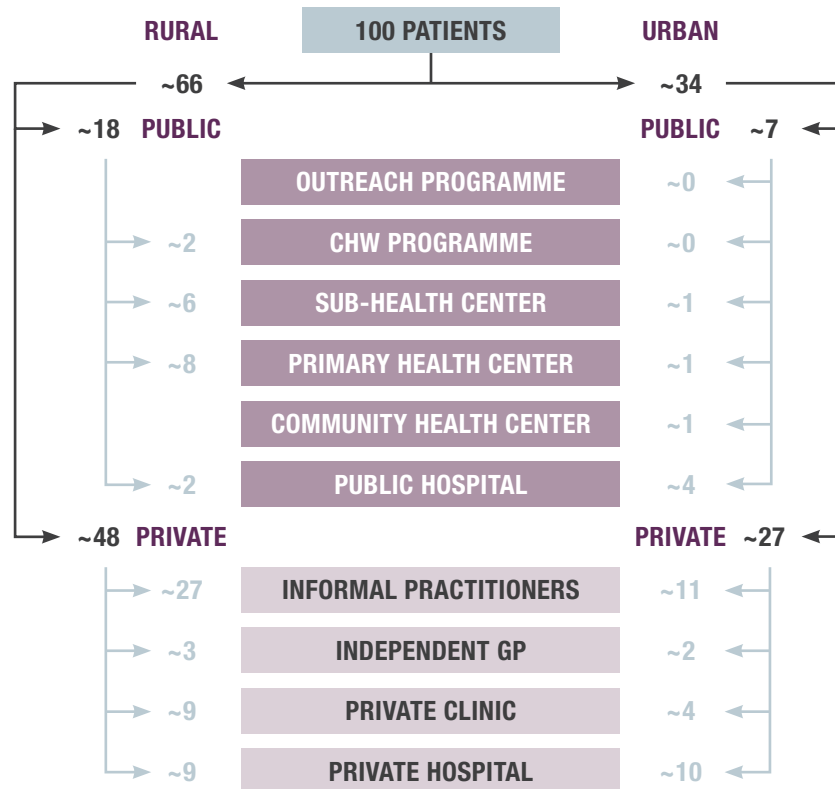


FEVER DIAGNOSTIC PRACTICES

PATIENT FLOW

PATIENT FLOW FOR INITIAL FEBRILE ILLNESS DIAGNOSTICS*



COMMENTS

Informal practitioners are the most common point of care for initial febrile illness diagnosis, particularly in rural areas

- “Many patients continue to visit AYUSH or informal practitioners as their first point of call when they have fever. In some cases it might be as high as 60-70% in rural communities.” FIND India, Regional Technical Director
- Informal practitioners are often consulted because they are more available, both financially and with regards to time for the patient
- Patients that do not see their condition improve after visiting an informal practitioner generally visit larger formal structures (hospitals, clinics, primary or community health centers) for a second diagnosis and treatment

Patients tend to visit the largest structure they have access to for febrile illness diagnosis

- As many patients defer diagnosis for several days after initial onset of fever and/or self-medicate, when they decide to seek medical care they have a strong preference for the largest structure available
- In rural areas, access to hospitals is limited by distance and time to reach the facility, which leads to a larger share of patients visiting smaller structures (private clinics and sub-health or primary public health centers)

Most patients with febrile symptoms go to private institutions, in particular informal practitioners

Note: (*) excluding self-diagnosis. Sources: WHO, World Bank, interviews, Advention



FEVER AND MALARIA DIAGNOSTIC ALGORITHM AND PRACTICES

DIAGNOSTIC GUIDELINES TREATMENT GUIDELINES

All suspected cases of malaria should be tested
 Physicians select the diagnostic technique
 All public health centers should be equipped with microscopy equipment capable of diagnosing malaria, including sub-health centers
 Type of RDT used: mainly Pf, some Pf + Pv

Severe malaria is treated as Pf until confirmation
 Uncomplicated malaria is treated as Pv until confirmation
 Mixed infections are treated as Pf with the Pv dosage of Primaquine
 Pf:
 • Artesunate + Sulfadoxine-Pyrimethamine + Primaquine
 • Northeastern States: Artemether Lumefantrine
 Pv: Chloroquine + Primaquine

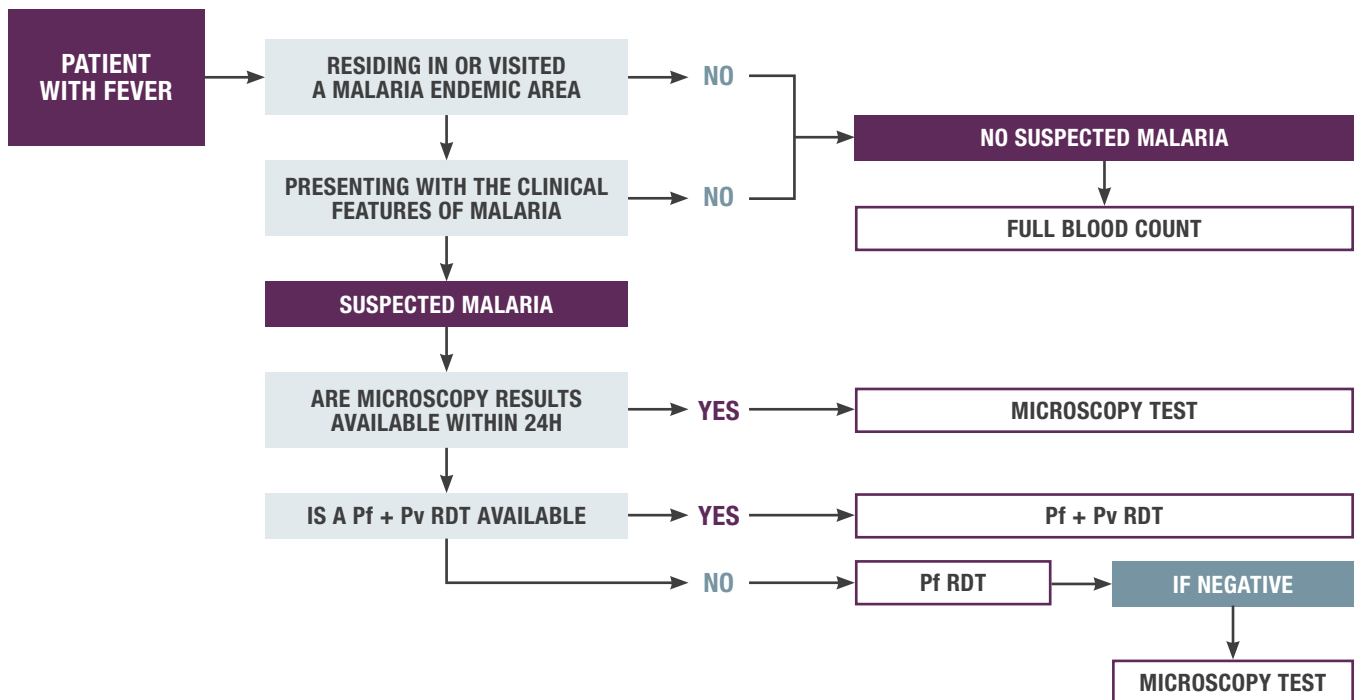
ADHERENCE TO GUIDELINES

Treatment is compliant with international guidelines
 Diagnostic guidelines have some differences:
 • CHWs do not provide malaria tests as per the iCCM guidelines
 • The iCCM and IMCI/IMAI recommend testing all fevers for malaria

- LEGEND**
- FULLY ALIGNED
 - GENERALLY ALIGNED
 - RARELY OR NOT ALIGNED

FEBRILE ILLNESS DIAGNOSTIC ALGORITHM

Guideline algorithm for all health providers (public and private) for all patients


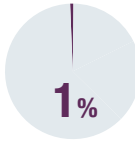
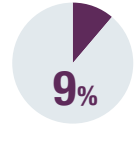
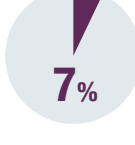
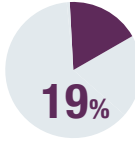




Malaria diagnosis practices in India are mainly oriented towards microscopy testing, and are generally aligned with international guidelines

Sources: WHO, Ministry of Health & Family Welfare, interviews, Advention



MALARIA TESTING PRACTICES AT DIFFERENT HEALTH FACILITY LEVELS

| | HEALTH FACILITY* | NUMBER OF FACILITIES | SHARE OF FEVER PATIENTS (EST.) | PREFERRED MALARIA DIAGNOSTIC TOOL | LEVEL OF RDT USE (MALARIA DIAGNOSTIC) |
|----------------|--------------------------------|----------------------|---|-----------------------------------|---|
| PUBLIC | Public Hospital | 24K |  6% | Microscopy | None / Very limited |
| | Community Health Center | 6K |  1% | Microscopy | None / Very limited |
| | Primary Health Center Hospital | 26K |  9% | Microscopy | None / Limited |
| | Sub-Health Center | 156K |  7% | Microscopy | Limited, mainly in high-transmission hilly/tribal areas |
| PRIVATE | Private Hospital | ~45K |  19% | Microscopy | None / Very limited |
| | Private Clinic | ~40K |  13% | Microscopy | None / Very limited |
| | Individual GP | ~500K** |  5% | Microscopy | None / Very limited |

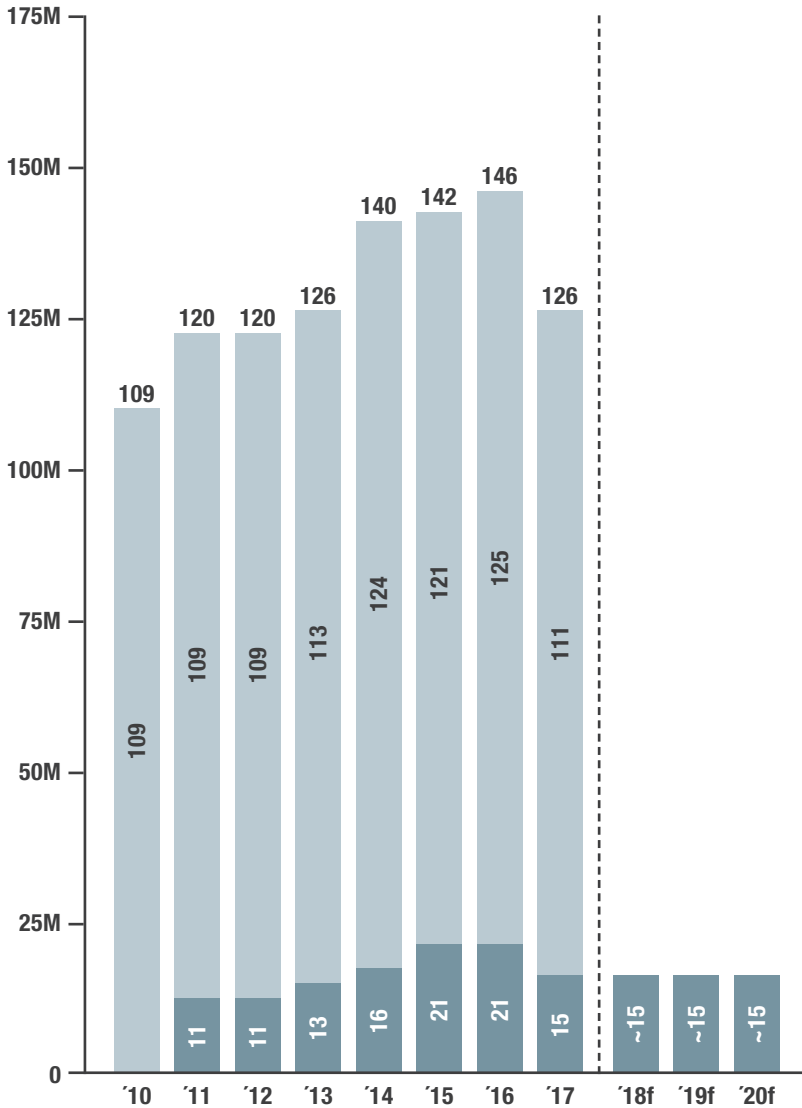
RDTs are mostly used in sub-health centers, where they are used at a higher rate than in other facilities, and in private hospitals and clinics, which treat the most fever patients

Note: (*) excluding AYUSH and traditional healthcare practitioners; (**) may include informal practitioners self-declaring as individual medical practitioners. Sources: interviews, MoH&FW, Advention












MALARIA TESTING PRACTICES

MALARIA TESTS PERFORMED



LEGEND
 RDTs
 MICROSCOPY

IDENTIFIED MALARIA RDTs USED*

| | | |
|---------------------------------------|-------------------------|---|
| Parahit-f Dipstick RDT | |  |
| | \$0.26 / test | |
| Pf-HRP2 | 13.5M RDTs 2008-2010 |  |
| | |  |
| Paracheck Malaria Pf Kit | |  |
| | \$0.46 / test | |
| Pf-HRP2 | 5.4M RDTs 2007-2008 |  |
| | |  |
| One Step Malaria Pf / Pan Test | |  |
| Pf-HRP2 | \$0.26 / test | |
| Pan-pLDH | 1.6M RDTs 2009-2010 |  |
| | |  |

Malaria testing is overwhelmingly performed by microscopy
RDTs used have very low price points, and the majority are Pf-specific

Note: (*) Most recent information available for specific tests. Sources: WHO, Ministry of Health & Family Welfare, Global Fund, Advention



MALARIA TESTING LANDSCAPE

PRIORITY COUNTRIES*



VIET NAM CAMBODIA S. AFRICA INDIA PAKISTAN MYANMAR THAILAND

| | VIET NAM | CAMBODIA | S. AFRICA | INDIA | PAKISTAN | MYANMAR | THAILAND | |
|---|--|--------------|------------------------|--------------------------|-------------------------|--------------------|---------------------------------|------------------------|
| HEALTHCARE INFRASTRUCTURE | Population (M) | 95 | 16 | 56 | 1,324 | 193 | 53 | 69 |
| | Healthcare expenditures per capita (\$) | 115-120 | 65-70 | 84 | 60-70 | 35-40 | 55-59 | 217-225 |
| | Health insurance coverage | ~70% | - | ~16% => NHI | ~5-10% | ~19% | Negligible | ~98% |
| | Universal health coverage index | 73 | 55 | 67 | 56 | 40 | 60 | 75 |
| | Patients with fever being tested (%)** | 80% | 69% | 82% | 71% | 68% | 55% | 83% |
| | Main distribution network | NIMPE | CNM | NDOH | State MoHs | Mix public/private | NVBDCP/CMSD | BVBD |
| MALARIA DIAGNOSTIC FUNDING & PROCUREMENT | Last year total malaria funding (\$M) | 16 | 20 | 24 | 226 | 38 | 78 | 21 |
| | Share of government funding (%) | ~18% | ~3% | ~100% | ~73% | ~58% | ~8% | ~40% |
| | Main procurement decision maker | NMCP | CNM/UNOPS | NDOH / Malaria programme | National and state MoHs | GF / NMCP | NMCP/PMI | NMCP |
| | Procurement concentration level | High | High | High | Low | Medium | Medium | High |
| MALARIA DIAGNOSTIC PRACTICES | Health facilities performing RDTs | Health posts | Lower level facilities | Lower level facilities | Sub-Health/Primary HC | GPs, clinics | Lower level facilities, clinics | Lower level facilities |
| | Share of RDT in malaria diagnostic (% of patients) | ~19% | ~74% | ~63% | ~13% | ~20% | ~96% | ~5% |
| | Community HCW RDT knowledge | Yes | Yes | Yes | No | Yes | Yes | Yes |
| | Quality management system performance | High | Medium | High | Medium | Medium | Low | High |

NIMPE: National Institute of Malaria, Parasitology, and Entomology (also CNM); **NDOH:** National Department of Health; **MoH:** Ministry of Health; **NVBDCP:** National Vector Borne Disease Control Programme; **CMSD:** Central Medical Store Depot; **BVBD:** Bureau of Vector-Borne Disease; **NMCP:** National Malaria Control Programme; **UNOPS:** United Nations Office for Project Services; **GF:** The Global Fund; **PMI:** Project Management Institute

Notes: (*) Last available year; (**) As per Advention's assumption based on interviews (base case scenario). Sources: WHO, World Bank, GF, interviews, Advention



MALARIA RDT STAKEHOLDERS MAP

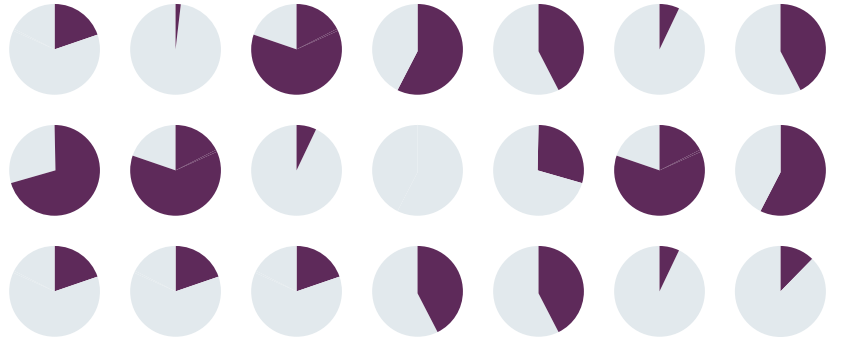


WHO IS PAYING FOR MALARIA RDTs?

Ministry of Health

Donors

Patients / Private insurances

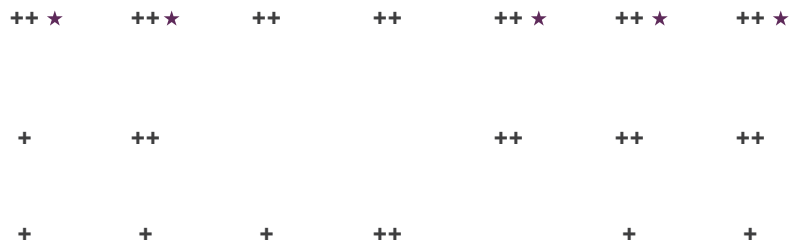


WHO IS SELECTING MALARIA RDTs?

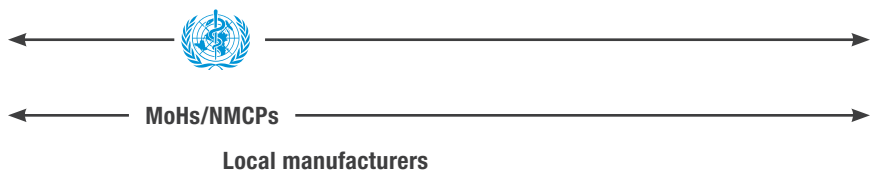
Ministry of Health / NMCP

Donors

Private sector



WHO ARE THE MAIN INFLUENCERS REGARDING MALARIA RDT SELECTION?



LEGEND

★ HEAVY USE OF DONOR'S PROCUREMENT POOLING SYSTEM ☆ USE OF DONOR'S PROCUREMENT POOLING SYSTEM

Malaria RDTs are mostly financed by international donors, except in India, Pakistan and South Africa

NMCPs are key decision makers regarding RDT selection in all countries

Source: Advention



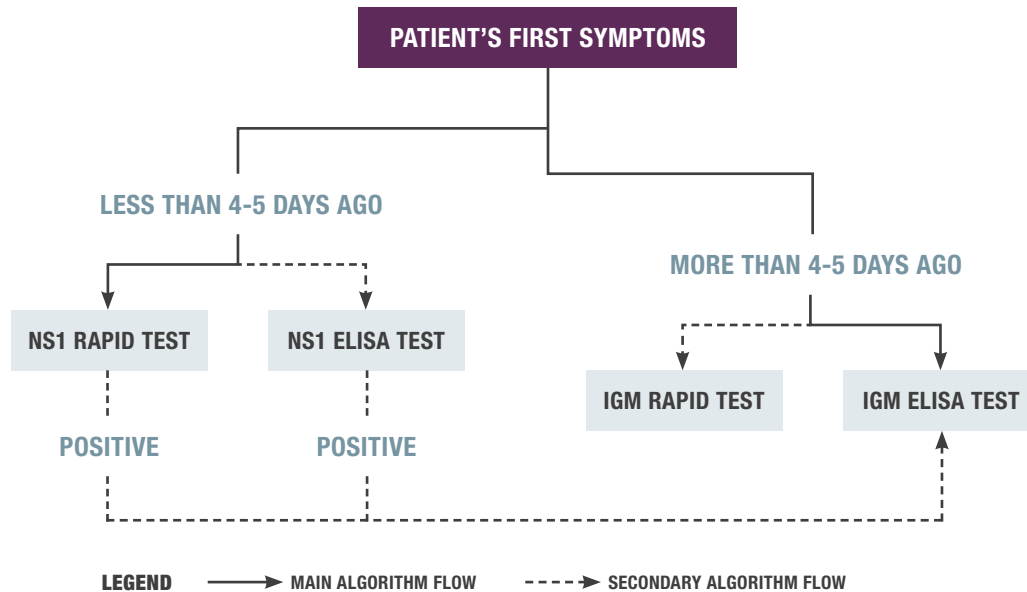
OTHER FEBRILE ILLNESSES TESTING PRACTICES

| | | |
|------------------------------------|-------------------|--|
| ARBOVIRUSES | Dengue | <p>Most large hospital labs perform dengue tests in-house, especially in endemic states</p> <p>Dengue is the most tested arbovirus in the country</p> <p>Most dengue tests are concentrated during the peak season (monsoon)</p> |
| | Chikungunya | <p>The vast majority of large labs seem to be testing for chikungunya in-house. Some of them outsource chikungunya tests due to a lower incidence of the virus in their regions</p> <p>Chikungunya tests are often performed for patients already screened for dengue: (1) higher prevalence of dengue in the country; (2) dengue infections carry the risk of severe complications; (3) sequential testing is less costly</p> |
| | Zika | <p>Zika tests are only performed by the 25 APEX labs appointed by the Indian health ministry (no routine test in other hospital labs)</p> <p>An estimated 40K zika tests have been performed in 2016</p> <p>Almost all tests are performed using PCR</p> |
| BACTERIAL FEVER-INDUCING PATHOGENS | Melioidosis | <p>Melioidosis is rarely tested for, in both the public and private sector</p> <p>Tests for melioidosis appear generally to be performed using PCR</p> |
| | <i>Leptospira</i> | <p><i>Leptospira</i> is rarely tested for, as it often presents with minimal clinical manifestations</p> <p>Tests can be performed using IgM ELISA or by microscopy depending on availability</p> |
| | Scrub typhus | <p>Diagnosis is usually clinical and based on the apparition of characteristic eschars</p> <p>When tested for, it is commonly done via microscope serology (Weil-Felix test)</p> |
| | Murine typhus | <p>Diagnosis is usually clinical and supported by blood test results</p> <p>When tested for, it is commonly done via microscope serology (Weil-Felix test)</p> |

Large Indian labs seem to routinely test febrile patients for dengue and chikungunya

DENGUE TESTING ALGORITHM (HOSPITAL LABS)

TYPICAL DENGUE TESTING ALGORITHM



COMMENTS

In all Indian labs we interviewed physicians were in charge of testing technique selection (incl. the choice of the antigen / antibody to be tested), usually following patients' examination and blood test.

Regarding lab confirmatory testing, the decisive factor seems to be the probable patient contamination time:

- Patients recently infected will be tested with NS1 tests, mostly with rapid tests
- Patients whose infection is older will be tested with IgM tests, mostly using ELISA

Confirmatory tests are seldom performed, but some labs do run confirmatory ELISA IgM tests (systematic confirmatory testing is not required by the national health authorities).

The choice between rapid and ELISA testing usually depends on:

- Test availability
- Perceived test sensitivity / sensitivity
- Test costs
- TAT (rapid tests usually takes 20-30 mn while ELISA tests require three to four hours)

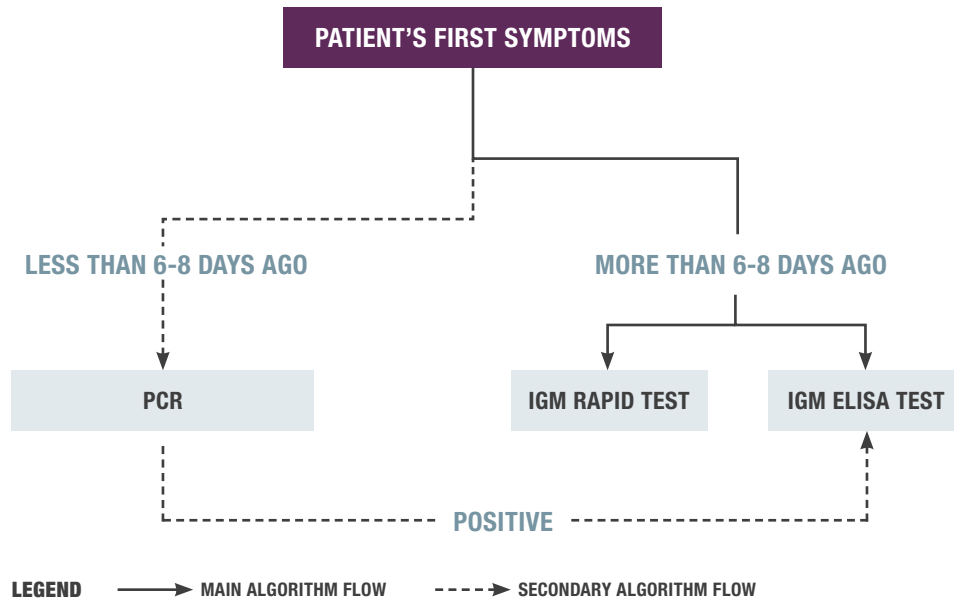
No national testing guidelines exist for laboratory dengue diagnostics (national guidelines only present the available testing techniques and their pros and cons).

Suspected dengue patients will be tested primarily using NS1 or IgM tests depending on their probable infection time



CHIKUNGUNYA TESTING ALGORITHM (HOSPITAL LABS)

TYPICAL CHIKUNGUNYA TESTING ALGORITHM



COMMENTS

In all Indian labs we interviewed physicians were in charge of testing technique selection (incl. the choice of the antigen / antibody to be tested), usually following patients' examination and blood test.

Regarding lab testing, the decisive factor seems to be the probable patient contamination time:

- Patients recently infected will be tested through PCR tests
- Patients whose infection is older will be tested with IgM tests, mostly using ELISA

A majority of chikungunya tests will be run on patients that have been infected more than 6 days ago:

- Higher dengue prevalence in the country leads most physicians to order dengue tests first
- The cost can also play a role with some physicians asking the patient to come back to be tested through cheaper than PCR techniques (ELISA or rapid test)

Confirmatory ELISA IgM tests can be run in case of a positive PCR result (systematic confirmatory testing is not required by the national health authorities).

No national testing guidelines exist for laboratory diagnostic (national guidelines only present the available testing techniques).

Suspected chikungunya patients will be tested primarily using PCR or IgM ELISA tests, depending on their probable infection time

Sources: interviews, Advention former work