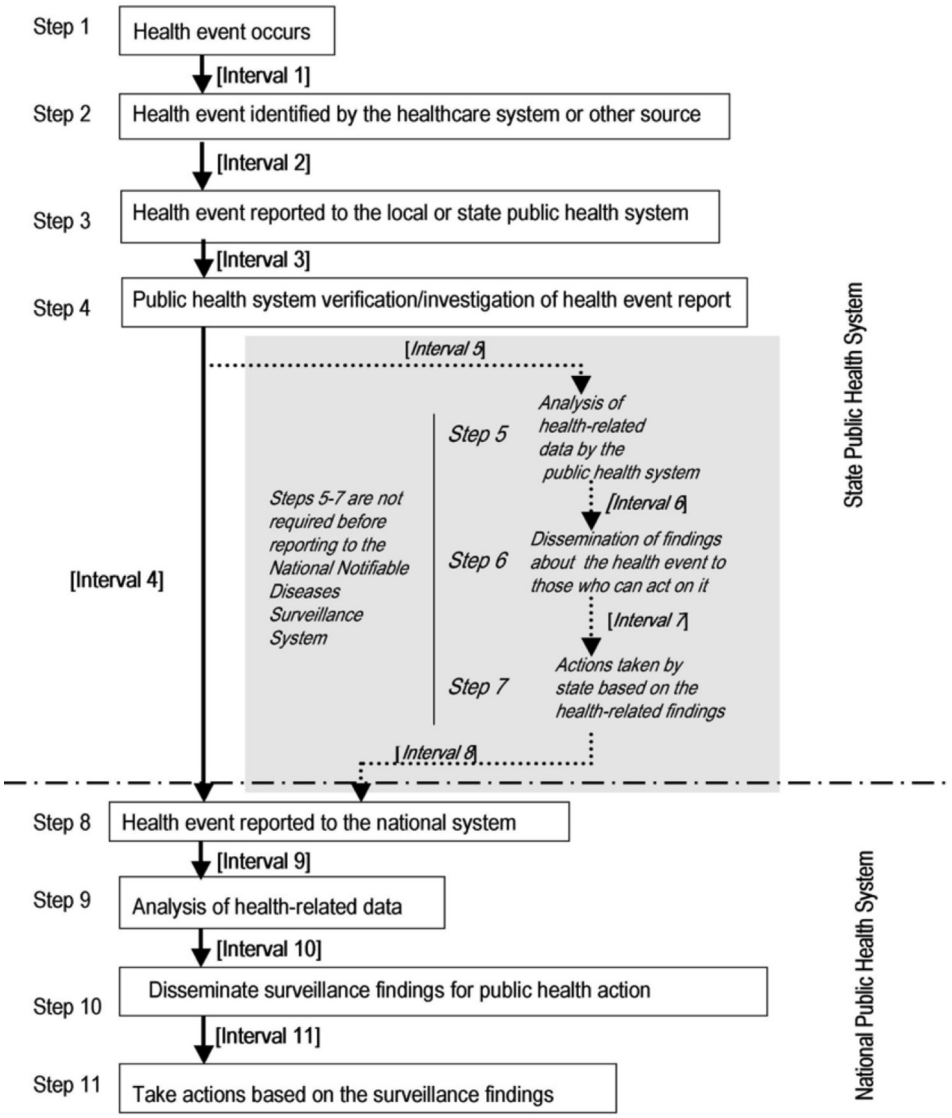
[a] Jajosky & Groseclose (2004).

[b] Tourdjman, Huy & Vong (2005); Standish et al. (2010); Wichmann et al. (2011); Vong et al. (2012); Undurraga, Halasa & Shepar (2013).

[c] CDC (2001).

Sources: Rediguieri (2009); Beatty et al. (2010); Runge-Ranzinger (2010); Yusa-diredja (2010); Abdulla (2011).

Flowchart 1. Steps to analyse reporting time



Source: CDC (2004).

2.1.2 Monitoring and evaluation of the surveillance system

Periodic internal and external evaluation of the passive routine surveillance system is needed to assess the minimum requirements for achieving the objectives. These evaluations include information on the system's purpose, process, outcome attributes, analysis and use of collected data as well as public health impact. Opportunities for improvement should be identified and acted on.

In a framework for the evaluation of public health surveillance systems, the usefulness of a disease surveillance system has been described as the sum of all outcome attributes listed as below in Table 1 (CDC, 2001).

Table 1. Assessing a public health surveillance system

Attributes	Brief definition
Sensitivity	Proportion of case/outbreaks detected out of all cases/outbreaks
Timeliness	Speed between detection, reporting and response
Stability	Ability to collect, manage and provide data properly
Simplicity	Ease of operation of the surveillance system
Flexibility	Ability to adapt during an epidemic and applicability in other settings
Data quality	Completeness and validity of the data recorded
PPV	Proportion of reported cases, actually having dengue
Representativeness	Ability to describe spatial and temporal dengue distribution in the whole population
Acceptability	Willingness of persons and organizations to participate
Accuracy/specificity	Ability to distinguish between a dengue outbreak and another outbreaks, between a dengue case and another illness, and between dengue and severe dengue Determined by especially representativeness, data quality, PPV, specificity of case definition
Usefulness	Sum of all attributes, documents the contribution to prevention and control, systems effect on policy decisions and control programmes

PPV: positive predictive value.
Sources: adapted from CDC (2001).

Several country evaluations have been performed using an adapted version. The summarized findings are presented below in Example 1 (Chairulfatah et al. 2001; Hyo-Soon Yoo et al. 2009; Rediguieri, 2009; Runge-Ranzinger, 2010; Yusadiredja 2010; Abdulla, 2011).

EXAMPLE 1. COUNTRY EVALUATIONS IN FOUR COUNTRIES IN ASIA AND LATIN AMERICA

Sensitivity
Factors explaining the high rate of underreporting (that is, low sensitivity) in the four study countries: (1) low sensitivity of the clinical case definition/classification; (2) underuse of health services (particularly for mild disease); (3) reporting by the public sector only, limited to certain age groups or inpatients; (4) limited contribution to the surveillance system in some countries; and (5) difficulties of classifying dengue with the previous dengue case classification – DF, dengue haemorrhagic fever (DHF), dengue shock syndrome (DSS). The sensitivity of outbreak detection depends on the accuracy of case reporting, the sensitivity of the epidemiological threshold, and the use of additional alarm signals.

Specificity/accuracy
Accuracy of case reporting was an issue in all settings as additional studies on the quality of the reporting process of cases have only been done in exceptional circumstances. Accuracy can be increased by laboratory confirmation (as highlighted in Brazil). The alarm signals to detect outbreaks seem to be generally too specific rather than too sensitive, as false alerts were not mentioned as a problem in the four countries. The inaccuracy of rumour alerts and the reluctant response to alerts due to mistrust in data quality was repeatedly mentioned as a problem.

Timeliness and acceptability of reporting and response
Timeliness depended primarily on the processes within the integrated public health reporting system. Early data entry seems crucial, and manual (paper-based) reporting a disadvantage. Further to this, the reporting process from the reporting institution (for example, health centre, clinic, etc.) to the local public health facility, which was often in a dengue-specific form, was time-consuming. This was because forms were manually delivered and variables to be reported were only available after the patient was discharged. The other cause of delay was slow data analysis, which was done either on a weekly or a monthly basis. The delay in the investigation of an event was mainly due to delayed data analysis or missing alarm signals for an outbreak investigation. Local investigations were faster, but less accurate due to missing human skills and laboratory support. Response at the local level (depending on local outbreak definitions or case-based approaches) was often in time, but response from higher levels based on thresholds of epidemiological data was often delayed. Reasons for this were said to be that interventions for the outbreak response were costly and data too inaccurate to launch a response.

2.2 Enhanced surveillance

Overview

Routine surveillance is the backbone of dengue information but there are other tools that strengthen the information system. These systems either contribute with additional alarm signals or increase data quality and/or timeliness. The potential value of enhanced surveillance lies in combining tools that complement the routine reporting but do not replace it.

Enhanced surveillance during the inter-epidemic period includes:

a) epidemiological sub-analysis of routinely reported data

b) syndromic surveillance

c) laboratory-based dengue reporting

d) other active surveillance approaches.

The options for enhanced surveillance to be selected by countries are presented below.

2.2.1 Epidemiological data sub-analysis

Dengue cases are reported to the authorities and the number of reported cases or incidence rates are analysed. Often additional information is available about age, disease outcome (disease severity including deaths), and geographical location of the cases. These data can provide useful information about a shift in age group distribution or increased numbers of hospitalized patients, which could be associated with a new serotype or with high transmission areas. They can also be used to monitor the spatio-temporal distribution of the disease.

Unfortunately, the final disease outcome (level of severity) can often only be reported at the end of the disease, so that a patient may be recorded at the beginning as “suspected dengue” and at the end as “severe dengue,” which may complicate the reporting system.

2.2.2 Syndromic surveillance

Syndromic surveillance was developed as an additional tool for the early alert of aberrant patterns in order to detect an outbreak early on. It is used here in a broader perspective and not limited to clinical syndromic definitions (syndroms) only. It may be based on increased numbers of school absenteeism, increased laboratory requests or proportion of positive laboratory results in the inter-epidemic period. In order to react in a timely manner, the systems are electronically based and use automated alerts when specific events pass a given threshold. These alarm signals can be used in an integrated risk assessment tool. The purpose of syndromic surveillance has been described in the following way (Henning, 2004):

> *Syndromic surveillance has been used for early detection of outbreaks, to follow the size, spread, and speed of outbreaks, to monitor disease trends, and to provide reassurance that an outbreak has not occurred. Syndromic surveillance systems use existing health data in real time to provide immediate analysis and feedback to investigation staff and decision makers and follow-up of potential outbreaks. Stakeholders need to understand the advantages and limitations of syndromic surveillance systems. However, syndromic surveillance does not replace traditional public health surveillance, nor does it substitute for direct physician reporting of unusual or suspect cases of public health importance.*

Table 2. Data sources for syndromic surveillance

Potential data sources	Potential alternative data sources
• Emergency department or total patient volume in hospital • Total hospital or intensive-care unit admissions from an emergency department • Emergency department algorithms for chief complaints • Outpatient department • Emergency medical care system • Provider hotline: increase of certain main complaints • Poison control centre • Unexplained deaths • Medical examiners: increase of specific syndromes • Insurance claims or billing data • Clinical laboratory or radiology: ordering volume	• School absenteeism (from primary and secondary schools) • Work absenteeism (from defined companies) • Over-the-counter medication sales (from pharmacies) • Health-care provider data-based searches • Volume of internet-based health inquiries by the public (social networks) • Internet-base illness reporting (social networks)

Source: adapted from Henning (2004).

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Syndromic surveillance may contribute important data on alarm signals in early warning systems for dengue outbreaks. A number of variables that potentially provide predictive warning have been identified (see Example 2).

EXAMPLE 2. ALARM SIGNALS FOR SYNDROMIC DENGUE SURVEILLANCE: APPROACHES REPORTED IN THE LITERATURE

Increase of virus positivity rate
Increased virus isolation rate as a percentage of positive blood samples for dengue viruses in the low season based on routine virological surveillance was used as an alarm signal in Puerto Rico (Rigau-Pérez et al. 2001; Rigau-Pérez & Clark, 2005) and Viet Nam (Tien et al. 1999). In Singapore during the 2007/2008 epidemic, the proportion of dengue virus (DENV) positive samples detected by polymerase chain reaction (PCR) rose from 57.9% in January 2007 to 91.0% in July 2007 at the peak of transmission (Lee et al. 2010), which was similar to the situation in Puerto Rico (Rigau-Pérez & Clark, 2005).

Increased malaria negative rate in fever patients in a malaria-endemic area
Increased numbers of dengue cases were detected when in fever patients the malaria positivity rate went down in French Guiana (Carme et al. 2003). Currently no judgement is possible, as this depends on the local setting.

Fevers or clinical syndromic definitions
Reported fever cases were used as an indicator in community-based surveillance systems. In Cambodia, an active community-based surveillance system using a syndromic definition (diagnostic algorithm) for haemorrhagic fevers increased case reporting in non-users of health services (64% of all cases) (Oum, Chandramohan & Cairncross, 2005). This approach was supposed to be more rapid and useful for the detection of focal, small-scale transmission. In Madagascar, a sentinel- based syndromic surveillance system for six diseases was evaluated. It detected 10 outbreaks, five were confirmed, two of which were dengue (Randianasolo et al. 2010). In French Guiana, a syndromic clinical surveillance system in a military population was compared with routine laboratory reporting (Meynard et al. 2008). Both were complementary but the syndromic approach detected an outbreak 3–4 weeks earlier and was six times more sensitive than laboratory-based surveillance, though the specificity was lower. A further analysis, using Centers for Disease Control and Prevention (CDC) criteria showed that the ideal reporting time was often not achieved due to barriers encountered with data entry. The risk of false alerts needs to be considered but all respondents perceived that this system detects outbreaks adequately (Jefferson et al. 2008). The subsequent countrywide introduction of sentinel-based syndromic reporting in French Guiana identified 80 signals for confirmed cases, 64 for clinical cases and predicted three major epidemics (Flamand et al. 2011). In Bolivia and Cuba, fever alert for the purpose of outbreak detection was not useful (Pirard et al. 1997; Kouri, 1998).

Rate of school absenteeism
Rocha et al. 2009, Lawpoolsri et al. 2014 and Fan et al. 2014 investigated the use of school absenteeism with mixed and context specific results.

Search Query Surveillance
Chan et al. 2011, Althouse et al. 2011, Hoen et al. 2012 and Gluskin et al. 2014 found that data on Internet searches and event-based surveillance correlated well with the epidemic curve derived from surveillance data, suggesting that this method may be useful to predict outbreaks.

2.2.3 Laboratory support of routine reporting

Purpose of laboratory testing

The purpose of laboratory support for dengue outbreak control is to:

- verify the clinical diagnosis for clinical management and outbreak confirmation;
- directly report positive test results to the authorities for surveillance purposes;
- increase the specificity of the reporting system by reporting laboratory confirmed cases instead of clinically suspected cases;[7]
- contribute to the syndromic surveillance system (for example, identify increased number of requests);
- generate sero/genotype specific data as an additional alarm signal.

General characteristics of dengue tests in the laboratory

Before day five of illness, dengue infections may be diagnosed by virus isolation in cell culture, by detection of viral ribonucleic acid (RNA); by nucleic acid amplification tests (NAAT), or by detection of viral antigens (for example, NS-1) by ELISA or rapid tests (for interpretation see Fig. 1). Virus isolation in cell culture is usually performed only in laboratories with the necessary infrastructure and technical expertise. NS-1 antigen detection kits, now commercially available, can be used in laboratories with limited equipment and yield results within a few hours. Rapid dengue antigen detection tests can be used in field settings and provide results in less than an hour. Currently, these assays are not sero-type-specific, are expensive and are under evaluation for diagnostic accuracy and cost-effectiveness in multiple settings. The dengue guide summarizes in Chapter IV various dengue diagnostic methods and their cost (WHO/TDR, 2009).

For serological testing, the time of specimen collection is more flexible than that for virus isolation or RNA detection because an antibody response can be measured by comparing a sample collected during the acute stage of illness with samples collected weeks or months later. Low levels of a detectable dengue IgM response – or the absence of it – in some secondary infections reduce the diagnostic accuracy of IgM ELISA tests. Results of rapid tests may be available within less than one hour.

7 This would allow the surveillance system to adopt a more sensitive clinical definition without loss in specificity.

Fig. 1. Interpretation of dengue diagnostic tests

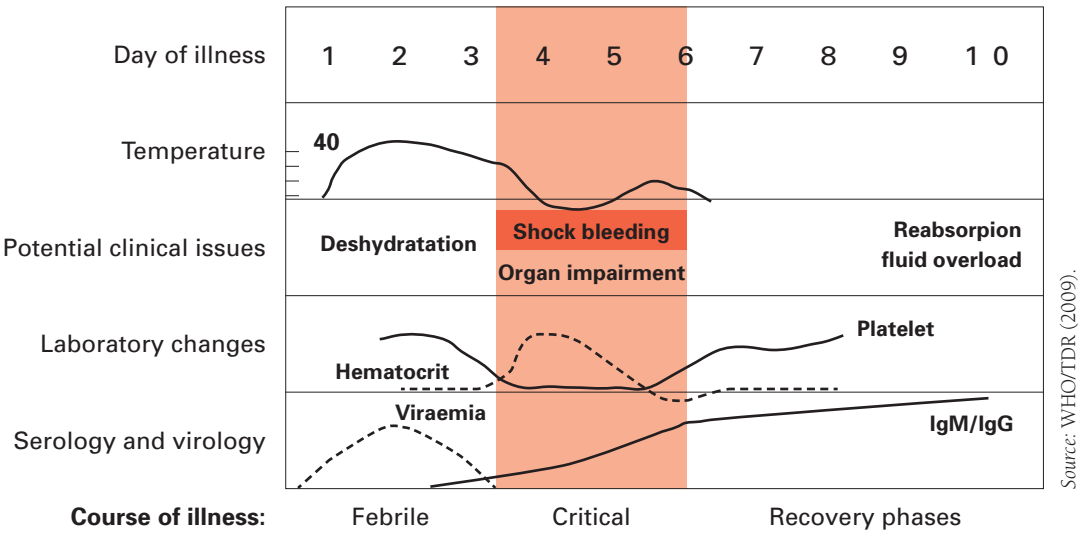
Highly suggestive	Confirmed
One of the following: 1. IgM + in a single serum sample 2. IgG + in a single serum sample with a HI titre of 1280 or greater	One of the following: 1. PCR+ 2. Virus culture + 3. IgM seroconversion in paired sera 4. IgG seroconversion in paired sera or fourlfold IgG titer increased in paired sera

HI: house index; PCR: polymerase chain reaction; IgG: immunoglobulin G; IgM: immunoglobulin M.
Source: adapted from dengue control (DENCO) study (WHO/TDR, 2009).

Unfortunately, an ideal diagnostic test that permits early and rapid diagnosis, affordable for different health systems, easy to perform, and with robust performance, is not yet available.

The dengue tests usually employed during the clinical illness are presented in Fig. 2 – see WHO/TDR (2009), tables 4.1 and 4.3, pages 93 and 96, respectively, for a summary of operating characteristics. But under resource constraints, it is important to consider additional ways to identify dengue outbreaks with limited availability of laboratory tests.

Fig. 2. Course of dengue illness



Source: WHO/TDR (2009).

The national contingency document should precisely specify how laboratory surveillance is going to function in an outbreak. For example, will laboratory surveillance just be used to confirm an outbreak or will it be performed continuously throughout an outbreak? What tests should be used, and to whom they should be sent, etc.? A flowchart and clear standard operating procedures (SOPs) are required. Details of laboratory-specific issues to be considered in a country contingency plan are summarized in Checklist 3.

Laboratory testing for outbreak investigations

During outbreaks, patients may present with fever with or without rash during the acute illness, others may present with signs of plasma leakage or shock, while others show signs of haemorrhage. Others may be observed during the convalescent phase. One of the priorities in a suspected outbreak is to re-confirm the causative agent (if it is dengue) so that appropriate public health and clinical measures can be taken. Samples collected from febrile patients could be tested by nucleic acid methods in a well-equipped laboratory or a broader spectrum of laboratories using an ELISA-based dengue antigen detection kit. If specimens are collected after day five of illness, commercial IgM ELISA or sensitive dengue IgM rapid tests may suggest a dengue outbreak, but results are preferably confirmed with reliable serological tests performed in a reference laboratory with broad arbovirus diagnostic capability. Serological assays may be used to determine the extent of outbreaks.

Dengue surveillance systems aim to detect the circulation of specific viruses in human or mosquito populations. The diagnostic tools should be sensitive, specific and affordable for the country. Laboratories responsible for surveillance are often national reference laboratories.

CHECKLIST 3. LABORATORY-SPECIFIC ISSUES FOR A NATIONAL CONTINGENCY PLAN

1. Laboratory confirmation of reported cases is recommended, but also suspected (probable) cases should be reported
2. Laboratories should report positive results directly to the surveillance system
3. Details for viral isolation, PCR, NS-1 ELISA, serological confirmation by IgM IgG, rapid diagnostic test (RDT) use, storage and transport of samples should be provided (see WHO/TDR, 2009)
4. The purpose of tests, test results and their interpretation should be stated
5. A flowchart about timing of tests and destination of samples should be provided
6. Laboratory specific processes of outbreak investigation and confirmation should be defined
7. Quality control of laboratory tests should be ensured (usually by the reference laboratory)
8. Training and capacity building for laboratory staff should be implemented
9. Prevention of stockouts in the laboratories should be in place
10. Laboratory networks need to be established
11. Information about the circulating serotype/genotype should be documented and used for surveillance purposes

Other forms of active surveillance[8]

Other forms of active surveillance can complement the enhancement strategies of a routine surveillance system described above, for example:

a) sentinel surveillance[9]

b) active case finding

c) motivation, calls and other outreach activities.

2.2.4 Sentinel surveillance

Virus surveillance is often performed in: (a) sentinel sites, mainly major hospitals, by sending a randomized subsample of blood specimens to national laboratories for serotyping and genotyping; (b) syndromic surveillance approaches are often sentinel based (Randrianasolo et al. 2010; Kuan et al. 2010); (c) in some systems, data are from a subsample of dengue patients, the information is analysed in depth so increasing data quality and allowing for more comprehensive laboratory testing – however, it is important to ensure representativeness of sentinel sites by proper randomization of samples (Huy et al. 2010); (d) sometimes travellers are used as sentinels when returning from disease endemic countries (Domingo et al. 2011; Schwartz et al. 2008), and the results are reported to international surveillance networks.

2.2.5 Active case finding

Active case finding around a dengue index case is appropriate to confirm local transmission or to investigate an imported case. Also it could help to assess the size of a local outbreak. See experience from Cuba (Kouri, 1998) and Taiwan (King et al. 2000; Lin et al. 2010).

2.2.6 Motivation

Different motivation strategies have been developed in order to improve doctors' and nurses' reporting mentality. This might be done by telephone calls[10] asking for the cases to be reported, but it might require additional staff.[11]

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[8] **Active surveillance** involves outreach by the public authority, such as regular telephone calls or visits to laboratories, hospitals and providers to stimulate reporting of specific diseases. It places intensive demands on resources and should be limited to specific purposes (Thacker et al 1986).

[9] **Sentinel surveillance** is a special form of active surveillance. It involves collecting case data from a sample of providers and then extrapolating them to a larger population. The advantage is that it is less expensive (being restricted to small areas) and produces data of higher quality. The disadvantage is the inability to ensure that the sample population is representative (Thacker et al. 1986).

[10] **Passive surveillance** plus sentinel sites using telephone calls with virus surveillance in Cambodia increased the sensitivity of detecting outbreaks (defined as crossing of case numbers the 2 SD line above the mean) (Runge-Ranzinger, 2010).

[11] One study described an enhanced routine surveillance system in Puerto Rico by motivating public health staff which resulted in an increased incidence of reported dengue three times above the incidence during the two most recent epidemics in 1994 and 1998 (Ramos et al. 2008).

2.2.7 Entomological surveillance

"Standard" entomological indicators of the presence of the urban yellow fever vector and dengue vector were developed primarily for monitoring the progress of the *Aedes aegypti* eradication campaign in the Americas in the late 1940s. The three classic *Stegomyia* indices – the house (or premise) index (HI), the container index (CI), and the Breteau index (BI) – are all based on the presence or absence of immature stages of the vector in water-holding containers and confined natural habits close to or inside dwellings or other buildings. When vector densities are very low, ovitraps have been used to determine presence or absence of the vector. While these indices can be used to monitor discrete abundance changes in localized areas, they do not define how much vector control would be needed to reduce, interrupt or prevent viral transmission – indeed no standardized, evidence-based thresholds exist (Bowman, Runge-Ranzinger & McCall, 2014). Of particular concern is that such thresholds for vector control measures in dengue are influenced by a variety of factors, especially serotype-specific (and perhaps genotype-specific) herd immunity and temperature. Focks (2003) showed that the pupal productivity survey technique was promising in identifying those container habitats that contributed disproportionately higher numbers of adult vectors, and thereby guide programme managers in the application of more cost effective, targeted approaches (Tun-Lin et al. 2009). It was envisaged that pupal productivity surveys could help to elucidate the transmission dynamics and identify the risks of dengue transmission (Nathan et al. 2006) by complementing "larval surveys" as a routine vector surveillance tool. Table 3 shows the attempt by Focks et al. (1995; 2000) to estimate the requisite vector abundance (using pupae per person – PPP – as a proxy measure) that would result in ≥10% rise in sero-prevalence of dengue antibody during the course of a year under conditions of a single viral introduction by one or two viraemic individual(s) (in brackets in Table 3) on day 90 of the year. In a series of simulations in a Dengue Simulation Model (DENSiM), these values resulted in a ≥10% rise in prevalence approximately 50% of the time (Focks et al. 2000). This means that at 32° C environmental temperature in a population with no herd immunity (sero-prevalence = 0), only 0.07 PPP are sufficient to increase the sero-prevalence in this community by 10% or more. In a community with 67% sero-prevalence, 0.26 PPP is needed for a similar increase. In areas with temperatures of 22 °C, it would require 30.55 for the same effect.

Table 3. Transmission thresholds by initial sero-prevalence of antibody

Temperature (°C)	0%		33%		67%	
22	9.57	(9.16)	14.10	(12.83)	30.55	(29.15)
24	2.92	(2.68)	4.47	(4.21)	9.22	(8.68)
26	1.42	(1.23)	2.03	(1.98)	4.26	(4.01)
28	0.53	(0.48)	0.75	(0.72)	1.69	(1.38)
30	0.13	(0.12)	0.19	(0.18)	0.38	(0.35)
32	0.07	(0.07)	0.10	(0.10)	0.26	(0.18)

Source: Focks et al. (1995; 2000).

A systematic literature review found little evidence of quantifiable associations between vector indices and dengue transmission that could reliably be used for outbreak prediction. It highlighted the need for standardized sampling protocols that adequately consider dengue spatial heterogeneity. Single values of BI or other indices were not considered reliable universal dengue transmission thresholds, especially the traditionally used BI where a threshold of BI>5 was shown to be inappropriate (Bowman, Runge-Ranzinger & McCall, 2014).

In summary, entomological indices may have a potential for outbreak alert, but the evidence is weak (see also Gubler, 2002). Additionally, the operational issues of routine vector surveillance are often hampered by the lack of resources, lack of local-level involvement in decision-making, limitations in supervision, increasing vector resistance to larvicides and difficulty in interpreting entomological indices (Badurdeen et al. 2013).

Chapter 3
Outbreak alert and outbreak detection

3.1 Seasonal increase of cases

The seasonal increase of dengue cases, usually during or just after the rainy season (see Fig. 3) has to be distinguished from the unexpected increase of cases above a defined threshold, which is usually called an outbreak (Stroup et al. 1989; Heymann, 2004). The number of reported cases exceeding expected levels is referred to as "aberrations" (Farrington & Andrews, 2004). Dengue control and clinical care systems need to respond differently to each of these scenarios. The expected increase of dengue vectors and subsequently of cases during the "dengue season" requires routine measures be stepped up at a relatively predictable point each year. The annual need for increased vector control staff should correspond to the weeks when the vector density increases, and preparations should be made for adequate staffing levels, equipment and supply (including chemicals and/or biological agents, IEC materials and other elements of social mobilization). Similarly, clinical services' annual plans should define the additional staff, equipment, reagents and treatment units needed, and identify whether clinical refresher courses are required. The dengue outbreak as an "unexpected increase of cases" requires additional efforts complementing the above mentioned as described below.

3.2 Outbreak as an unexpected increase of cases

3.2.1 Outbreak definition

From a public health perspective, a clear and universally accepted definition of an outbreak is important even if the thresholds of case numbers may vary among countries or regions. A standardized outbreak definition can help to send uniform messages to inform the general public and make the outbreak analysis comparable within and between countries. However, it has to be emphasized that the response to an outbreak should be triggered much earlier than the start of the outbreak. Possible thresholds and alert algorithms are described below.

3.2.2 Challenges of using surveillance data for detecting an outbreak

Outbreak definitions based on thresholds of epidemiological data (number of cases or incidence rate) rely on the timely analysis of local surveillance data (for example, at district level and the number of cases per week) to establish if cases are above a pre-defined threshold, which varies according the season. The reliance on surveillance data to detect an outbreak at an early stage is challenging when there is inadequate data to determine a reference or baseline value. Thresholds, such as an excess of reported dengue cases in low- or high-transmission seasons above a defined level (for example, z times SD above the "moving mean" of cases in the previous five years), have been considered useful (Stroup et al. 1989; Rigau-Perez et al. 1999). However such thresholds should be integrated into a locally adapted early warning tool that also includes other alarm signals.

A multi-country study in 10 countries found a wide variety of outbreak definitions used as the alert threshold (Badurdeen et al. 2013).

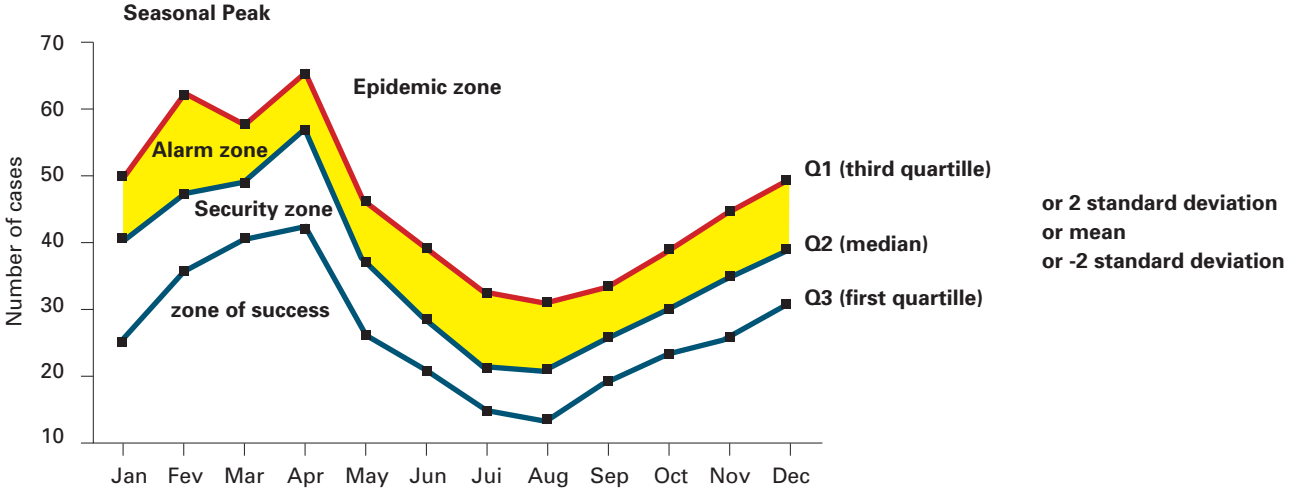
3.2.3 Definitions of a dengue outbreak showing marked differences

- Case numbers 2 SD above the mean of the preceding five years shown in endemic channels – Columbia, the Dominican Republic, Peru (partially), Viet Nam (national level).
- Case numbers >2 SD "4–weekly average" above the mean of "three 4-weekly averages" in the five preceding years ("moving mean" in Brazil; in Malaysia the five-year moving median is used as an alert at state and national levels).
- > 300 cases per 100 000 population at the local level (Brazil).
- > 10 cases per week in a local area (Sri Lanka).
- Two or more connected dengue cases at local level (in Malaysia and Mexico, and partially in Sri Lanka).
- Case number in a commune within two weeks: 2–20 cases = mild outbreak; 20–100 cases = moderate outbreak; > 100 cases = severe outbreak (Viet Nam).
- No clear outbreak definition but larval indices as trigger for response: BI <6= routine response; BI = 6–20 = house-to-house checks; BI> 20 = fogging (Sri Lanka).

3.2.4 Outbreak detection using the "epidemic channel"

Many countries use, in some way or another, the "endemic channel" for visualizing the expected case levels with the weekly (or monthly) average number of cases over the last five years and above a line which "traditionally" represents the arbitrary threshold value of +2 SD; others use the median and the third quartile (see Fig. 3).

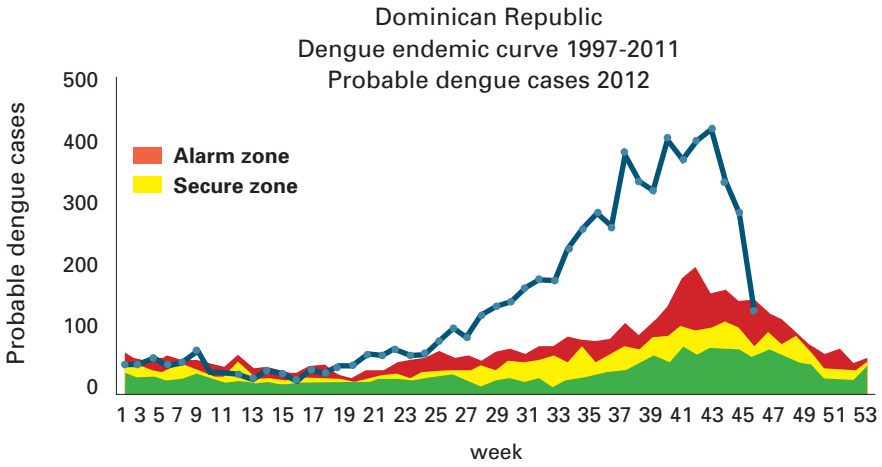
Fig. 3. Illustration of the seasonal variation of a vector-borne disease like dengue



Source: authors' calculations.

The area between the lines of the mean and +2 SD is called "alert zone" or "alarm zone" and the area above the +2 SD line or third quartile line is called the "epidemic zone" showing the aberrations (Fig. 3). If the weekly number of dengue cases crosses the "historical" 2 SD line, then it is called an "outbreak". Fig. 4 shows a dengue outbreak with the blue line of "weekly number of cases" crossing the +2 SD line several times between week one and 17 until the case numbers shoot up in week 18.

Fig. 4. Illustration of a dengue outbreak



Note: shows the number of new cases crossing the "historical" +2 SD line from week one to 17 several times before in week 18 the case numbers rise definitively.
Source: Ministry of Health, Dominican Republic, personal communication (2015).

According to experts at an international WHO meeting (Badurdeen et al. 2013), the following advantages of using the endemic channel for the outbreak definition were: (a) the "endemic channel" is a simple instrument and the crossing of the upper threshold line is easy to assess; (b) there is a standard definition of a dengue outbreak that can be used to inform the mass media and the public about the actual situation; (c) it is possible to determine the size of an outbreak in terms of duration, the total number of dengue cases, and the case fatality rate during the outbreak, thereby facilitating in-country and cross-country comparisons; and (d) it helps to assess the effect of response mechanisms and to define "stopping rules" (when the intensified response can be terminated).

Possible disadvantages of such a definition are: (a) programme managers may be tempted to use the crossing of the upper threshold line as a trigger for response to an outbreak rather than as an outbreak definition indicating that the outbreak is effectively already underway and thus initiate a delayed emergency response (see below); (b) the limited sensitivity and specificity of the definition – only 40% of such events when case numbers crossed the +2 SD threshold

were followed by a "massive" increase of cases in Puerto Rico (Rigau Perez et al. 1999a) and, using a similar predictor with a 1 SD threshold, Barbazan et al. (2002) found a sensitivity of 66%; (c) outbreaks in previous years can result in thresholds that are too high, however, no satisfactory algorithm for recognizing past aberrations has been devised (Farrington & Andrews, 2004) and consequently the values of "outbreak years" are usually not deleted from calculations of the historical (moving) average.

3.2.5 The moving average or deviation bar chart

The seasonal increase of cases may come earlier than in the five preceding years giving the impression of an outbreak. This phenomenon has been handled by using the "deviation bar chart" (Rigau-Perez et al. 1999) or the "moving average" used for instance in Brazil and Malaysia[12] ("moving median"); in this case, the average number of dengue cases across four weeks is compared with the average number of cases during a period of 12 weeks in the preceding five years (that is, the same four weeks as the actual observation period plus four weeks before and four weeks after the observation period) (Stroup et al. 1989). In Puerto Rico, the sensitivity of such a "deviation bar chart" for indicating a dengue outbreak was 40% and the specificity was 90% (Rigau-Perez et al. 1999). For practical reasons, it was suggested that it might be better to use the historical moving average to calculate the epidemiological week of observation plus six weeks before and six weeks after the week of observation, in total 13 weeks (Bowman et al. 2016b). When the geographical units are too small, the variation of cases increases and may show wide oscillations.

3.2.6 Other outbreak definitions

The "incidence threshold" (that is, when the number of cases during a week passes a pre-defined threshold level, such as 300 per 100 000 population, as used in Brazil), probably needs more research regarding advantages and disadvantages, and especially with respect to sensitivity and specificity. The definition of "two interconnected dengue cases" should be limited to non-endemic areas. However, such an event may be used to trigger routine operations (combined peri-focal interventions) in local areas. Clustering is used for local settings, for example, two dengue cases in 28 days in one village or neighbourhood (as used in Singapore) triggering interventions.

Brady et al. (2015) modelled five different types of outbreak thresholds (recent mean, monthly mean, moving mean, cumulative mean and fixed incidence threshold) and, by doing so, identified highly heterogeneous outbreak characteristics in terms of frequency, duration and case burden. All definitions identify outbreaks with characteristics that vary over time and space. Definitions differ in their timeliness of outbreak onset, and thus may be more or less suitable for early intervention. They vary widely in their capacity to enable effective preventative outbreak measures, such as early detection and early response, with the conclusion that preventative control may be more heavily reliant on early warning systems that predict outbreaks based on temporal anomalies in epidemiological and environmental warning signals.

[12] Numbers >2 SD "4-weekly average" above the mean of "three 4-weekly averages" in the five preceding years ("moving mean", Brazil; in Malaysia the five-year moving median is used as alert at the state and national level).

3.3 Alarm signals

An alarm signal is when the weekly case numbers enter the "alarm zone" (Fig. 4). In addition to the alarm signals based on "excess reporting" of cases, there are a variety of other potential alarm signals. They may either be thresholds based on syndromic surveillance systems or other indicators associated with high dengue transmission such as climatic indicators.[13] Specific alarm signals used in the low transmission season ("dry season") may also trigger an early response.[14] Such alarm signals are considered to be important for triggering early response but they have to be validated before using them in a national programme. Additionally, the feasibility of applying such signals varies from country to country meaning that each country has to select the set of signals most useful for them. A WHO expert meeting proposed the candidate alarm signals[15] summarized in Table 4. Also compare to Example 2 page 12.

[13] Fan et al. (2014a) analysed systematically from 1589 identified articles 137 full text, with 33 satisfying inclusion criteria and found that the closest associations between dengue and **temperature** were observed between mean temperature from the included studies (23.2–27.7° C) and dengue fever (odds ratio – OR – 35.0% per 1 ° C; 95% container index (CI) 18.3–51.6%) positively. Additionally, minimum (18.1–24.2 °C) (29.5% per 1 °C; 20.9–38.1%) and maximum temperature (28.0–34.5 °C) (28.9%; 10.3–47.5%) were also associated with increased dengue transmission. The OR of dengue fever (DF) incidence increased steeply from 22 °C to 29 °C, suggesting an inflexion of DF risk between these lower and upper limits of DF risk.

[14] In Cambodia, reporting of dengue **surpassing the threshold of 2 SD during the low season was predictive for an outbreak** (2 SD above seasonal variation) during the following dengue season (Tourdjman, Huy & Vong, 2005).

[15] Candidate indicators for predicting a dengue outbreak or for early outbreak detection through "syndromic surveillance" (Buehler et al. 2004) in order to trigger an early response have been proposed. However, a literature review (Runge-Ranzinger et al. 2008) found that there were no systematic analyses or validations of these putative indicators or of their operational reliability and cost-effectiveness.
Retrospective studies, particularly from Singapore, suggested that a **serotype or even genotype shift is associated with increased dengue transmission**, often with a lag time of around six months. A serotype switch from DENV-2 to DENV-1 in 2004/2005 was associated with the 2005 epidemic (Lee et al. 2010; Koh et al. 2008). According to Schreiber et al (2009), viral genome sequencing would not have been sufficient to predict this outbreak. A switch from DENV-1 back to DENV-2 in early 2007 was used as a warning sign and led to response actions, which were perceived to reduce the impact of the outbreak six months later in 2007/2008. A clade replacement within DENV-2 was also discussed as a contributing factor to the 2007 outbreak (Lee et al. 2010) and was involved in a larger outbreak at the end of 2010 (Lee et al. 2012). However, the studies did not include negative controls and it may have been a site-specific event, depending on the herd immunity, population size, co-circulation of dengue viruses and other factors. Only countries with serotype/genotype-specific surveillance will be able to follow up their pattern.
Three surveys in Surabaya/Indonesia investigated prospectively the correlation of DENV type and disease incidence. An increase in case numbers in 2010 was attributed to a genotype shift in DENV-1 from genotype DENV-4 to DENV-1, which took place between April and September 2009 (Yamanaka et al. 2011).
Retrospective analysis of serotype-specific surveillance data in the Pacific region (Li et al. 2010) demonstrated that the rapid replacement of DENV-1 by DENV-4 in the region was associated with dengue outbreaks in 2008 and 2009 in Kiribati, New Caledonia, Samoa, Tonga and other islands. The appearance of a new serotype as a warning sign is described in Rio de Janeiro, Brazil (De Simone et al. 2004), Bolivia (Pirard et al. 1997), Grenada (Schiøler, 2006), Puerto Rico (Rigau-Pérez et al. 2002) and Viet Nam (Tien et al. 1999).
In Bolivia, a dengue serotype 2 (DENV-2) outbreak occurred at the same time as DENV-2 was detected as a newly introduced virus (Pirard et al. 1997). In Grenada, an epidemic occurred with a two-month delay after the index case with a new serotype (Schiøler 2006). In Brazil, the first autochthonous DEN-3 transmission was detected in December 2000, but the outbreak in 2001 was due to DENV-1/DENV-2 and the expected DENV-3 epidemic started only in 2002 with a delay of almost two years (De Simone et al. 2004). In Viet Nam, DENV-3, which was first detected in 1994, spread gradually and led to an epidemic in 1998. In Puerto Rico, virus surveillance revealed an unexpected paradox: the 1998 epidemic after DENV-3 introduction was predominantly due to DENV-1/DENV-4, while DENV-3 took over in 1999 but without causing an outbreak. Rigau-Pérez et al. (2002) also described a change of predominant serotype, or the introduction of a new one.
Virus isolation rate as a percentage of positive blood samples in the low season based on routine virological tests was a predictor of dengue outbreaks in Puerto Rico (Rigau-Pèrez et al. 2001) and Viet Nam (Tien et al. 1999). One study from Singapore mentioned that, during the 2007/2008 epidemic, the proportion of DENV positive samples detected by PCR rose from 57.9% in January 2007 to 91.0% in July 2007 at the peak of transmission (Lee et al. 2010). This had also been observed in Puerto Rico (Rigau-Pérez & Clark, 2005).

Table 4. Proposed candidate alarm signals (triggers for early response)

Trigger	Evidence or expert opinion	Evidence from the literature	Feasibility	Further research needed
New predominant serotype introduced	+++	++	Most countries	+++
Changes in age group distribution	++	+	Most countries	+++
Increased number of hospitalized/ outpatient fever cases/probable dengue* (threshold)	+++	++++	Most countries	+++
Increase in vector presence	++	+	Most countries	+++
Increase in news reporting dengue outbreaks, social network comments	+	++	Few countries	++++
Climate changes: increase in rainfall/ temperature/humidity	++	++	Most countries	+++
Increase in % positive serology*	++++	++++	Most countries	++
Increase internal displacement/ population mobility	+	+	Context dependent	++++
Cluster identified through GIS mapping	++	+++	Few countries	+++
Identification of outbreak in a neighbouring geographical unit (state, district, province, country)*	++++	++++	Most countries	++

GIS: geographic information system; *Particularly useful indicators/triggers.
Source: WHO/TDR expert meeting recommendations (2012).

Syndromic surveillance may contribute important alarm signals for early dengue outbreaks (see Chapter 2). These include: level of school absenteeism; volume of Internet-based health inquiries; malaria negative rate in fever patients; non-specific laboratory requests as malaria negativity rates or as thrombocytes requested; and fever alerts or clinical syndromic definitions.

Other approaches such as the use of socioeconomic indicators for risk assessment or environmental parameters as well as modelling tools are being discussed; however they are either very site-specific or not yet sufficiently developed. However they may play a relevant role in the identification and prioritization of the 'risk areas' within a geographical area in order to specify where interventions need to be focused after an alert is given.

In order to clearly link increased dengue transmission as predicted by defined alarm signals to the required response, it is crucial to define the level of transmission at which a specific response should be started. A WHO expert meeting in 2012 suggested the triggers for early or late response (Baburdeen et al. 2013) as presented below:

3.3.1 Staged alerts/outbreak alarms

Small-scale interventions or preparedness activities have to be put in place prior to a full outbreak (see Fig. 5).

If case numbers rise above a pre-defined threshold and/or the alarm signals and/or integrated alert algorithm is positive, some action has to be taken (initial, early or late response, see Chapter 4).

Control measures come too late when they are implemented at the start of an outbreak ("late or emergency response", see Brookmeyer & Stroup, 2004). It is therefore recommended to react in a timely and structured way when the alarm signals indicate the threat of a dengue outbreak e.g. by using a staged response scheme. The combination of these signals may vary between countries and also depends on the availability of resources. The real difficulty lies in "…setting up appropriate protocols for deciding which signals to investigate and which to ignore and for communicating effectively the role and limitations of automated systems" (Farrington & Andrews, 2004).

An example of a comprehensive surveillance system is given in Fig. 5.

3.3.2 A new evidence-based model of outbreak alert

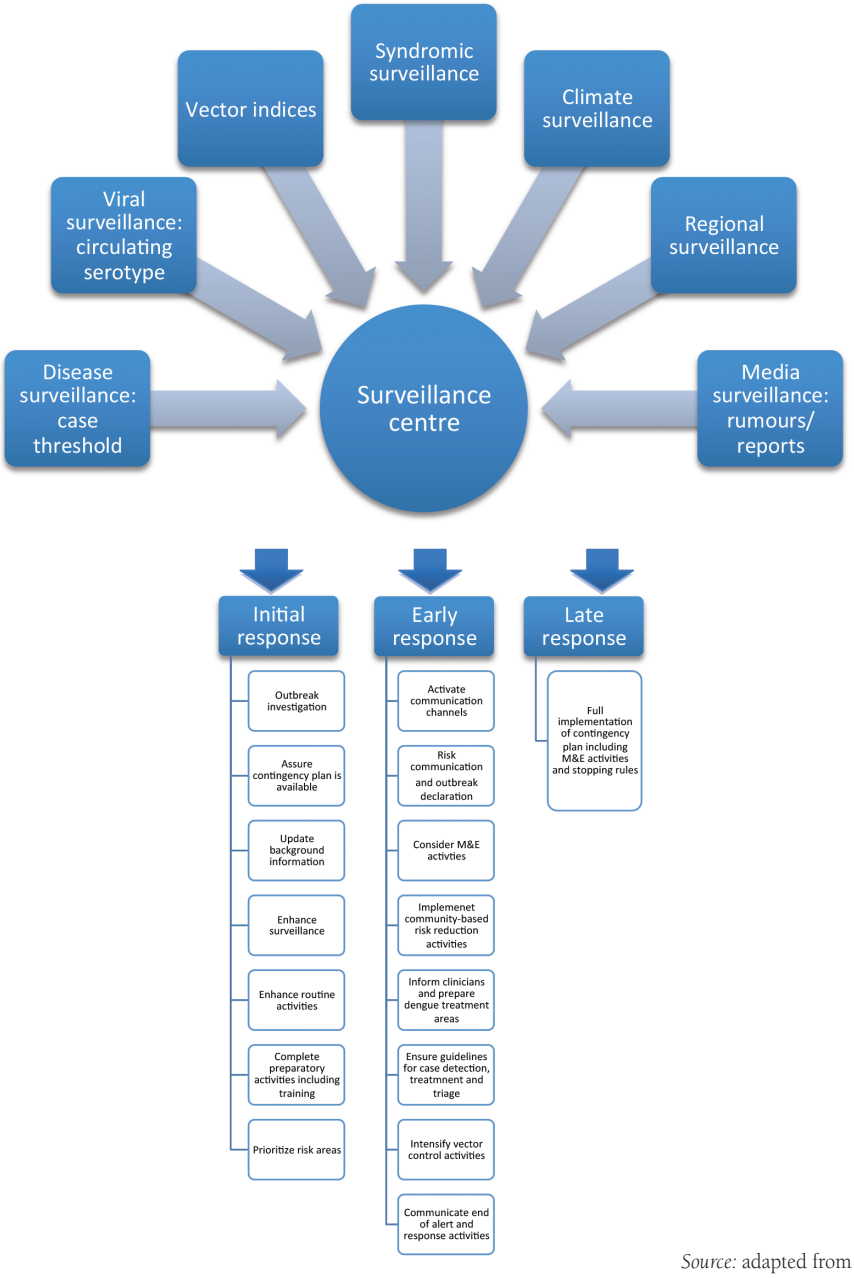
A retrospective analysis of five countries in Asia and Latin America demonstrated that it was possible to sensitively detect outbreaks with a low false alarm rate using a combination of the Shewhart method to define alarm signals, and the endemic channel to define outbreaks.

Outbreaks were defined when incident dengue cases were above 1.25 times the SD of the moving mean for two consecutive weeks, and ended when incidence was below the SD for two consecutive weeks. Alarms were triggered after two or more observations in the explanatory variable were above a threshold within a period of one to 12 weeks prior to the outbreak. This threshold was calculated using the outcome of logistic regression analyses between explanatory and response variables among the historic dataset.

An increase in probable cases was indicative of outbreaks, while meteorological variables, particularly mean temperature, demonstrated predictive potential in some countries, but not all. Notably, some of the highest metrics were across Mexico and the Dominican Republic, where an increase in probable cases predicted outbreaks (incident hospitalized cases) with sensitivities and PPV of 93%/83% and 97%/86%, respectively, at a lag of one to 12 weeks. Also, an increase in mean temperature predicted outbreaks (incident hospitalized cases) in Mexico and Brazil, with sensitivities and PPVs of 79%/73% and 81%/46%, respectively, again at a lag of one to 12 weeks (Bowman et al. 2016b). Additional indicators such as rainfall and mean relative humidity also showed promise, but were inconsistent across the countries.

In summary, incident-probable dengue cases could be used in early warning systems to highlight the onset of dengue outbreaks, while meteorological variables may be used to indicate an increased risk of epidemic dengue transmission. This mirrors findings reported elsewhere (Hii et al. 2009; 2012). However, further research is needed at increasingly granular scales to capture the finer dengue transmission dynamics that exist across neighbourhoods and smaller urban/rural areas (Bowman et al. 2016b). In addition, improved outbreak definitions that focus on the earliest phase of incidence, when interventions are likely to have a greater impact on transmission, should be a priority.

Fig. 5. Outbreak indicators potentially triggering Interventions



Source: adapted from Harrington et al. (2013).

3.4 Outbreak investigation

Elements of outbreak investigations (see also Hills et al, 2002) are presented in Checklist 4 and should be considered in the contingency plan.

CHECKLIST 4. **OUTBREAK INVESTIGATION**

1. Specific stakeholders responsible for investigating the outbreak (see list of possible stakeholders, Chapter 4.6, Table 6)
2. Description of the risk assessment scheme
3. Preparation of technical equipment
4. Designated person(s) to carry out the outbreak investigation
5. Interview with the index case, or alternative method of establishing clinical and epidemiological details
6. Analysis of epidemiological data, epidemic channel
7. Active case finding strategies to confirm local transmission and assess size of the event

3.5 Outbreak declaration and risk communication

Once an outbreak has been detected by applying a set of pre-defined criteria fulfilling the outbreak definition (for example, case numbers cross the 2 SD line), it should be declared in order to make stakeholders and the general public aware of the epidemic. Risk communication is a fundamental element of managing an emergency public health threat to encourage positive behavioural change and maintain public trust (WHO 2010). However, outbreaks are highly charged political and social events whereby "outbreak declaration and transparency from expert to audience is surrounded by political and economic overtones, often bogged down with questions of blame which may be critical in a fractious political system" (Abraham, 2011). In order to avoid politically biased decision-making, an institutional, automated or algorithm-based system for verification and declaration of an epidemic is of importance.

Checklist 5 summarizes elements of the contingency plan for risk communication and Fig. 5 the outbreak indicators potentially triggering interventions.

CHECKLIST 5. **RISK COMMUNICATION**

1. Who is the responsible technical person with the mandate to declare the outbreak? Who is the official spokesperson?
2. Method and interval timing for informing clinicians/health workers should be specified
3. Method and timing for informing the public of an outbreak should be specified
4. How to work cooperatively with the media?
5. The risk communication methods and channels should be determined based upon the urgency of the communication (risk or crisis communication), resources and trusted national/ local communication channels

Chapter 4
Outbreak response

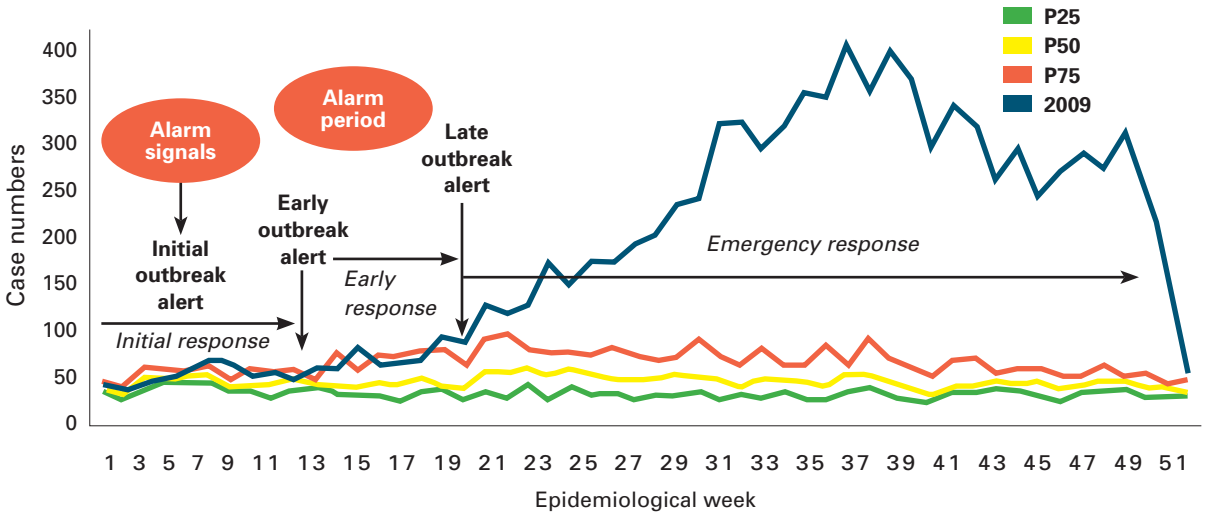
4.1 Characteristics of a dengue outbreak

The term "'outbreak'" (used synonymously with "epidemic") is defined as a "'sudden unexpected increase of cases'" or as "the occurrence in a community or region of cases of an illness clearly in excess of expectancy" (Heymann et al. 2004). Such a "sudden and unexpected increase" (outbreak) is different from the seasonal peak, which is an "expected increase in cases" that usually occurs during or immediately after the wet season (see Chapter 3). In an analysis of dengue outbreaks in 10 countries, it was found that the average duration of a dengue outbreak at provincial, regional and state levels was recorded as 10 months (range five to 13 months) and the average number of cases was 26 732 (range 12 171 to 69 680 cases) (Badurdeen et al. 2013). A more detailed analysis in Brazil showed that the average incidence rate of dengue cases during outbreaks was 538 per 100 000 population (Teixeira et al. 2013).

4.2 Staged response

Staged response means that response activities are initiated according to the level of alert (Fig. 6).

Fig. 6. Illustration of the different phases in the development of a dengue outbreak and different levels of response



Source: Badurdeen et al. (2013).

4.2.1 Example of trigger signals for response activities

The following initial/early/late alarm signals are applied in the above-mentioned retrospective study (Bowman et al. 2016b) and are currently being tested in a prospective study.

Initial response

- One alarm indicator with one alarm signal (that is, one observation above the alarm threshold) for two weeks.
- Two or more indicators with one alarm signal where a maximum of one indicator has two alarm signals, for example, temperature one alarm signal (positive for one week), probable cases, two alarm signals (positive for two weeks), OR temperature, rainfall and probable cases with one positive signal each.

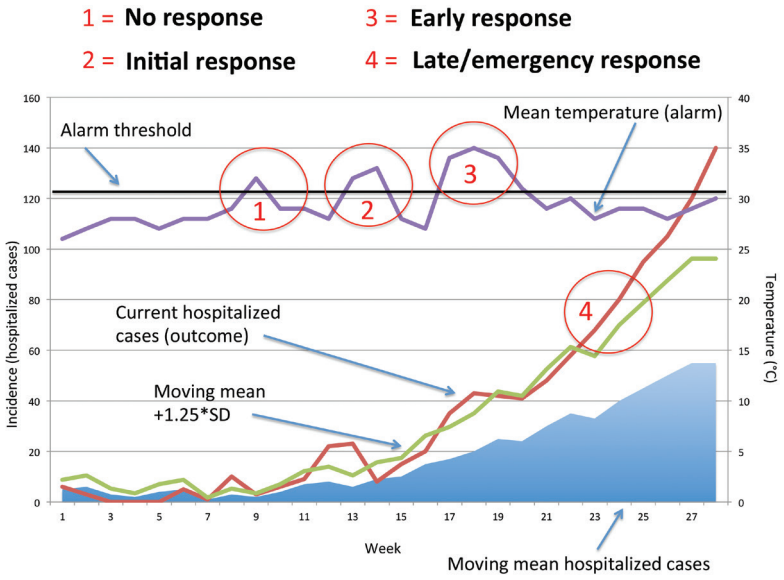
Early response

- A single alarm indicator has three alarm signals.
- Two or more alarm indicators with presence of alarm signals for two or more weeks.
- When dengue case numbers cross the z* SD threshold.

Late response (= emergency response)

Response is initiated when the outbreak has started, that is, when case numbers are above z* SD for three weeks (note: the need for an emergency response would be further reinforced if alarm signals had been present before the start of the outbreak).

Fig. 7. Illustration of how alarms are captured triggering the staged response system



4.2.2 Example of staged response activities

The following sets of interventions at the three different outbreak response levels were selected by the study countries according to their national context, and summarized here as an example.

Initial response

- Conduct thorough outbreak investigation.
- Ensure contingency plan is ready (including specification on how to inform, what exactly needs to be done and who is responsible for each activity), as well as the application of existing vector control guidelines.
- Update the necessary background information (cartography, demographics, etc.).
- Convene Dengue Task Force and trigger the Health Promotion and Communications team to make sure outbreak messages and materials are ready (for example, radio/TV spots, messages for release via social media, pamphlets, posters, school-based activities, workplace-based activities, etc.) for the implementation of risk communication and dengue risk-reduction activities.
- Prioritize risk area for interventions informed by: (a) current epidemiological metrics; (b) high-risk locations such as cemeteries and construction sites; and (c) areas that experienced recurrent or recent outbreaks.
- Ensure human, financial and logistic resources.
- Convene local dengue committees.
- Enhance surveillance by activation of syndromic surveillance, sentinel sites or active components and scale-up laboratory confirmation.
- Enhance other routine activities, such as vector control and alerts for hospitals.

Early response

- Declare and communicate the risk: the Dengue Task Force in collaboration with the Health Promotion and Communication team will ensure communication of consistent risk messages to national, regional and local authorities, public and private health systems (hospitals, clinics, providers, laboratories, pharmacies), local dengue committees, and the private sector (safety officers at construction sites, factories, office buildings, etc.).
- Activate established communication channels to the appropriate sectors – public health, clinical care, education system, media, the public, and the national and international authorities.
- Ensure training of relevant workforce, if still not done.
- Implement community-level risk communication and dengue risk-reduction activities (for example, reduce mosquito breeding potential of water-holding containers, eliminate items not in use) in priority areas through community outreach teams, vector control field staff, local, municipal, regional health staff, private health providers in the priority areas.
- Implement communications outreach and dengue risk-reduction activities to schools and businesses in the priority areas.
- Intensify vector control by source reduction and fogging activities in prioritized high-risk areas (as defined above in **Initial response**) while ensuring quality of interventions (ideally impact assessment) and community support (messages should be disseminated to residents with clear steps on how to collaborate with fogging activities: leave

windows and doors open during fogging actions; close the house once the fogging has been completed; and do not enter the house for two to four hours after fogging).

- Identify high-risk areas for intervention by environmental, socioeconomic indicators or by GIS.
- Prepare dengue treatment areas in major hospitals and in high-risk areas (see below).
- Cease intervention activities after two negative alarm signals while conducting impact assessment by surveillance of vector population.
- Management of health services: (a) national/provincial/district steering committees; (b) circulate Hospital Dengue Preparedness and Contingency plans which should include plans for the mobilization of doctors/nurses within the region and from other specialties, and for surges in bed requirements.
- Alert hospitals and health centres: (a) distribute guidelines for case detection and treatment; (b) alert an outbreak management team; and (c) disseminate information about the end of the alert.

Early response in clinical settings

- Alert the outbreak management team; alert hospitals and health centres, district officer and distribute guidelines for case detection and treatment.
- Provide information developed by the Dengue Task Force Communications team.
- Prepare dengue treatment areas in major hospitals and high-risk areas.
- Engage the private health sector, including clinics, outpatient ambulatory offices, hospitals, pharmacies, and laboratories.
- Install and staff the Dengue Operations Centre/Dengue Command Centre/Dengue Situation Room (seven days a week).

4.2.3 Emergency response (or late response) after the outbreak has started

- Declare and communicate the urgency of the outbreak: The Dengue Task Force in collaboration with the Health Promotion and Communication team will ensure communication of consistent risk and crisis messages, should the ongoing outbreak warrant declaration of a crisis to national, regional and local authorities, public and private health systems (hospitals, clinics, providers, laboratories, pharmacies), local dengue committees, and the private sector (safety officers at construction sites, factories, office buildings, etc.). Full implementation of the contingency plan in collaboration with key partners such as Security Council, Ministries of Education and public works, local authorities, municipal sanitation services, representatives from the private sector and the media, and nongovernmental organizations (NGOs), among others.
- Maintain all activities described in the Early Response checklist while increasing the intensity and geographical scale of the vector control actions. Hence, where positive dengue cases are confirmed, the vector control response should be delivered throughout the entire district.
- Implement outreach and dengue risk reduction activities with schools, businesses and markets in the expanded geographical areas.

- Sustain response measures until the outbreak has been officially declared ended (that is, case numbers have been below the z* SD threshold for three weeks). If activities are terminated too early, the outbreak may simply be shifted to a later date, but if the measures are stopped too late, resources may be wasted.

4.3 Elements of a successful outbreak response

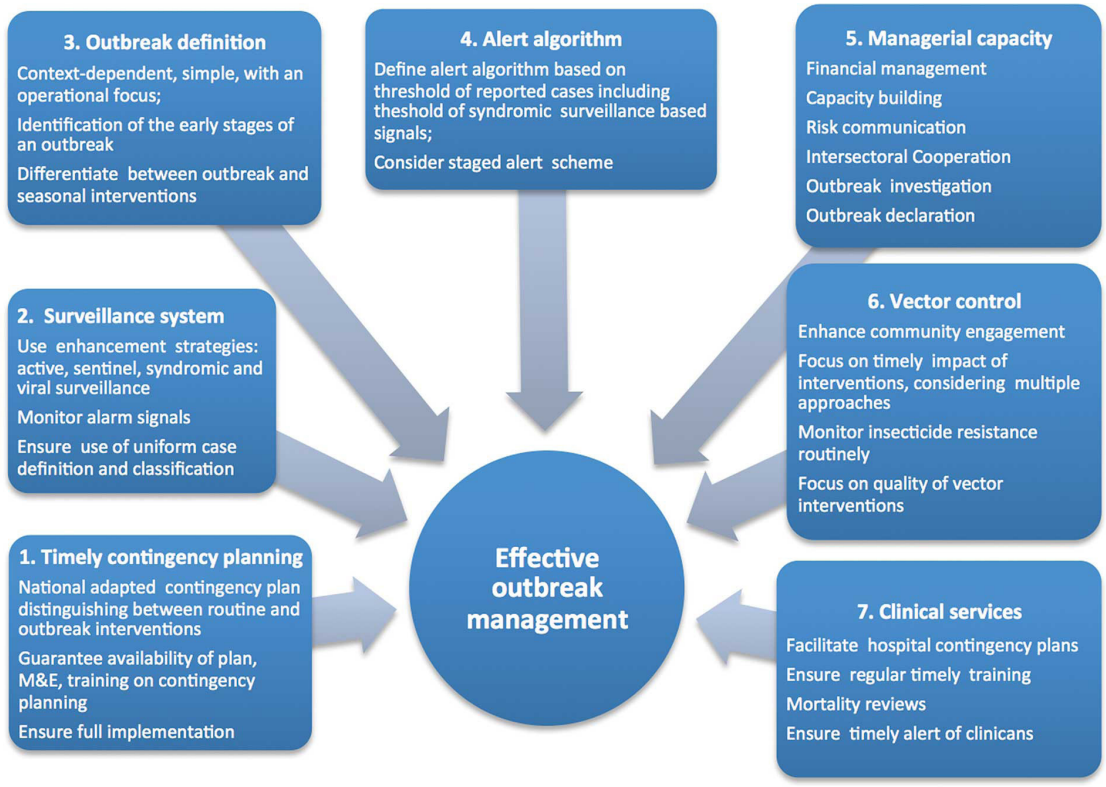
Following a systematic literature review (Pilger et al. 2010), the elements of a successful outbreak response were extracted and are presented in Table 5. Further details of good practices leading to an adequate response are given in Fig. 8. They will be presented in the following sections.

Table 5. Elements of a successful outbreak response

I. Management of outbreak response	• Organization of multidisciplinary response teams • Incorporation of public organizations in multidisciplinary response teams • Use of mass media, print and interpersonal communication to update the public on the outbreak, reassure the community that actions are being taken, and encourage public participation in dengue risk-reduction activities • M&E of all control activities
II. Management of vector control services	• Organization of "search and destroy" teams • Incorporation of communities in vector control activities • Systematic geographical coverage of activities • Collection of data on cases to enhance surveillance • Education of households on the elimination and control of mosquito breeding sites and importance of neighbourhood fogging
III. Management of health services	• Training of hospital personnel in rapid diagnosis and correct treatment • Training of laboratory personnel • Provide adequate supplies for laboratory analysis and case management • Use of mass media, print and interpersonal communication to inform the community of appropriate health-care seeking, including immediate care in the presence of the dengue warning signs • Use of mosquito nets in hospitals to reduce transmission • Establishment of case report conferences

Source: Pilger et al. (2010).

Fig. 8. Different elements of good practices leading to effective outbreak management



4.4 Health system and management aspects

The contingency plan should briefly summarize the structure of the health system defining stakeholder involvement in dengue prevention and control activities as below:

- the landscape of stakeholders;
- the political level that will coordinate the outbreak response;
- the roles, responsibilities and communication pathways of:
  - public health sector
  - entomologists and assistants
  - environment sector (waste disposal unit/urban development sector/water services)
  - private health sector
  - NGOs, civil society and other organizations (including religious groups)
  - education sector
  - any other relevant sectors of the locality (sports groups, youth clubs, etc.).

Specifically, an Outbreak Response Team/Action Committee should be established at the national (for example Dengue Task Force) and local level. Possible members are presented in Table 6.

The description of the teams and their tasks includes:

- defining team members;
- defining the objectives of the team;
- define the roles of each member of the team;
- setting out when and how often the team should meet to discuss and monitor the outbreak response;
- describing how the team will communicate during inter-epidemic and outbreak phases;
- ensuring information links with neighbouring countries (for national team), and neighbouring districts (for local team) for early outbreak detection.

CHAPTER 4
Outbreak response

It is important to guarantee intersectoral compliance with a regulatory framework in terms of financial and operational participation after a thorough capacity analysis. The focus on 'what' should be implemented and 'who' should do it is crucial. Functional details of the roles of stakeholders in relation to their capacity (for example, NGOs, civil society and the education sector) should be defined and updated.

The contingency plan should include information on M&E of the outbreak preparedness and response activities. This should include a matrix for the different elements to be monitored.

It is important to assess the additional human resources that will be required in a dengue outbreak, both in clinical management of cases and vector control. This includes redistribution of staff, scaling up of existing staff and extension of shifts (Barbosa da Silva et al, 2002; Badurdeen et al. 2013). Overwork and subsequent demotivation of health staff has been identified as a problem, such as increased demands by politicians and the community (Horstick et al. 2010). Therefore, staff training for an outbreak in the inter-epidemic period and supportive supervision during the epidemic can help staff cope with excessive challenges during the epidemic (Pilger et al. 2010). Investment in human resources training must be made prior to the outbreak and the outbreak response plan requires a section that documents all the activities to be performed in the inter-epidemic period in preparation for an outbreak, particularly related to outbreak preparedness as opposed to preventative control (see Chapter 3). The contingency plan should also include the "stopping rules", that is, when and how to stop the outbreak response and continue with routine interventions.

Actions be considered for organization and management of the outbreak response is summarized below in Checklist 6.

CHECKLIST 6. **ORGANIZATION AND MANAGEMENT**

1. Identify who is responsible for organizing the actions, when and for how long should they be performed ("stopping rule")
2. Establish the M&E process at all levels (national, regional, local)
3. Determine staffing levels required for full vector control coverage and social mobilization
4. Define details of logistic/operational considerations of chemical mosquito control
5. State the role of the community, government teams and NGOs in vector control actions, and how to map and prioritize the risk area that needs to be covered
6. Mobilize the community to prompt appropriate health-care seeking behaviours, in particular regarding the dengue warning signs, and to participate in vector control activities e.g. fogging activities by opening the doors and windows of their homes, and to promote the destruction or proper management of mosquito breeding sites according to the national policy
7. Encourage strong local-level involvement
8. Identify individuals who are responsible for training at all levels (municipality, state, local authority, hospital, etc).
9. Train staff on their roles and responsibilities prior to an epidemic, with short, targeted training during an epidemic when necessary
10. Recruit additional staff during the outbreak, for example, from other geographical areas or systems
11. Maintain an emergency staff roster
12. Engage members of civil society, volunteers and the private sector
13. Mobilize resources and financial management
14. Create the appropriate legal framework for your activities

4.5 Vector management

Dengue prevention and outbreak mitigation still rely on vector control. Many approaches and tools are available to pursue this goal, and the likelihood of each method being successful depends on numerous factors, such as frequency of treatment, the geographical area treated and coverage, and the likelihood that communities within the target population will accept and adopt it. In some cases, the potential for success will be limited by the inherent properties of the method itself, while the potential for others may differ according to social or geographical contexts. Virtually all approaches should be considered within an integrated pest management programme. Many methods have been used frequently in dengue endemic localities worldwide and a number of recent reviews have evaluated the evidence for their effectiveness. In the examples below, the main results of the systematic literature reviews analysing specific interventions are presented initially, followed by systematic reviews (SR) analysing all interventions in a comparative analysis, SRs looking at specific services related to outbreak interventions, and finally SRs looking at vector control services in general. Clear conclusions are rarely possible, as the quality and comparability of available literature is quite limited.

4.5.1 Control of dengue vectors with insecticides

Insecticidal space spraying/fogging for adult mosquito control

Peridomestic space spraying, using different insecticides, is one of the most commonly used dengue vector control methods. The systematic review by Esu *et al.* (2010) included 15 studies of which 13 showed reductions in immature entomological indices that were not sustained for long periods. The remainder showed space spray interventions to be ineffective at reducing adult and/or immature entomological indices. Only one study measured human disease indicators, but its outcomes could not be directly attributed to space sprays alone. Although peridomestic space spraying is commonly applied by national dengue control programmes, there are very few studies evaluating the effectiveness of this intervention and there is no clear evidence for recommending peridomestic space spraying as a single effective control intervention.

Control of immature mosquito stages with insecticides (larvicides)

Temephos

The systematic literature review by George *et al.* (2015) assessed the community effectiveness of the organophosphate temephos (or Abate®) in controlling both vectors and dengue transmission when delivered either as a single intervention or in combination with other interventions. A total of 27 studies were included, comprising 11 single and 16 combined intervention studies. All single intervention studies showed consistently that temephos applications reduced entomological indices. Although 11 of the 16 combined intervention studies showed that temephos application together with other chemical vector control methods also reduced entomological indices, this was either not sustained over time or failed to reduce immature stages. Temephos alone was effective at suppressing entomological indices, but not when it was applied in combination with other interventions. There is no evidence to suggest that temephos use is associated with reductions in dengue transmission.

Bacillus thuringiensis israelensis (Bti)

Fourteen studies were included in a systematic review of the biological insecticide Bti of which 12 reported a reduction in entomological indices for an average control duration of two to four weeks (Boyce et al. 2013). Bti can be effective in reducing the number of immature *Aedes* in treated containers but there is very limited evidence (one study) that dengue morbidity can be reduced through the use of Bti alone. Hence, there is currently insufficient evidence to recommend its use as a single agent for the long-term control of dengue vectors and prevention of DF.

4.5.2 Biological control of dengue vectors

Predatory copepods

A systematic review of the use of copepods (microscopic predatory crustaceans) identified 11 articles, focusing on efficacy and community effectiveness (Lazaro *et al.* 2015). There was limited evidence from Viet Nam that *Mesocyclops spp.* had the potential to impact on vector populations in the long term, contributing to reductions in dengue cases. However, this success has not yet been replicated elsewhere (six further studies). With this limited evidence for the use of copepods as a single intervention, further implementation studies in other communities/environments are needed.

Larvivorous fish

Han *et al.* (2015) reviewed the evidence for effectiveness of larvivorous fish for *Aedes* control and dengue prevention. The 13 articles identified incorporated a wide range of interventions and outcome measures, with three efficacy studies, 10 of which assessed community effectiveness. None were randomized or cluster-randomized controlled trials. All efficacy studies reported that *Aedes* larvae were eliminated from treated containers, while community effectiveness studies reported reductions in immature vector stages, two of which also detected a continuous decline over two years. An impact on adult mosquitoes was shown in only two community effectiveness studies. Reductions in dengue cases following intervention were not proven. While the use of larvivorous fish as a single agent or in combination with other control measures could lead to reductions in immature vector stages, considerable limitations in all the studies restricted any conclusions with respect to the evaluation of community effectiveness.

4.5.3 Systematic reviews and meta-analysis of all methods and approaches for dengue prevention and control

Bowman *et al.* (2016a) reviewed the available evidence for all methods in a more quantitative approach. Restricting their search to studies published after 1980 (that is, in the era of the modern mega-city, high levels of global trade and passenger travel, the presence of all four dengue viruses in all regions, and the emergence of insecticide resistance), they included 41 studies, 19 of which provided sufficient data for meta-analyses. All studies presented vector index data, but only 18 studies reported an impact on dengue incidence. In general, the overall number of studies was low, and the power of those included was limited by weaker study designs: for example, none of the reports that investigated the impact of vector control on dengue incidence were randomized controlled studies (RCTs). No randomized controlled trials have been undertaken anywhere in the past 35 years to evaluate the effectiveness of space-spraying or fogging to reduce dengue transmission or dengue incidence, despite its widespread use. On a more positive note, limited but significant evidence indicated that house screening could have an impact on vector indices and reduce dengue transmission. Regarding the impact on vectors, there was some evidence to support the use of combination community-based campaigns (clean-up campaigns, refuse collection) to reduce vector abundance, although there is no evidence for an

impact on transmission (Bowman *et al.* 2016a). Subsequently, evidence of both an impact on vector abundance and dengue transmission was reported (Andersson *et al.*, 2015). Further research in this area is merited. Insecticide-treated materials may confer protection but only when coverage is high and in communities where house structure is suitable. There was some evidence to suggest that indoor residual spraying (IRS) does not have a significant impact on dengue transmission, although further research is needed due to the low number of studies.

Horstick and Runge-Ranzinger (2016) analyzed household based vector interventions focusing on four vector borne diseases including RCTs and cRCTs only. For dengue this systematic review included 12 studies: one cluster-randomised intervention trial, one parallel group cRCT, one cluster randomised community trial and 9 cRCTs. For dengue, single interventions if correctly delivered, could impact on the vector but not on transmission, although results were likely to have been compromised by weak study designs. The use of ITMs (curtains/screens) could impact (good evidence) on the vector depending on the suitability of the housing structure. Environmental management including clean-up campaigns, has a weak effect (not consistent, good evidence), including India and Nicaragua. No studies assessing the use of insecticides for peridomestic/space spraying were identified. Measuring human transmission remains scarce, only two studies showed a reduction (Andersson et al. 2015 and Kroeger *et al.* 2006).

Insecticide-treated materials

In cluster randomized control trials (cRCTs) in Mexico and Venezuela (Kroeger et al. 2006), ITMs (specifically insecticide-treated curtains or ITCs) were found to impact on vector populations. This was not the case in Thailand, where the open character of local housing cancelled out any impact (Lenhart et al. 2013). A cRCT in Mexico using permanently mounted, insecticide-treated netting screens fitted to the doors and windows of residential houses, followed in a second year by additional larviciding with Spinosad, demonstrated a rapid and sustained impact on the vector population for over 12 months (Che-Mendoza et al. 2015; Manrique-Saide et al., 2015). A cRCT in Colombia (Quintero et al. 2015) also reported impacts on the vector population by long-lasting insecticide-treated netting used as window and door curtains, both alone or in combination with insecticide-treated netting water container covers. Impacts of ITMs on dengue transmission have not yet been reported.

Biological and environmental methods

In Thailand, no significant impacts were reported in a cRCT (Kittayapong et al. 2012) using a combination of Mesocyclops aspericornis (copepods), *Bacillus thuringiensis var.* israelensis toxins (Bti sacs), screen net covers (MosNet®) for water jars, mosquito traps (MosHouse®), and portable vacuum aspirators (MosCatch™). Since then, a cRCT in Nicaragua (Andersson et al. 2015) tested a combination of environmental management and reported evidence of both an impact on vector abundance and dengue transmission.

Environmental methods only (not including the mode of delivery of an intervention, but the intervention itself)

An assessment of waste management as a single intervention in a cRCT in Sri Lanka (Abeyewickreme *et al.* 2012) reported a reduction in pupal indices. A cRCT in India (Arunchalam et al. 2012) established the effectiveness of a combination of water container covers, clean-up campaigns, including community mobilization. In a cRCT in Brazil (Caprara et al. 2015), a combination of a clean-up campaign, the use of container covers, and community mobilization failed to have a substantial effect.

4.5.4 Systematic review for a service-oriented purpose

For interventions focusing on a particular service delivery in the context of vector control, there is existing work on outbreak response (Pilger et al. 2010). In total, 24 studies showed different strategies in the organization of outbreak response emphasizing an intersectoral approach. Studies that managed the outbreak response by creating multidisciplinary response teams, including vector control teams working door-to-door, and studies that monitored and evaluated their activities, all achieved successful outbreak control. A combination of vector control (the elimination of larval habitats with community involvement, and the appropriate use of insecticides in and around houses), and training for medical personnel with laboratory support, was crucial for the successful control of outbreaks. Spatial spraying of insecticides alone proved ineffective in achieving outbreak control and its usefulness in combination with other interventions was unconvincing. The available evidence suggested that, in order to achieve rapid control, the outbreak response must employ a multidisciplinary approach combined with M&E.

4.5.5 Systematic review of the organizational context of vector control

A systematic review of vector control service delivery highlighted many shortcomings globally (Horstick et al. 2010). Three out of nine studies on vector control services showed that there was little change in control operations over time, though there were attempts at strategic changes via decentralization and intersectoral collaboration. Staffing levels, appropriate capacity building, management and organization, sustained funding and mechanisms for achieving community engagement were inadequate and were key problem areas. Case studies in four countries confirmed most of the information gleaned from the systematic review. Key public health stakeholders' doubts about the effectiveness of services in reducing vector densities and significantly reducing virus transmission were widespread, although they believed that, given the availability of resources, interventions could be effective. The reviewers stressed the need for: (i) the development of operational standards for vector control services, including minimum financial and personnel requirements relative to the geographical area(s) to be covered, their demography, and the vector control methods to be implemented; (ii) evidence-based selection and delivery of different interventions or combinations of interventions, adapted to different settings; (iii) the development and application of M&E tools for vector control service delivery; and (iv) needs-driven capacity building, especially in public health, entomology and communication.

After considering the limitations of the systematic reviews described above the following practical recommendations emerged (see also Checklist 7).

- Vector control has the potential to be effective, although implementation remains an issue. No clear evidence exists for a recommended structure for vector control delivery services.
- At present, a lack of evidence prevents decisions about which interventions are most effective, particularly for responding to dengue outbreaks. The likelihood of success of any method depends on numerous factors including the frequency of treatment, the geographical area to be treated, the coverage to be achieved and the probability of its acceptance and adoption by communities within the target population. In order for the method to be effective and acceptable to communities, careful implementation of measures may be as or more important than the actual choice of the combinations of vector control methods.
- A key element in delivering effective vector control measures is likely to be timely alerts of outbreaks, as provided by surveillance systems, followed by immediate and frequent vector control measures and allied health promotional campaigns.

- There is an urgent need for the development of standards to estimate vector population sizes accurately, for use in evalu-ating interventions under trial conditions, as well as for routine use in surveillance.
- Where feasible, dengue vector control studies should endeavour to include some measure of dengue transmission as ultimate proof of efficacy and community effectiveness.

CHECKLIST 7. **VECTOR MANAGEMENT FOR OUTBREAK CONTROL**

1. Determine the quantity (number of houses treated, coverage, treatment frequency) of insecticide, equipment, personnel required, particularly for ultra-low volume (ULV), outdoor spraying and indoor spraying, and develop relevant SOPs
2. Repeat these procedures as they apply to larval control (chemical and biological control)
3. Conduct insecticide susceptibility assays frequently to ensure that insecticides being used remain effective
4. Conduct vector surveys in the inter-epidemic period. In addition to immature stage/breeding sites, pupal data are critical in identifying productive container types for targeted interventions during the outbreak. Adult mosquito data are the most accurate indices
5. Ensure resources required for next level responses are available, and are functional and prepared for action (that is, insecticide, spray and other equipment, skilled personnel)
6. State details of how larval control will be deployed – SOPs
7. Describe the SOPs for vector-control services, including minimum financial and personnel requirements (in accordance with the geographical area to be covered)
8. Select and describe different vector-control interventions adapted to different settings or productive container types.
9. Customize dengue mosquito control programmes in schools, hospitals, etc.
10. Develop and apply M&E tools for vector control. Continue to conduct vector surveys throughout the year in order to detect rises in vector populations and to evaluate the impact of vector control (particularly important during outbreaks)
11. Ensure that a vector control plan of action is in place[16]
12. If any planned vector control tools or strategies have not previously (or recently) been used in the targeted community, ensure advanced warning and education is provided to optimize correct usage and compliance
13. For existing strategies, ongoing promotion and education should be continued (and reviewed at frequent intervals)
14. Target breeding sites of immature mosquito stages, particularly the productive containers, aiming to reduce the number of potential sites (eliminating, covering or larviciding containers), and deliver an impact on the adult vector population, approximately 2–3 weeks later
15. Promote house screens, advocate clean-up campaigns
16. Ensure risk reduction messages are communicated in a timely fashion and that the messages reflect the status of the outbreak
17. Inform communities what will NOT be effective (buzzers, grass cutting, etc.)

[16] http://www.who.int/whopes/resistance/en/ (accessed 11 March 2016).

4.6 Stakeholder involvement

Control activities for a dengue outbreak need to be multisectoral, multi-disciplinary and multi-level. They require environmental, political, social and medical input to be coordinated so that the successful activities of one sector are not weakened by the lack of commitment of another (Pilger et al. 2010).

It has been argued that effective communication between stakeholders at all levels of surveillance, clinical management and transmission control is paramount, as the chain of events is only as strong as its weakest link (Ng et al. 2011). In order to coordinate an effective response, it is crucial to document the relevant stakeholders involved in an outbreak response at both local level with regards to implementation, and at higher political levels with regards to decision-making (Table 6).

Table 6. Example of stakeholders with or without to the Outbreak Response Team

Stakeholders	Responsibilities (examples)
Ministry of health	Usually the coordinating body. Vector control services, clinical services, communication and health promotion (social mobilization), national public health laboratory
Ministry of education	Involvement of schools, social mobilization
Youth and women's affairs	Social mobilization
Sanitation and environment sector	Guarantee water supply, solid waste management
Construction sector	Keep construction sites water and container free
NGOs	Social mobilization
Private medical sector	Case reporting, apply measures in private clinics and premises
Civil society	Social mobilization
Media	Information policy through defined spokespersons
Outbreak response team	As defined, see Table 6
Entomologists	Determine vector resistance, analyse entomological indices and issue recommendations
Epidemiologists	Analyse clinical data, assess case fatality rate, analyse verbal autopsies
Laboratories	Networking, stockout management, define specimens to be analysed
Hospitals, outpatient departments, primary care clinics	Organize triage, "dengue treatment units", staff-bed-stockout management
Logistics	Supply management
Public health offices – local, regional, etc.	Coordinate local actions

NGOs: nongovernmental organizations.

4.7 Communication and social mobilization

Due to the complexity of dengue prevention and control, multisectoral cooperation that includes local health services, trained personnel and civil authorities is required for effective vector control and to reduce disease transmission (Heintze et al. 2007). Multifaceted interventions are more effective than single interventions, and collaboration between the community and authorities is crucial for their success (Parks & Lloyd, 2004; Sommerfeld & Kroeger, 2012). Thus, a combination of government commitment, local authority involvement and civil society mobilization is essential for success. How these community-based interventions are developed and the mix of the strategies available will depend upon the engagement of the community, and how specific behavioural changes in the target audiences can be achieved (Perez et al. 2007; Al-Muhandis & Hunter, 2011).

Communication is a key component of a dengue contingency plan. While behaviour change communication (BCC) planning methodologies such as WHO's Communication for Behavioural Impact (COMBI) (Parks & Lloyd, 2004) and the BCC Planning Cycle (Salem, Bernstein & Sullivan, 2008) are more widely used to create strategic communication interventions focusing on behaviour, there is a general lack of understanding on what type of communication process should be used during different epidemiological moments (that is, inter-epidemic, pre-outbreak, outbreak, recovery). Each type of communication process requires a mix of communication channels based upon the messages, urgency of the call to action, and the target audiences and actors involved in the response.

Health communication is the planned and systematic use of communication strategies to inform, influence and motivate individual and community decisions that enhance health, health outcomes and quality of life. It is a two-way process that creates mutual understanding between the participants, and thus goes beyond IEC approaches, a didactic, one-way communication process based upon the provision of information and recommendations to a target audience. Health communication processes are generally used during inter-epidemic periods and may overlap with risk communication processes in pre-outbreak interventions.

4.7.1 Behaviour change communication

BCC moves beyond the basic assumption of IEC that people will change their behaviour once provided with the "right" information. It is an evidence- and research-based process founded upon an in-depth understanding of why people "do what they do," perceptions of the target audience on the issue, what internal and external factors facilitate or serve as barriers to the behaviour, and effective strategies to reduce behavioural barriers (Parks & Lloyd, 2004; Fox, 2012). BCC promotes behaviour change at individual, community, organizational, or society levels to improve health outcomes using a mix of communication strategies such as interpersonal communication, media (mass, traditional, alternative, social, print) and social mobilization (see Checklist 8).

CHECKLIST 8. **SOCIAL MOBILIZATION**

1. Develop a risk communication plan that includes communication and social mobilization activities for:
   - pre-outbreak (preparation of messages, identification of appropriate communication channels, training of spokespersons, organization of social mobilization activities);
   - outbreak (dissemination of messages, call to action to reduce mortality, increase personal protection practices and prevention of mosquito breeding);
   - recovery phases (dissemination of messages informing affected populations the outbreak is over, acknowledging their efforts to contain the outbreak, and encouragement of the broader population to maintain prevention actions). See COMBI toolkit and field workbook for outbreak response (WHO 2012c; 2012d).
2. Identify the groups/communities/leaders to be targeted and their specific information needs
3. Define staff training needs
4. Develop key messages: encourage early health seeking should symptoms arise and immediate care should the patient have any one of the dengue warning signs, protective measures, preventative measures
5. Detail steps to be taken for collaboration/communication between community, community actors and government (for example, community meetings, stakeholder meetings with schools, NGOs, religious organizations, local businesses, municipal staff)
6. Describe advertising (number of spots, frequency of each spot, length of time each spot will air) via radio, television, newspapers, social media, etc.
7. Advocate for release of funds to support implementation of Contingency Communication and Social Mobilization Plan
8. Describe M&E for the communication and social mobilization activities

The BCC and COMBI planning methodologies bring a behavioural focus to social mobilization, defined as a process of dialogue through which diverse actors are brought together to take action on an issue by creating a sense of shared responsibility (Parks & Lloyd, 2004; UNICEF, 2015). Social mobilization can take place at the local level through the mobilization of schoolchildren, women's groups, youth groups, environmental coalitions, and professional associations, among others, to promote specific behaviours related to routine prevention and control or outbreak response. Social mobilization also takes place at the senior management level within different branches of the government at national, regional and municipal levels as resources are mobilized to implement the outbreak response.

4.7.2 Risk communication

A key element in managing any type of public health risk is about how it is communicated. Thus, risk communication is both a strategy and an interactive process of exchange of information and opinions between people, groups and institutions. This interactive process can be described as a dialogue whereby multiple messages are discussed together with the preoccupations, opinions and reactions of the population at risk (National Research Council, 1989; CDC, 2012). It includes planning communication measures for the preparation, response and recovery from a public health emergency, and discusses types of risk, levels of exposure, and methods for managing risks (CDC, 2012). Community participation at all levels is organized and managed through the risk communication process prior to, during and after an outbreak. Within this context, specific measures should be initiated, such as the use of mass media, social media,

social mobilization and interpersonal communication. Incorporation of social media as a channel for health communication is still not widely practised and even less so in risk communication (CDC, 2012; Infanti et al. 2013). Infanti et al. (2013) highlight the need to update risk communication resources "…to meet new and developing needs (for example, strategies for effective web-based and social networking communication are notably absent yet highly relevant in today's world)..." Individuals with expertise in the use of social media for health communications are notably absent from departments of health promotion and communication, yet the importance of social media in reaching specific populations is recognized (CDC, 2012).

According to Gutierrez Blanco (2012), risk communication allows the "…expeditious control and mitigation of activities before a public health event occurs," which are, among others, "…the identification and training of spokespersons, who are responsible for the rapid, reliable, and transparent delivery of information; the elaboration of key messages; and the efficient use of communication channels." It is important to note that a good communication strategy supports a variety of actions, including surveillance, containment and control actions, during a public health emergency. Planning for outbreak response is as important, if not more important, than implementation of the response.

Seven key principles of risk communication are: (1) accept and involve the public as a legitimate partner; (2) listen to the audience; (3) be honest, frank and open; (4) coordinate and collaborate with other credible sources; (5) meet the needs of the media; (6) speak clearly and with compassion; and (7) plan carefully and evaluate performance (US Department of Health and Human Services, 2002). Unfortunately, the value of risk communication is often not understood or appreciated by senior management, resulting in poor communication with the affected communities, communication that is too late to be useful, conflicting messages issued by officials, and recommendations that are inappropriate or not feasible, among others. As noted by the National Research Council (1989), "…even though good risk communication cannot always be expected to improve a situation, poor risk communication will nearly always make it worse." [17]

Recognizing this, WHO developed, tested and published a COMBI toolkit and field workbook (WHO 2012c; WHO 2012d). These documents are practical and include activities across the risk communication continuum of pre-outbreak, outbreak and recovery. In spite of adequate planning, barriers to successful communication programmes that address different epidemiological moments throughout the year continue to be constrained by: (a) limited budgets; (b) a lack of continuous and systematic planning of communication interventions; (c) a lack of M&E; (d) challenges in measuring impact (Badurdeen et al. 2013); and (e) a lack of skilled staff in behaviour change and risk communication processes.

4.8 Clinical management contingency measures

Good clinical case management (see Checklist 9) in an outbreak has been crucial in reducing case fatality of dengue from 10–20% to less than 1% in some countries over the past two decades (Tomashek et al. 2012). The training of health professionals in diagnosis and management, as well as robust laboratory facilities must by prioritized, as this will effectively guide case management and influence mortality rates. The best ways to achieve successful training may be through hands-on training during ward rounds and case conferences (Pilger et al. 2010). Emergency resources and funding for outbreak response including clinical supplies have been highlighted as important elements of preparedness and response planning (WHO, 2009; Badurdeen et al. 2013).

[17] Page 3.

The low sensitivity of the DF/DHF/DSS case classification was a common barrier (Bandyopadhyay, Lum & Kroeger, 2006). With the revised WHO classification (WHO, 2009) and case management instructions (WHO, 2012e) according to severity level this problem has been overcome (Horstick et al. 2012; 2014b). Identifying clinical warning signs, and knowing how to triage patients in the absence of laboratory test results may be crucial. For further reading see WHO's handbook on the clinical management of dengue (WHO, 2012e).

CHECKLIST 9. **FOR CLINICAL MANAGEMENT IT IS RECOMMENDED TO**

1. Ensure hospital outbreak management plan (including recommendations for avoiding stockouts of oral rehydration salts, intravenous fluid, blood products, reagents, see Annex 3)
2. Prepare special dengue units for enhanced dengue clinical management
3. Prepare for additional beds (using stretchers, discarded beds or beds from other wards, trolleys and foldable beds, mattresses on the floor, etc., and, if needed, establish tents with beds for intravenous fluid and observation)
4. Plan for additional staff (to be hired or transferred)
5. Establish a laboratory network which is able to handle the surge in specimens
6. Triage system for case management and referrals (WHO, 2012e) and examples in annexes 4 and 5)
7. Ensure mortality review to help improve case management
8. Ensure transmission control in hospitals
9. Ensure timely clinical training
10. Organize emergency rooms in regional hospitals
11. Consider Hotlines for consultation

The following points should be considered when preparing a hospital outbreak management plan according to recommendations at a WHO consensus meeting.

Development and circulation of national guidelines on clinical management of dengue

- Separate guidelines for children and adults
- Case detection and assessment of the patient as well as admission criteria should be defined
- Inpatient management should be standardized
- Referral, discharge and follow-up should be described

Ensure training of all relevant health workers, including officers in state and private hospitals

- Serial system: national to provincial to district
- Mobile dengue team to recognize training needs given changing workforce
- Highlight need for training junior staff
- Regular training including outside outbreak period to include practical/bedside training
- Training of all health staff – enables reorganization in outbreak periods
- Referral criteria and interim stabilization, management during transfer, taking into account country geography
- Involvement of professional colleges to make dengue training part of continuous professional development (CPD)

Engagement of private sector

- Training: may need incentives
- Referral of dengue patients requiring admission to public hospital

Establishment of specialist treatment areas in major hospitals and in high-risk districts

- Dedicated dengue wards
- Dedicated high-dependency units – bypasses limitation of intensive care unit (ICU) beds with specifically trained staff
- Specific dengue management team
- Early review by consultant physicians
- Consider possible stockouts in the dengue prepardness plan
- Identification of resources for back-up stock (for example, urinary bladder catheters, bed pans, fluid-measuring containers for oral fluids and urine, blood pressure sets, pulse oximeters)

Dengue mortality reviews as learning tools with national input

- Maintenance of good record-keeping system, for example, special monitoring charts
- Improve notification of suspected dengue by all clinicians for early detection of epidemics
- Delegate responsibilities to designated officers to ensure recording and dissemination information documentation and development of a Health Information System.

Glossary of terms: list of essential elements of a dengue outbreak contingency plan

"Outbreak" (used synonymously with "epidemic") is defined as a "sudden unexpected increase of cases" or as "the occurrence in a community or region of cases of an illness clearly in excess of expectancy" (Heymann, 2004). A "sudden and unexpected increase" (outbreak) is different from the **seasonal peak**, which is an "expected increase of cases" that usually occurs during the wet season.

Dengue outbreak response has been defined as the sum of measures specifically addressing a dengue outbreak, with the aim of reducing case fatality rates, numbers of cases and entomological parameters (Pilger et al. 2010).

The seasonal increase of dengue cases, usually during the rainy season (see Fig. 2) has to be distinguished from the unexpected increase of cases above a defined threshold, which is usually called an outbreak (Stroup et al. 1989; Heymann, 2004); the number of reported cases exceeding expected levels is referred to as **"aberrations"** (Farrington & Andrews, 2004).

Passive surveillance relies on standardized reporting forms provided by the state or local health departments. These completed forms are returned to the health department when cases of disease are detected. Passive reporting systems are generally less costly than other reporting systems and data collection is not burdensome to health officials, but the challenge is how to increase the reporting mentality of health providers and ensure a standardized case classification (Thacker et al. 1986).

Active/enhanced surveillance involves outreach by the public authority, such as regular telephone calls or visits to laboratories, hospitals and providers, to stimulate reporting of specific diseases. It places intensive demands on resources and should be limited to specific purposes (Thacker et al. 1986).

Sentinel surveillance is a special form of active surveillance. It involves collecting case data from a sample of providers and then extrapolating them to a larger population. The advantage is that it is less expensive (being restricted to small areas) and produces data of higher quality; the disadvantage is the inability to ensure that the sample population is representative (Thacker et al. 1986).

Syndromic surveillance systems seek to use existing health data in real time to provide immediate analysis and feedback to those charged with investigation and follow-up of potential outbreaks (Henning 2004).

Shift of genotype/serotype is a change in the predominant dengue serotype or genotype in an area (WHO, 2009).

Pupal productivity surveys identify the most productive containers by counting pupae (pupal indices) in a variety of potential containers in an area (WHO, 2009).

Larval surveys assess the level of *Aedes* infestation by establishing larval indices as BI, CI and HI (WHO, 2009).

Expansion factor is a multiplication factor calculated by a cohort, sero-survey or capture-recapture studies to better estimate the level of dengue cases underreported in an area (Undurraga, Halasa & Shepar, 2013).

Positive/negative predictive value (NPV); sensitivity/specificity

	Dengue outbreak occurred	No dengue outbreak occurred	Total
Alarm (WS) present	A	B	a+b
Alarm (WS) absent	C	D	c+d
Total	**a+c**	**b+d**	

WS: warning sign.

Interpretation in the context of warning signs and dengue outbreaks:

sensitivity = a/a+c = % of outbreaks with warning signs present

specificity = d/b+d = % of non-outbreaks without warning signs

PPV = a/a+b = % of warning signs which predicted an outbreak

NPV = d/c+d = % without warning signs with no subsequent outbreak.

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Annexes

Annex 1. Framework for planning and implementation of a national dengue contingency plan

Activities	Task
1. **Situational analysis, monitor and assess the epidemic situation**	Summarize background information, such as national dengue burden, national characteristics of outbreaks, health system aspects, financial, administrative, legal and managerial environment
	Activate and maintain the situation room
	Establish routine communication mechanisms with relevant national and international organizations
	Analyse and interpret weekly data and develop a weekly outbreak report
	Provide support and technical assistance to affected areas
2. **Preparedness planning**	Review the existing protocols and develop a standardized contingency protocol for the country, e.g. by a planning workshop using the handbook and its checklist
	Consider all relevant stakeholder
	Adapt the standardized contingency protocol to national plans. Consider all relevant documents for consistency, e.g. national dengue response plans, surveillance guidelines, etc.
	Disseminate the standardized contingency protocol and the standardized method for the declaration of the epidemic
3. **Risk/crisis communication plan**	Conduct ongoing training in risk/crisis communication
	Activate the risk/crisis communication team
	Coordinate the communication partners (media, community leaders, private and public sector, NGOs, stakeholders) and develop a communication mechanism and establish a mechanism to monitor communication messages and channels
	Enact the national agreement on making the public announcement and ongoing release of information
	Implement and monitor risk/crisis communication plan according to the phase: pre-epidemic epidemic alert epidemic declare post-epidemic
	Mobilize additional resources to support the communication plan

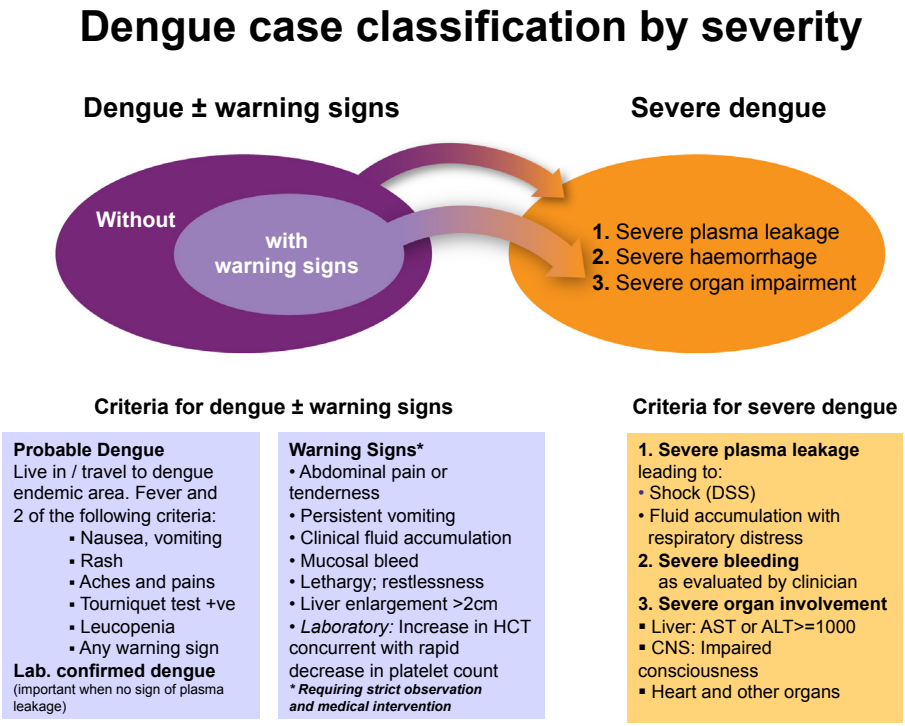
Activities	Task
4. Disease surveillance system	Standardize the methods used to determine the criteria to confirm the start of a dengue epidemic.
	Declare the occurrence of a dengue epidemic and notify the International Health Regulation (IHR) and national focal points (IHR website)
	Implement standardized contingency protocols, e.g. are guidelines about management of surveillance system as well as the national dengue control plan available, updated and accessible to users?
	Activate the multisectoral committee to implement the national contingency plan
	Involve the private sector as well as outpatient departments in dengue reporting, at least via sentinels
	Establish enhanced surveillance ("active surveillance") components (e.g. sub-analysis of routine data, syndromic surveillance, laboratory support, sentinel surveillance, motivation calls)
	Monitor alarm signals for dengue outbreaks regularly and use in an integrated alert tool. Decide which alarm signals should be monitored
	Achieve adequate timeliness of reporting (to be able to detect alarm signals and unusual increase of cases and to respond early) in the routine reporting as well as for the alarm signals
	Establish a routine quality control (monitoring) of the surveillance system, conduct evaluation and implement recommendations
	Conduct periodic training of surveillance and reporting staff
	Analyse data at district level weekly, including the preparation of a epidemic curve, apply alarm signals and integrate into an integrated alert tool
5. Case notification, confirmation and reporting	Guarantee uniformity of reporting of suspected and confirmed cases according to definitions stated in the new WHO case classification
	Prepare legal framework to include all relevant sectors/departments in reporting
	Prepare standardized, easy-to-fill reporting form
	Opt for electronic case reporting
6. Optimize the use of laboratory resources	Reduce lag times for receiving laboratory results (to report confirmed cases early to clinicians and for surveillance)
	Use laboratory parameters as alarm signals, such as increased seropositivity and change of serotype and directly report to the surveillance system
	Standardize the laboratory support (flowchart about timing of test, destination of samples etc.) and establish quality control
	Decide on the optimal proportion of laboratory confirmation (ratio: tested/suspected) for your setting
6. Optimize the use of laboratory resources (continued)	Monitor the proportion of laboratory positive (dengue-specific laboratory confirmations to dengue-specific tests requested) and decide if its increase can be used as alarm signal

Activities	Task
	Establish laboratory networks
	Conduct regular laboratory training
	Decide where to mobilize additional resources when necessary
	Implement the sampling criteria for confirmation of suspected cases of dengue to monitor the epidemic according to WHO guidelines
7. Virological surveillance	Record weekly information on seropositivity ratio and decide if it could be integrated into the alert tool
	Record monthly information on predominate serotypes and decide if it could be integrated into the alert tool
8. Vector surveillance	Eventually perform routine larval surveys in sentinel areas and decide on how to do this (e.g. perifocal, over the year, before the season) and clearly describe
	Conduct occasional pupal productivity surveys to identify productive containers for targeted interventions
	Decide on the use of climate data for surveillance
9. Community participation/ social mobilization	Decide on communication and social mobilization strategies to be implemented
	Decide area to be covered-entire district or focused on hot spots
	Enhanced existing outreach activities following positive alarm signals
	Decide whether routine activities should be carried out throughout the year or initiated before the dengue season (seasonal activities)
10. Outbreak preparedness at district level (implementation)	Make the response plan available to relevant staff
	Conduct regular training sessions
	Develop outbreak response committee and define responsibilities. Ensure implementation of standardized information flow that is regularly updated
	Ensure that financial management is adequate for unforeseen events
	Describe special arrangements for holiday periods and major festivities
11. Outbreak preparedness in hospitals and health centres. Organize patient-care services	Develop guidelines for response to surge of cases and case management, and update them Review and adapt the patient-care protocol according to the epidemic situation
	Make guidelines available to relevant staff
	Perform regular training on outbreak preparedness and case management for all relevant staff
	Organize laboratory support and describe in guidelines (including additional staff requirements and additional reagents)
	Define process to obtain additional budget in a timely manner

Activities	Task
11. Outbreak preparedness in hospitals and health centres. Organize patient-care services (continued)	Describe details on procurement issues (e.g. how to obtain additional staff and beds, deal with stockouts)
	Describe special arrangements for holiday periods and major festivities
	Conduct triage to optimize resources
12. Outbreak detection	Agreed on outbreak definitions available
	Is the integrated alert tool implemented and human resources/capacity for data analysis sufficient?
	Decide on and define outbreak investigation process
	Monitor the number of false alerts
	Implement a process to declare an outbreak in place using an integrated alert tool and standardized risk and outbreak communication
	Define a person/position who (technically) declares the outbreak
	Agree on a method and timing on how to inform the clinicians/public about an outbreak
	Establish the standardized use of alert signals for early response
13. Outbreak response. Organize the intervention, mobilization and redistribution of materials, pesticides, medicines, inputs, reagents, response coordination teams, and regional collaboration. Intensify vector control measures	Develop guidelines for outbreak response and update them (see section on outbreak preparedness)
	Make guidelines available to relevant staff and committee members
	Staged response described: initial response early response emergency response
	Determine the needs for additional resources and regional collaboration
	Ensure necessary resources are provided
	Establish technical and logistical cooperation for: communication plan national laboratory services patient-care service vector control service
	Implement emergency vector control procedure according to WHO recommendations and national contingency plan
14. Monitor and evaluate the contingency plan	Monitor the implementation of the contingency plan (surveillance, vector control, patient care, risk communication, costs)
	Evaluate the efficacy of the contingency plan
	Prepare and disseminate a comprehensive final report

Source: adapted from PAHO/WHO (2010).

Annex 2. Dengue case classification



Source: WHO/TDR (2009).

Annex 3. Estimates for the organization of health-care activities

Estimate of dengue cases notified:

Consider three risk scenarios according to the information of the local epidemiological surveillance system. To estimate inputs, equipment and materials, consider the distribution of cases within six months of the year, with the highest concentration in three months.

Risk scenario 1 – 1% of the population

Risk scenario 2 – 2% of the population

Risk scenario 3 – 4% of the population

Example for a municipality of 100 000 inhabitants

Risk scenario 1 – 1000 dengue cases during six months of transmission

- Month 1 – 130 cases
- Month 2 – 140 cases
- Month 3 – 200 cases
- Month 4 – 200 cases
- Month 5 – 200 cases
- Month 6 – 130 cases

Risk scenario 2 – 2000 dengue cases during six months of transmission

- Month 1 – 260 cases
- Month 2 – 280 cases
- Month 3 – 400 cases
- Month 4 – 400 cases
- Month 5 – 400 cases
- Month 6 – 260 cases

Risk scenario 3 – 4000 dengue cases during six months of transmission

- Month 1 – 520 cases
- Month 2 – 560 cases
- Month 3 – 800 cases
- Month 4 – 800 cases
- Month 5 – 800 cases
- Month 6 – 520 cases

Estimate of the patients that require intravenous hydration (observation):

Consider 15% of the estimate of dengue cases

Example for a municipality of 100 000 inhabitants

Risk scenario 3 – 4000 dengue cases during six months of transmission

- Month 1 – 520 cases – 78 patients that require intravenous hydration
- Month 2 – 560 cases – 84 patients that require intravenous hydration
- Month 3 – 800 cases – 120 patients that require intravenous hydration
- Month 4 – 800 cases – 120 patients that require intravenous hydration
- Month 5 – 800 cases – 120 patients that require intravenous hydration
- Month 6 – 520 cases – 78 patients that require intravenous hydration

Estimate of patients that require admission to the infirmary (ward):

Consider the number of admissions to be 7% of dengue cases
For every bed, consider seven admissions in a month (occupancy – 4 days).

Example for a municipality of 100 000 inhabitants

Risk scenario 3 – 4000 dengue cases during six months of transmission

First step: estimate the number of admissions: 280 admissions during the transmission period:

- Month 1 – 520 cases – 36 admissions
- Month 2 – 560 cases – 40 admissions
- Month 3 – 800 cases – 56 admissions
- Month 4 – 800 cases – 56 admissions
- Month 5 – 800 cases – 56 admissions
- Month 6 – 520 cases – 36 admissions

Second step: estimate bed requirements: 1 bed/7 admissions:

- Month 1 – 520 cases – 36 admissions – 5 inpatient beds
- Month 2 – 560 cases – 40 admissions – 6 inpatient beds
- Month 3 – 800 cases – 56 admissions – 8 inpatient beds
- Month 4 – 800 cases – 56 admissions – 8 inpatient beds
- Month 5 – 800 cases – 56 admissions – 8 inpatient beds
- Month 6 – 520 cases – 36 admissions – 5 inpatient beds.

Estimate of patients that require admission for intensive care

Consider the number of admissions to be 0.7% of dengue cases.
For every bed in intensive care, consider 6 admissions in a month (occupancy – 5 days).

Example for a municipality of 100 000 inhabitants

Risk scenario 3 – 4000 dengue cases during six months of transmission

First step: estimate admissions: 28 admissions during the transmission period:

- Month 1 – 520 cases – 3 admissions
- Month 2 – 560 cases – 4 admissions
- Month 3 – 800 cases – 6 admissions
- Month 4 – 800 cases – 6 admissions
- Month 5 – 800 cases – 6 admissions
- Month 6 – 520 cases – 3 admissions

Second step: estimate bed requirements: 1 bed/6 admissions:

- Month 1 – 520 cases – 3 admissions – 1 bed in intensive-care unit (ICU)
- Month 2 – 560 cases – 4 admissions – 1 bed in ICU
- Month 3 – 800 cases – 6 admissions – 1 bed in ICU
- Month 4 – 800 cases – 6 admissions – 1 bed in ICU
- Month 5 – 800 cases – 6 admissions – 1 bed in ICU
- Month 6 – 520 cases – 3 admissions – 1 bed in ICU.

Prevision (forecast) of inputs, medicines and equipment required for patients in outpatient care and hospitalized cases

a) Complete blood count (CBC), e.g. haemogram

Consider 2 tests per patient during the transmission period (six months)

Example for a municipality of 100 000 inhabitants

Risk scenario 3 – 4000 dengue cases during six months of transmission

8000 tests required during the transmission period

- Month 1 – 520 cases – 1040 CBC tests
- Month 2 – 560 cases – 1120 CBC tests
- Month 3 – 800 cases – 1600 CBC tests
- Month 4 – 800 cases – 1600 CBC tests
- Month 5 – 800 cases – 1600 CBC tests
- Month 6 – 520 cases – 1040 CBC tests.

b) Oral rehydration salts (ORS)

Consider the number of dengue cases estimated x 2 x 3 (2 ORS packets per day during three days).

Example for a municipality of 100 000 inhabitants

Risk scenario 3 – 4000 dengue cases during six months of transmission

24 000 ORS packets required

- Month 1 – 520 cases – 3120 ORS packets
- Month 2 – 560 cases – 3360 ORS packets
- Month 3 – 800 cases – 4800 ORS packets
- Month 4 – 800 cases – 4800 ORS packets
- Month 5 – 800 cases – 4800 ORS packets
- Month 6 – 520 cases – 3120 ORS packets.

c) Saline for intravenous fluid therapy

Consider that 15% of dengue cases require intravenous hydration x 8 x 500ml-bottles of physiological saline each.

Example for a municipality of 100 000 inhabitants

Risk scenario 3 – 4000 dengue cases during six months of transmission

600 patients require intravenous hydration – 4800 bottles of 500 ml required

- Month 1 – 520 cases – 78 patients that require intravenous hydration – 624 bottles (500 ml) required
- Month 2 – 560 cases – 84 patients that require intravenous hydration – 672 bottles (500 ml) required
- Month 3 – 800 cases – 120 patients that require intravenous hydration – 960 bottles (500 ml) required
- Month 4 – 800 cases – 120 patients that require intravenous hydration – 960 bottles (500 ml) required
- Month 5 – 800 cases – 120 patients that require intravenous hydration – 960 bottles (500 ml) required
- Month 6 – 520 cases – 78 patients that require intravenous hydration – 624 bottles (500 ml) required.

d) Chair for intravenous fluid therapy

Consider 15 % of the dengue cases seen per working day/month

Example for a municipality of 100 000 inhabitants

Risk scenario 3 – 4000 dengue cases during six months of transmission

- Month 1 – 520 cases – 78 patients that require intravenous hydration per month – 4 chairs
- Month 2 – 560 cases – 84 patients that require intravenous hydration per month – 4 chairs
- Month 3 – 800 cases – 120 patients that require intravenous hydration per month – 6 chairs
- Month 4 – 800 cases – 120 patients that require intravenous hydration per month – 6 chairs
- Month 5 – 800 cases – 120 patients that require intravenous hydration per month – 6 chairs
- Month 6 – 520 cases – 78 patients that require intravenous hydration per month – 4 chairs.

It is important to note that, if necessary, the chairs can equip different health facilities according to the occurrence and distribution of cases. It is also necessary to assess the amount of serum stands (stand poles), taking into account that every stand can serve two chairs simultaneously. Equipment requirements should be assessed for the month with the highest number of cases in order to ensure sufficient equipment reserves.

e) Medicines

Dipirona/paracetamol: consider the number of cases per period x 3 g (daily dose) x 3 days (febrile period)

Example for a municipality of 100 000 inhabitants

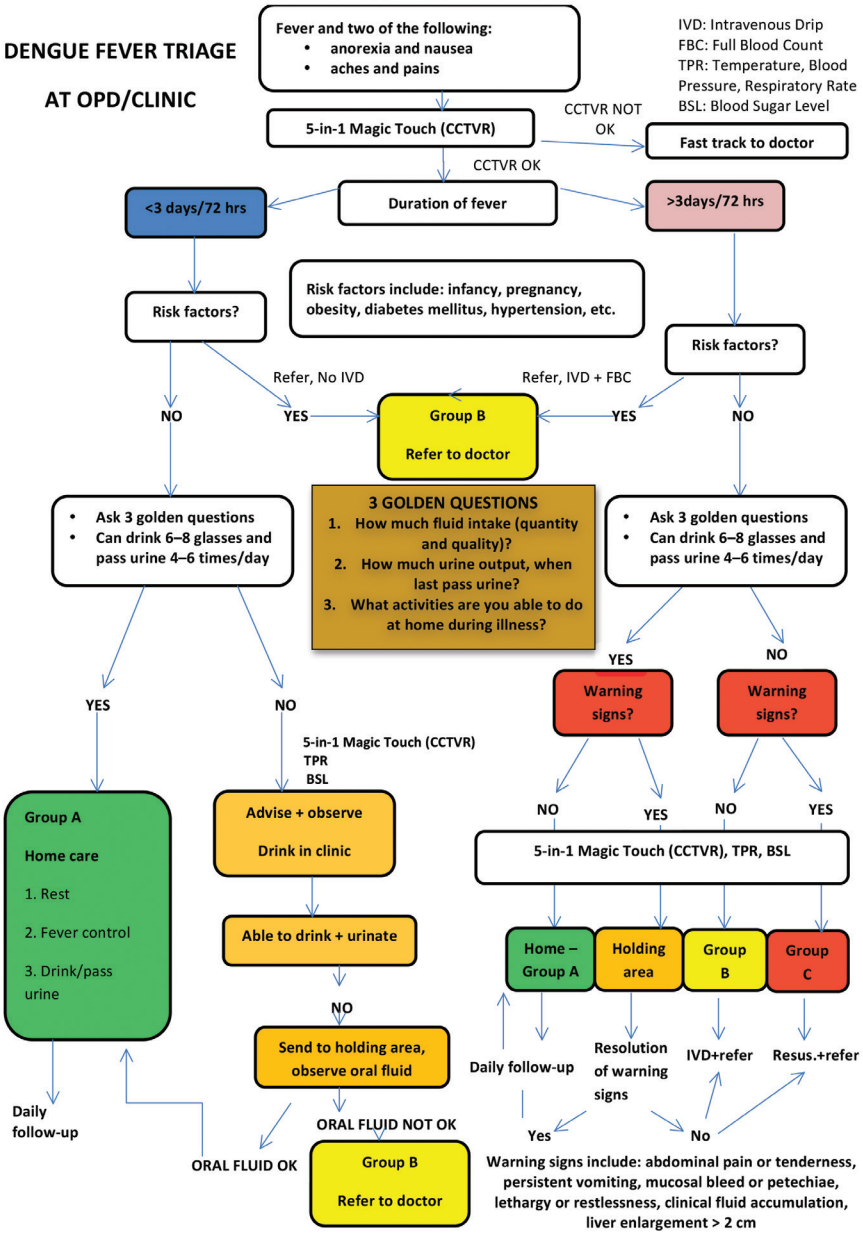
Risk scenario 3 – 4000 dengue cases during six months of transmission

36 000 g of medicine required during the transmission period

- Month 1 – 520 cases – 4680 g of medicine required
- Month 2 – 560 cases – 5040 g of medicine required
- Month 3 – 800 cases – 7200 g of medicine required
- Month 4 – 800 cases – 7200 g of medicine required
- Month 5 – 800 cases – 7200 g of medicine required
- Month 6 – 520 cases – 4680 g of medicine required.

Source: adapted from Ministry of Health, Brazil (2013).

Annex 4. Example flowchart for triage



Source: Lum, personal communication (2015).

Annex 5. Example assessment form for triage

Dengue Fever Assessment Form (PPUM) **Patient sticker**

Date and time today: _____ Date & time of onset of fever: _____

>72 hrs fever: Yes / No Place of residence:_____

Initial Triage:

Cold & clammy hands:	Yes / No	Pulse Volume:	Normal / weak

Level of Triage: Green ☐ Yellow ☐ Red ☐

Symptoms:

_____

_____

Risk factors: (Tick the boxes if yes)

Infants (<1 yr old) ☐	Hypertension ☐	Liver Failure ☐
Pregnancy ☐	Heart Disease ☐	Staying alone ☐
Diabetes mellitus ☐	Renal Failure ☐	>60 years age ☐
Other diseases, describe:		**NO risk factors** ☐

5-in-1 Magic Touch (CCTVR):	
Colour of extremities	
Capillary refill time	Sec.
Temp of extremities	
Pulse **Volume** (most impt)	
Pulse Rate	

TPR:	
Body Temperature	
Blood Pressure	
Respiratory rate	
SpO_2	

3. Golden Questions (for all fever patients):

1. Could drink at least 3 to 4 glasses in the last 12 hours	No ☐	Yes ☐
2. Passed urine at least twice in the last 12 hours	No ☐	Yes ☐
3. Able to walk around the house	No ☐	Yes ☐

Danger signs (for all fever patients):

Severe abdominal pain	No ☐	Yes ☐
Vomiting > 3X	No ☐	Yes ☐
Weakness/lethargy/confusion	No ☐	Yes ☐
Mucosal bleeding	No ☐	Yes ☐
Cold hands and feet/Pale	No ☐	Yes ☐
Breathing difficulties/Chest Pain	No ☐	Yes ☐
Dizziness/Fainting	No ☐	Yes ☐

Management:

Discharge for Follow-up ☐ **Observation ward** ☐ **Refer for Admission** ☐

Source: Lum, personal communication (2015)

ANNEXES

The Special Programme for Research and Training in Tropical Diseases (TDR) is a global programme of scientific collaboration established in 1974. Its focus is research into neglected diseases of the poor, with the goal of improving existing approaches and developing new ways to prevent, diagnose, treat and control these diseases. TDR is sponsored by the following organizations:

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