Emerging Viral Haemorrhagic Diseases

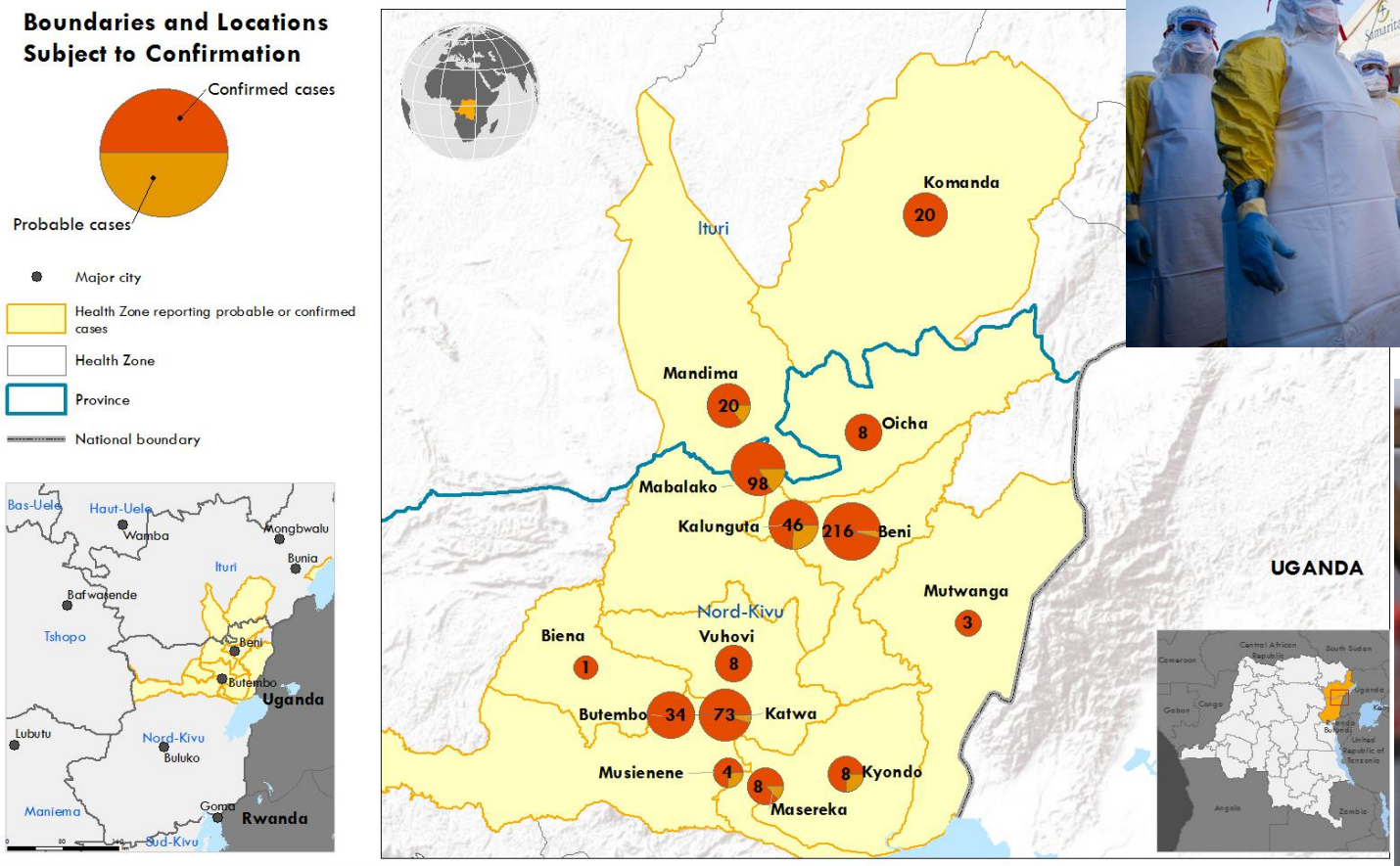
Prof. Arunkumar Govindakarnavar. PhD
Director, Manipal Institute of Virology (MIV)
Manipal Academy of Higher Education, Manipal

"Emerging" Viral Haemorrhagic Diseases

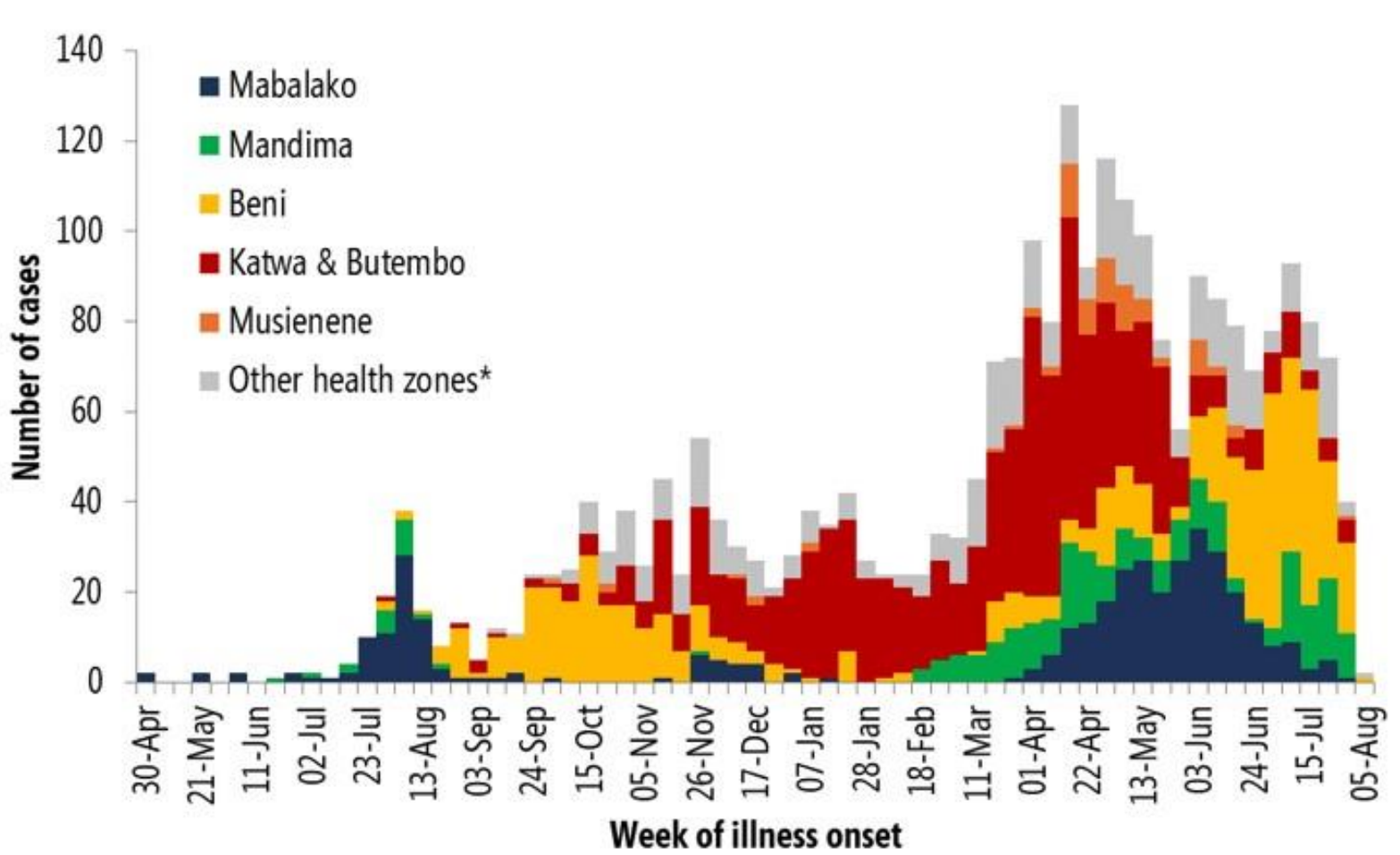
- Ebola Virus Disease (EVD)
- Yellow Fever (YF)
- Lassa Fever (LF)
- Dengue Haemorrhagic Fever (DHF)
- Crimean Congo Haemorragic Fever (CCHF)
- Kyasanur Forest Disease (KFD)

Ebola Virus Disease

Ebola virus disease cases by health zone, North Kivu and Ituri provinces, Democratic Republic of the Congo, data as of 18 December 2018



Ebola Virus Disease – DRC Africa- 2018-19 – Multiple outbreaks



www.who.int

Yellow Fever

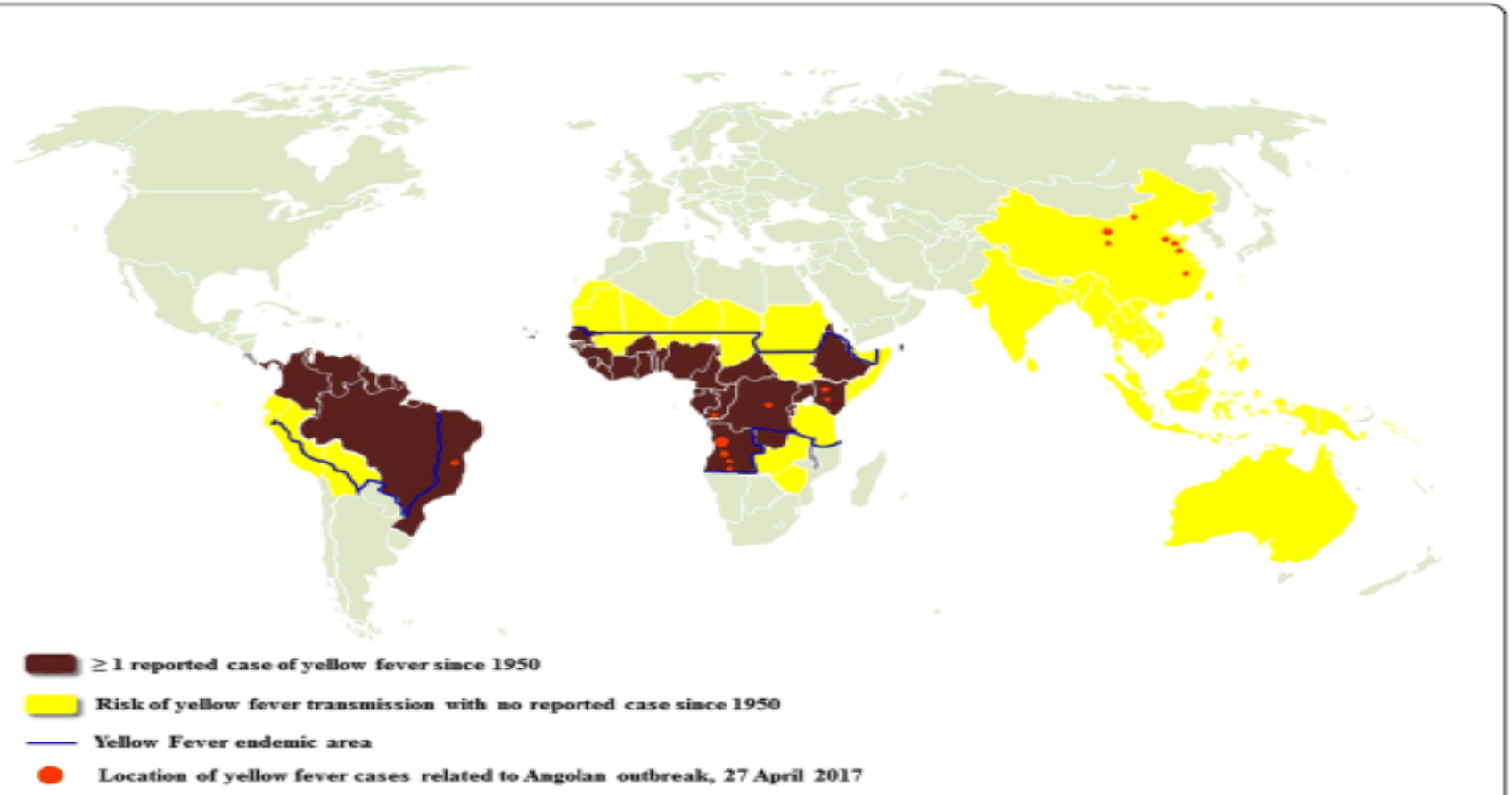
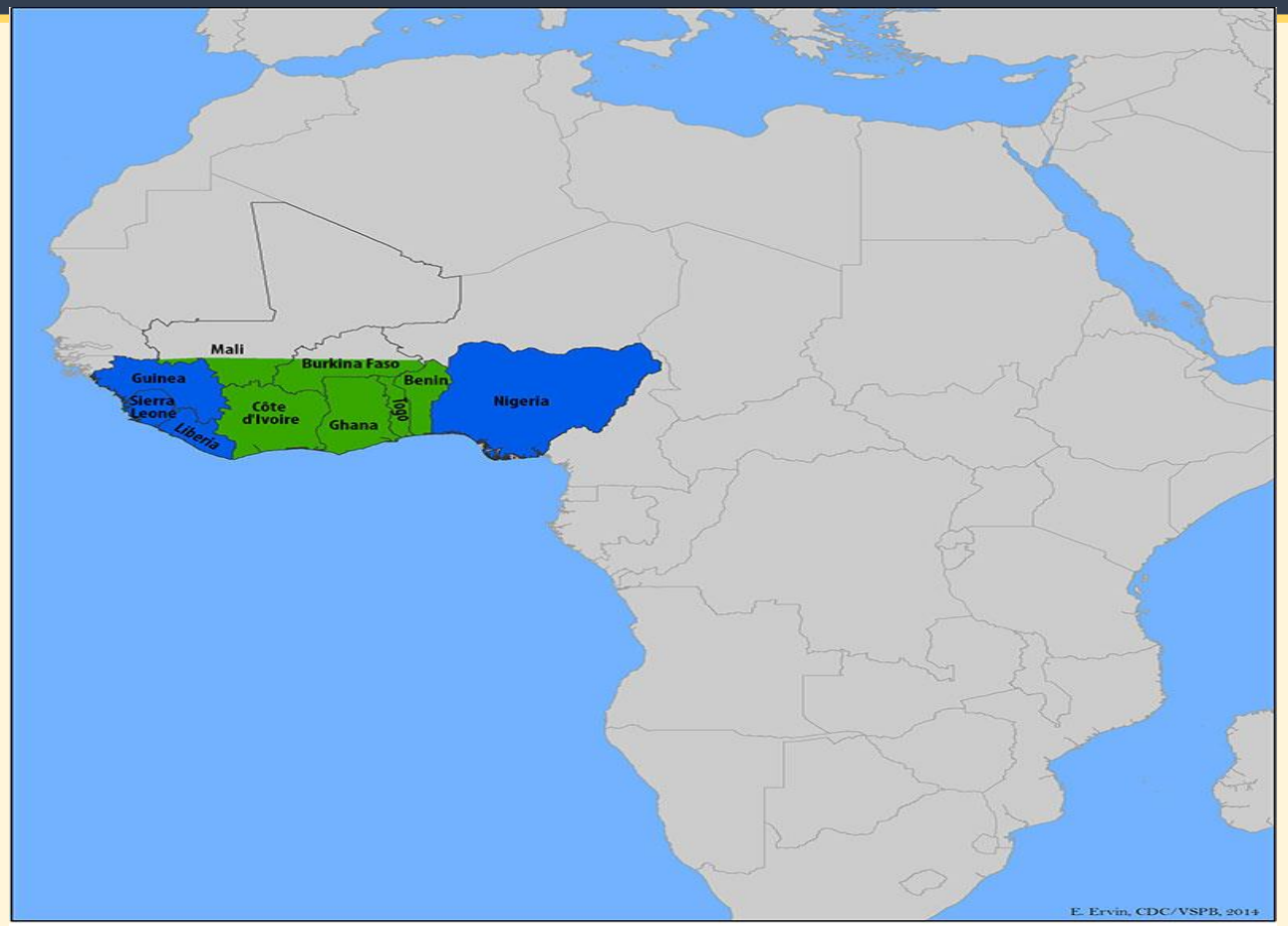


Figure 1: Global distribution of yellow fever virus (YFV) across Africa, America and the Asian subcontinent regions [15].

Lassa Fever



LASSA FEVER DISTRIBUTION MAP

Countries reporting endemic disease and substantial outbreaks of Lassa Fever

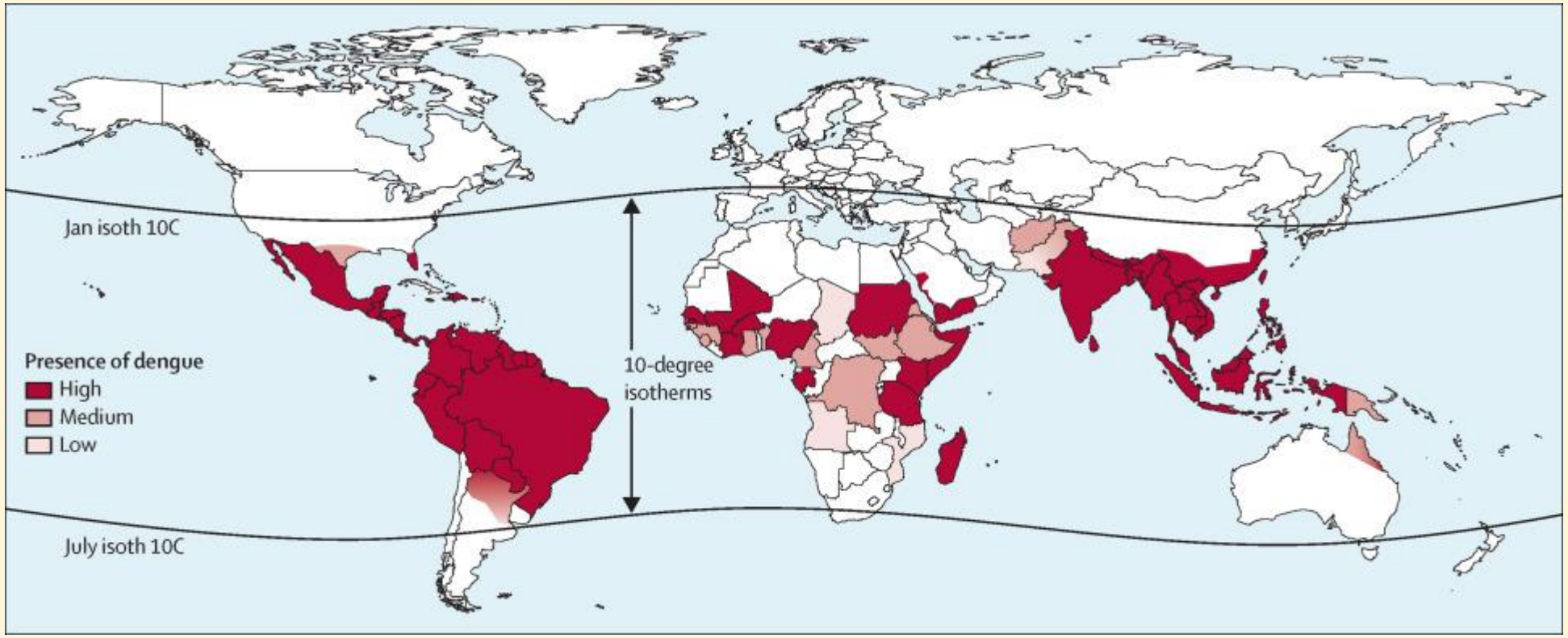
Countries reporting few cases, periodic isolation of virus, or serologic evidence of Lassa virus infection

Lassa Fever status unknown

0 240 480 960
Miles

www.cdc.gov

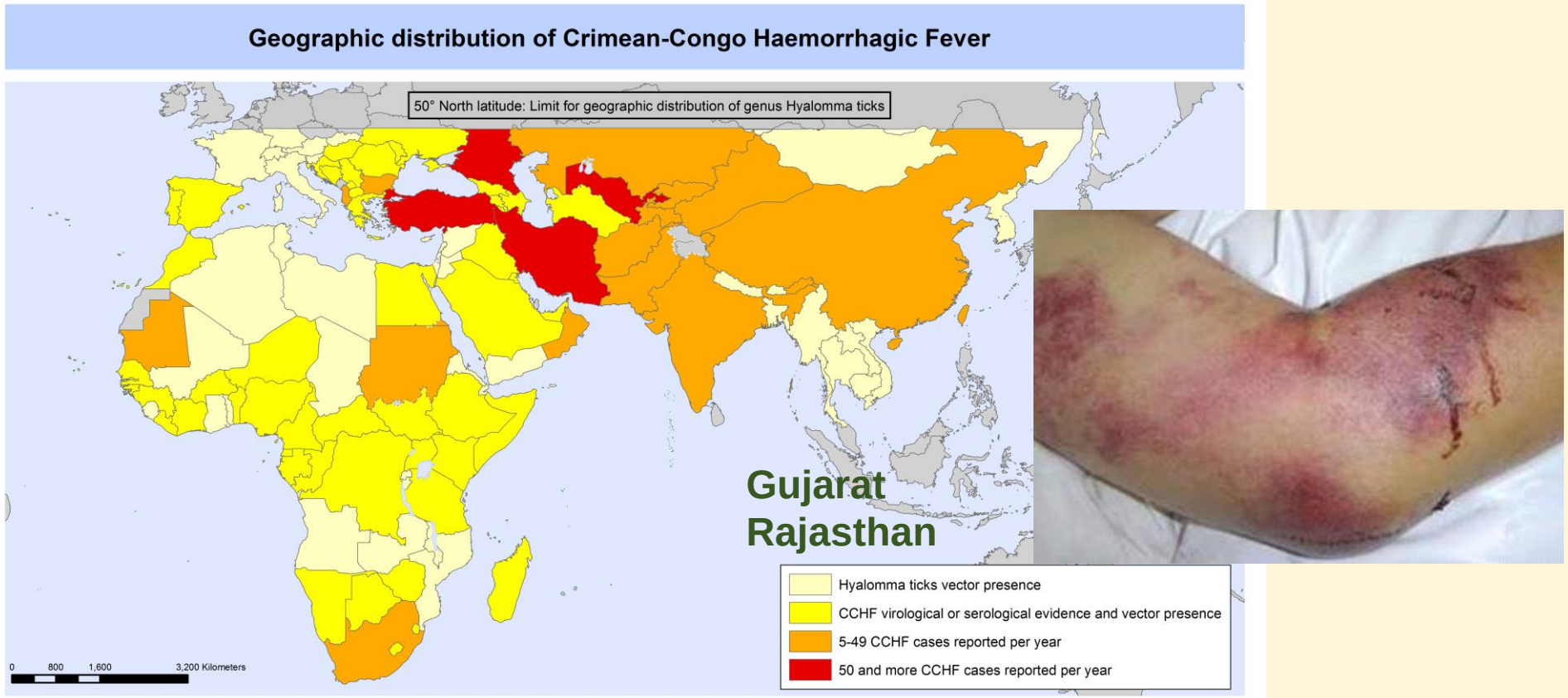
Dengue Haemorrgahic Fever - Continuing challenge



- Urban to Rural spread
- More secondary cases
- Diagnostic challenges

- More and More Severe Dengue
- Encephalopathy, Hepatitis
- Increased Mortality

Crimean-Congo Haemorrhagic Fever



MANIPAL
ACADEMY of HIGHER EDUCATION
Deemed to be University under Section 3 of the UGC Act, 1956

Kyasanur Forest Disease (KFD) (Monkey Fever)

Monkey Fever- Shimoga, India 1957

Early Summer, 1957 (February)

- Unusual death of red faced **Bonnet macaques** and **Black faced langurs** in the **Kyasanur forest, Karnataka, South West India.**
- Few weeks later severe **acute febrile illness with encephalitis/ haemorrhage** among locals with **high mortality (10%)**

- **Dr. Work (VRC, Pune) and team isolated a new pathogen**

- Named **Kyasanur Forest Disease Virus (KFDV)**

Epidemiology of KFD

- **Agent** : **KFDV**
- **Vector and Reservoir host** : Ticks
- **Hosts** :

  Porcupines, rats, squirrels, mice, shrews, cattle
- **Amplifying host** :

  Red faced Bonnet – *Macaca radiata*

  Black faced Langur –*Semnopithecus entellus*
- **Principal Vector** :

  Haemophysalis spinigera
- **Accidental host** : Human

(Dead end host- No human to human transmission)

- **Transmission** :

  Bite of infected hard ticks

  Transoveraian and Transtadial transmission

Haemophysalis spinigera

Red faced Bonnet Monkey

Black faced Langur Monkey

Life Cycle of KFD

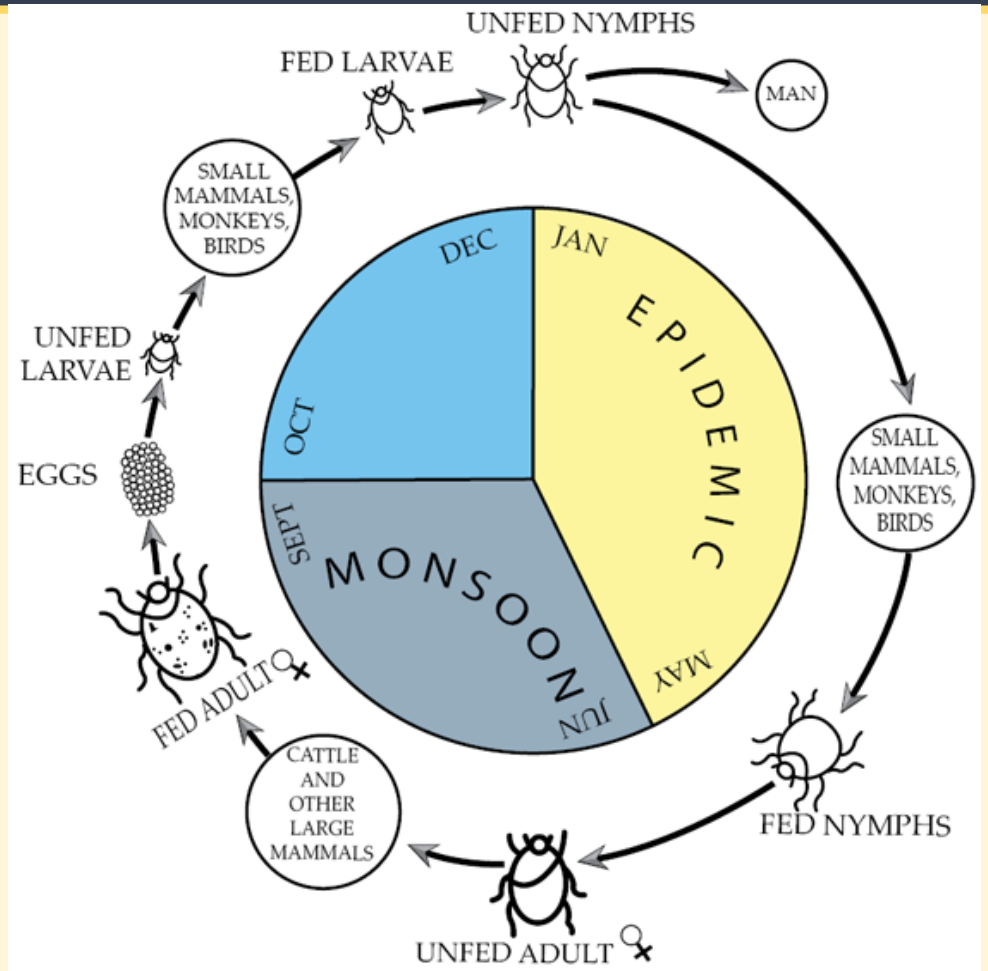


Fig. 1: Life cycle of KFD virus with seasonal incidence of KFD

KFD- Clinical features in human

- **Incubation period - 3 to 8 days**
- **Sub-clinical, clinical and fatal (Mortality 1-10%)**
- **Bi-phasic illness, viral haemorrhagic fever (VHF)**

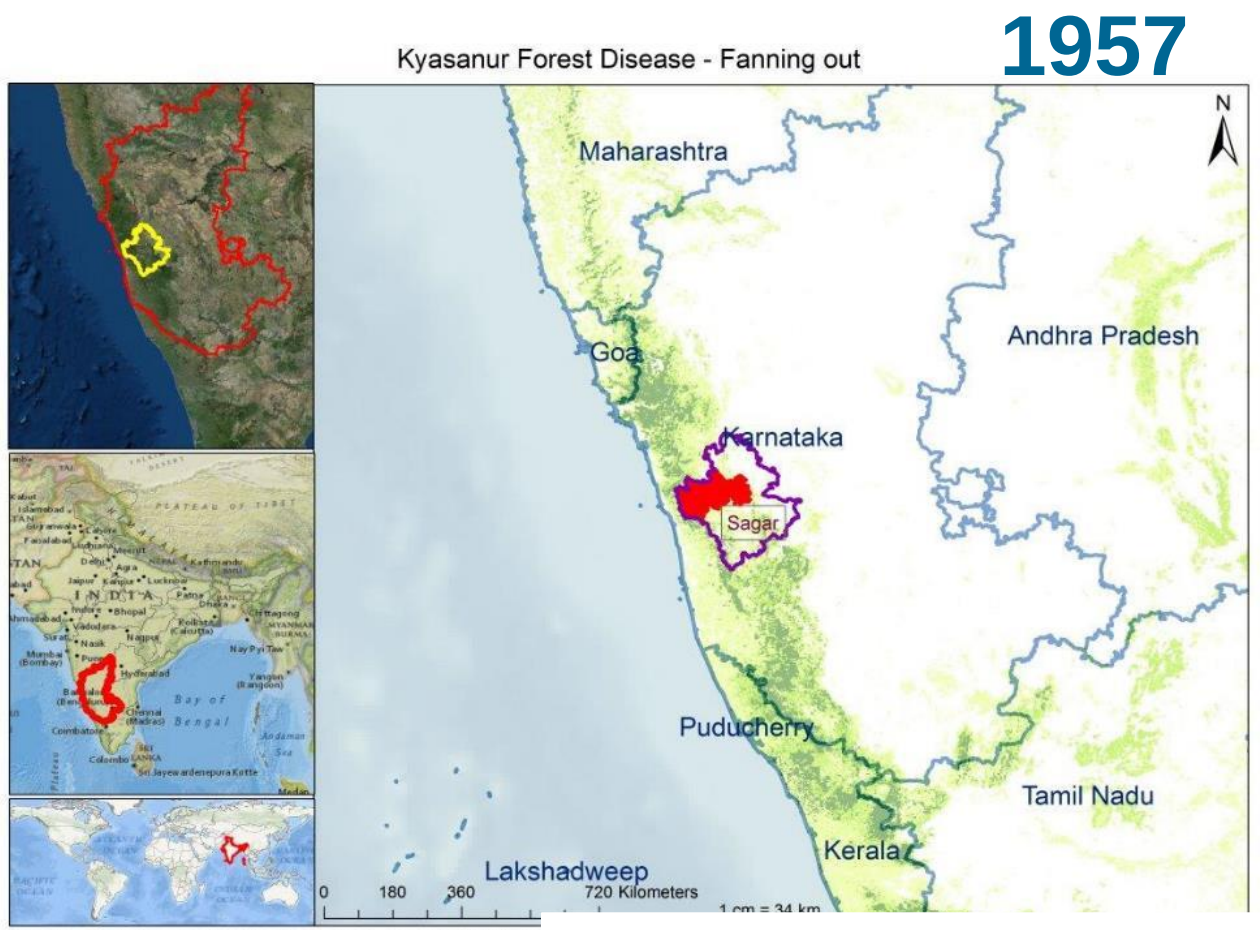
- **First phase: 7-12 days post incubation period**
  - Sudden onset of continuous high grade fever
  - Diarrhea, vomiting
  - Severe prostration, myalgia and headache

- **Second phase: 2-12 days after an afebrile period of 1-2 weeks**
  - Meningeal signs, altered sensorium, seizures
  - Bleeding manifestations

- **Prolonged convalescent period (may last for few months)**

(Khorshed Pavri; Reviews of Infectious Diseases, Vol 11, Supplement 4, May – June 1989)

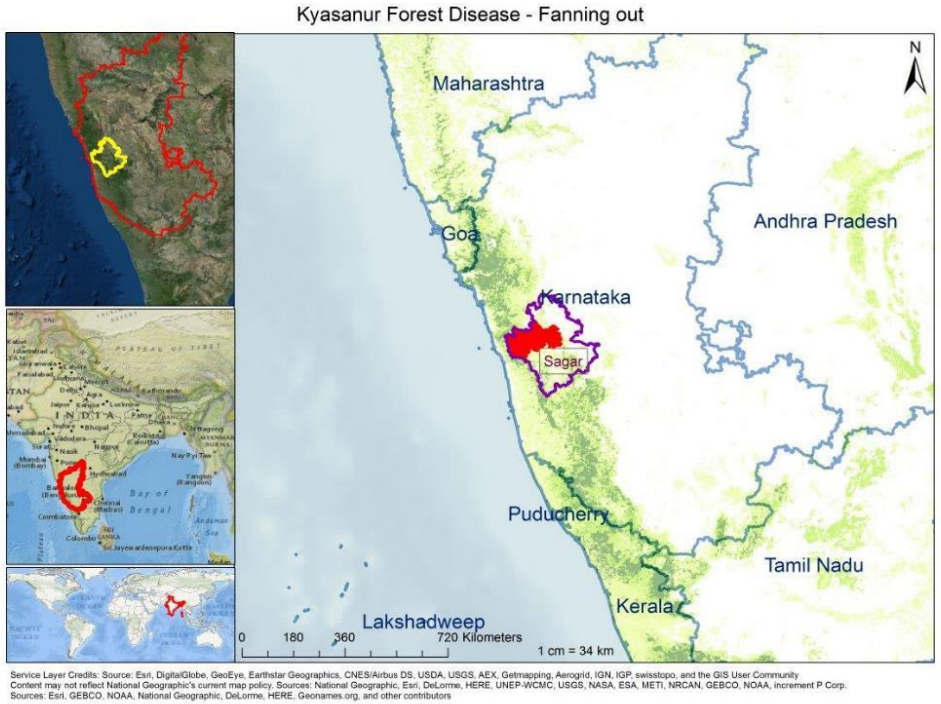
Expanding boundaries of KFDV geographical distribution



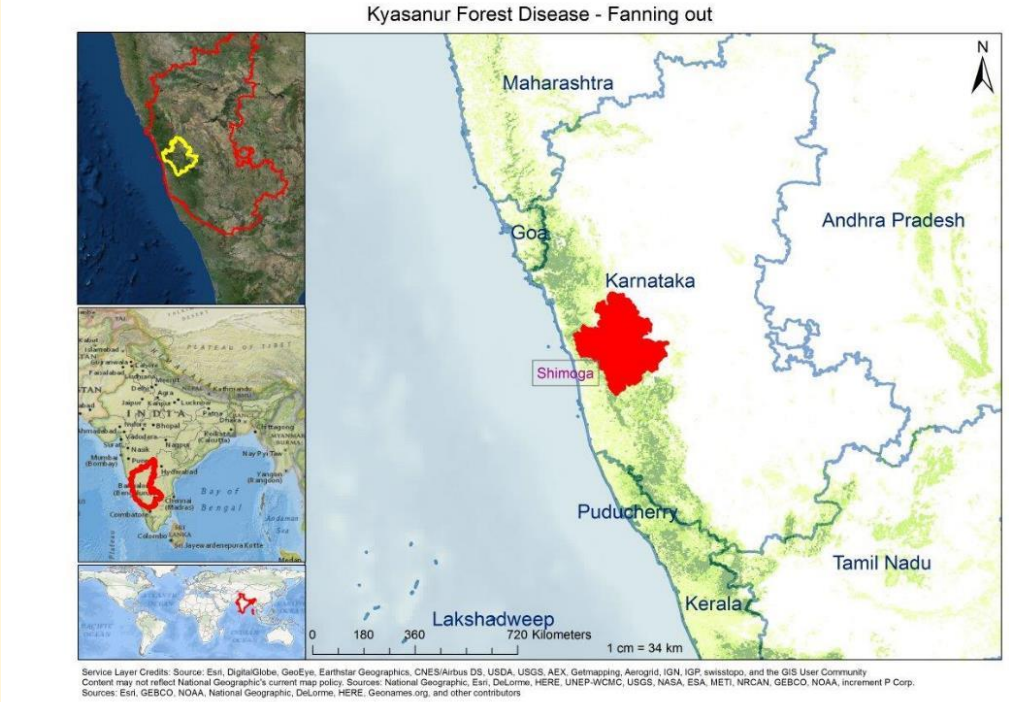
(Limited to Karnataka State of India)

Outcome : Redrawing boundaries of KFD

1957



1958-1960

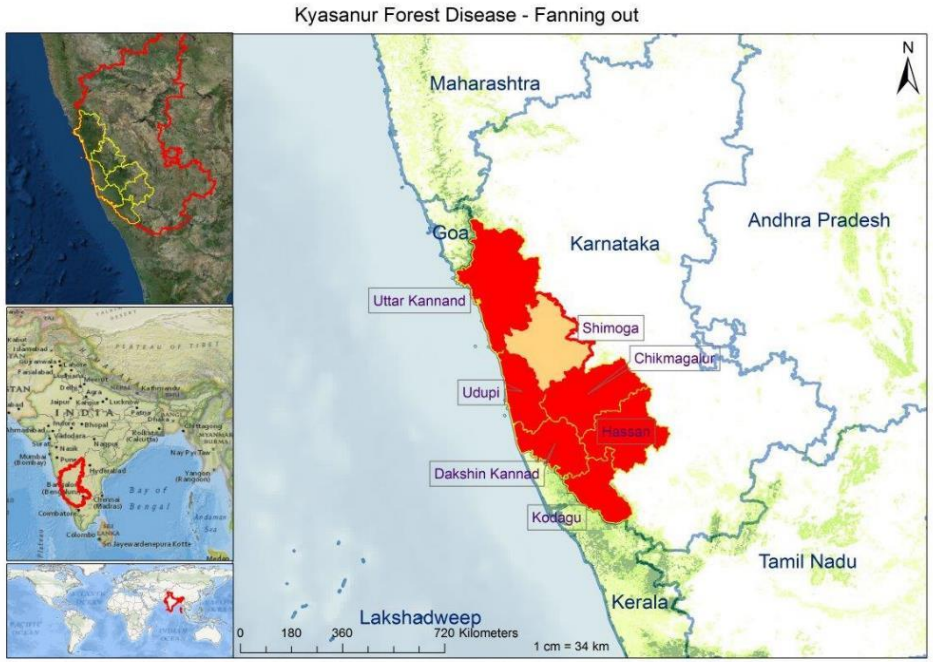


(Limited to Karnataka State of India)

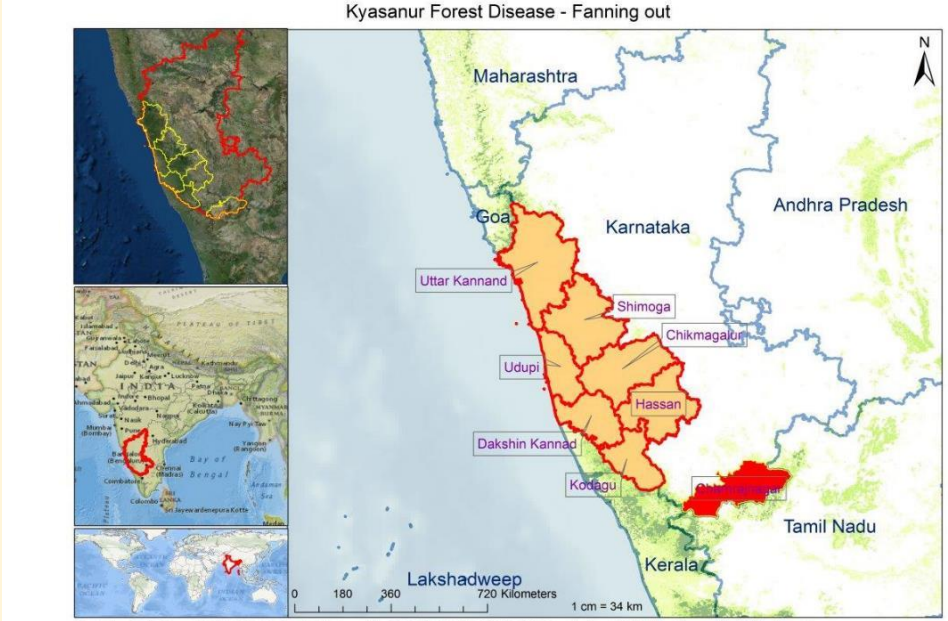
Unpublished data

Outcome : Redrawing boundaries of KFD

1961-2011



2012



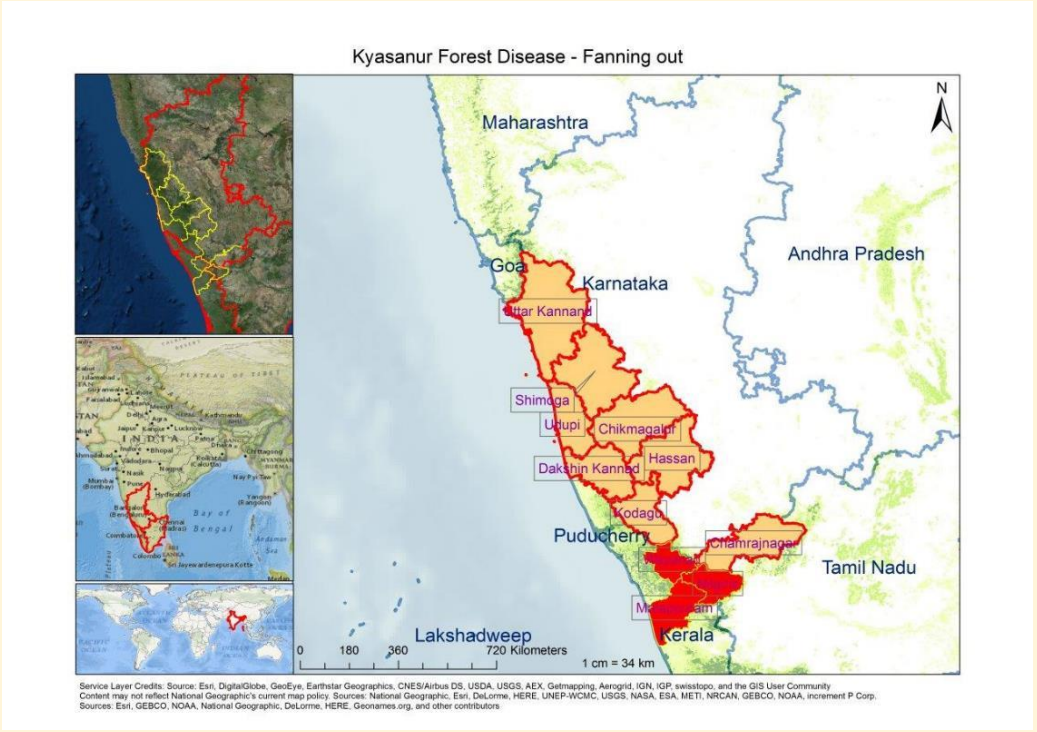
(Limited to Karnataka State of India)

Unpublished data

MANIPAL ACADEMY of HIGHER EDUCATION
(Deemed to be University under Section 3 of the UGC Act, 1956)

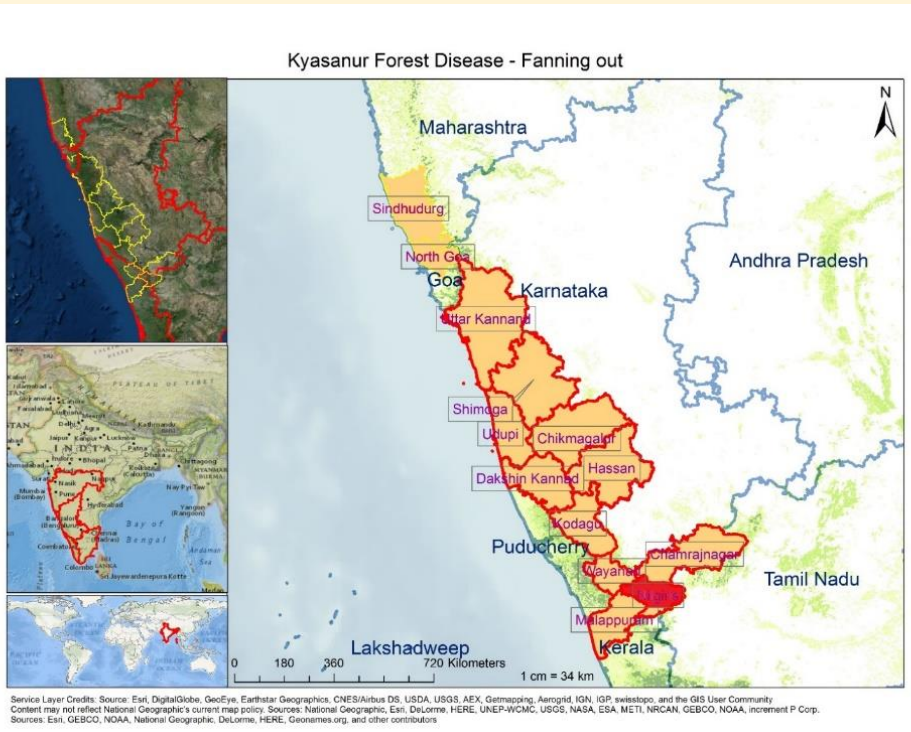
Outcome : Redrawing boundaries of KFD

2013-2014



(Karnataka and Kerala States of India)

2015-2017

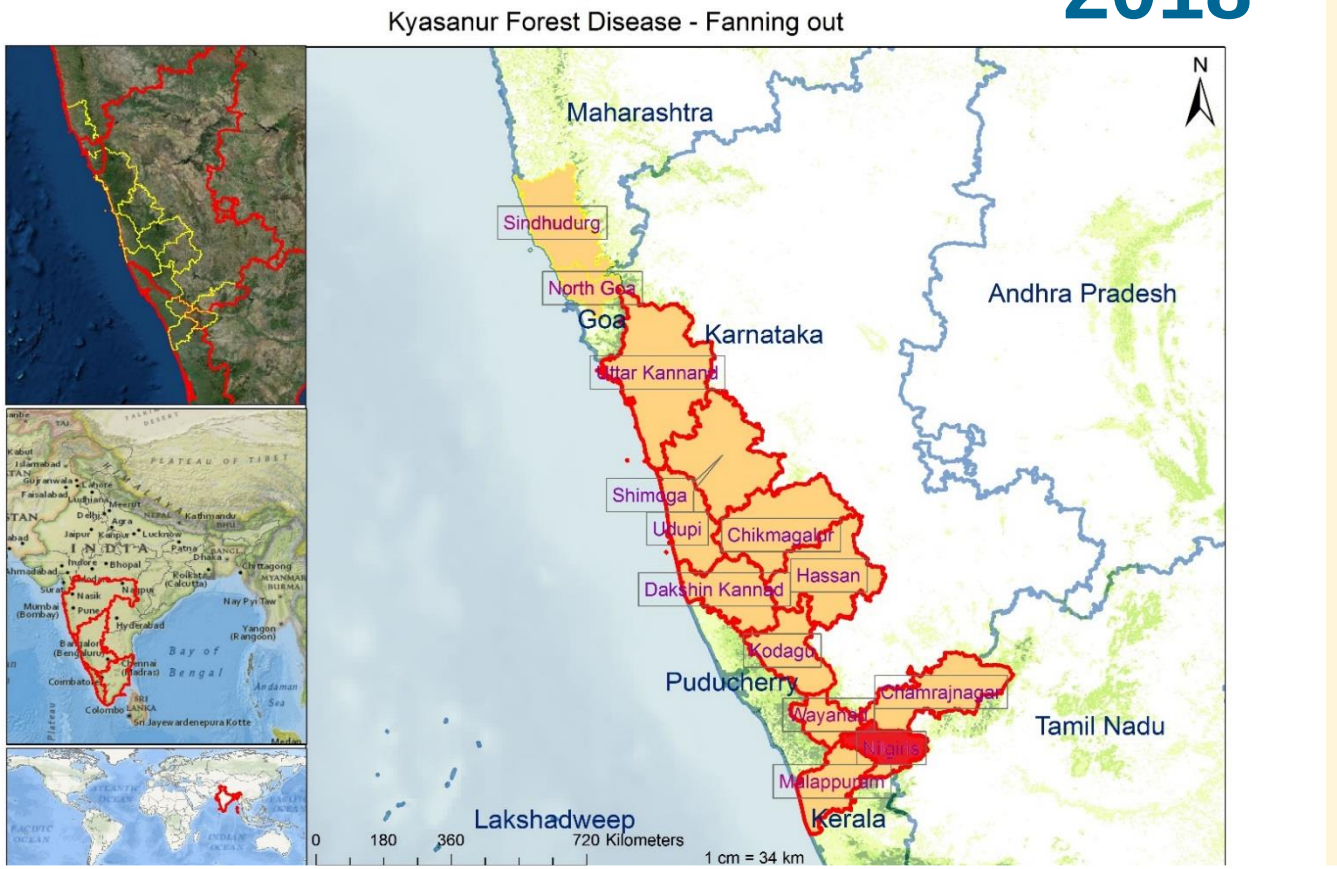


(Karnataka, Kerala, Tamil Nadu, Goa and Maharashtra)

Unpublished data

Expanding boundaries of KFDV geographical distribution

2018



(Karnataka, Kerala, Tamil Nadu, Goa ans Maharashtra)

Unpublished data

Distribution of KFD among AFI cases n=723

Total cases recruited= 41,008 | Study period: June 2014 to Sept 2018

- **723 (3.5%) were KFDV real-time PCR-positive**

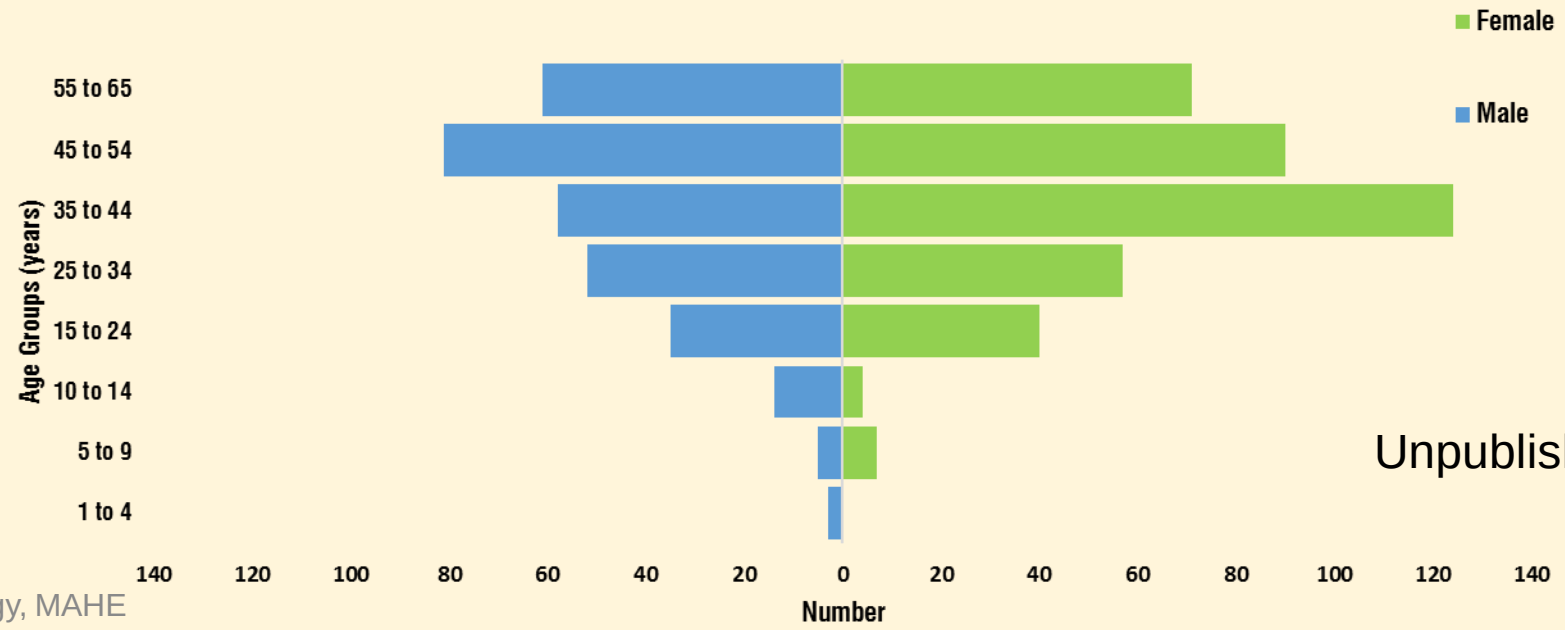
State	KFD positive n (%)
Goa	374 (51.7)
Karnataka	163 (22.5)
Maharashtra	112 (15.5)
Kerala	46 (6.4)
Tamil Nadu	28 (3.8)
Total	**723**

Unpublished data

KFD by Age and Gender

KFD Positive (N = 723)	
Age, Mean (SD)	40 (14.1)
Female, n (%)	408 (56.4)

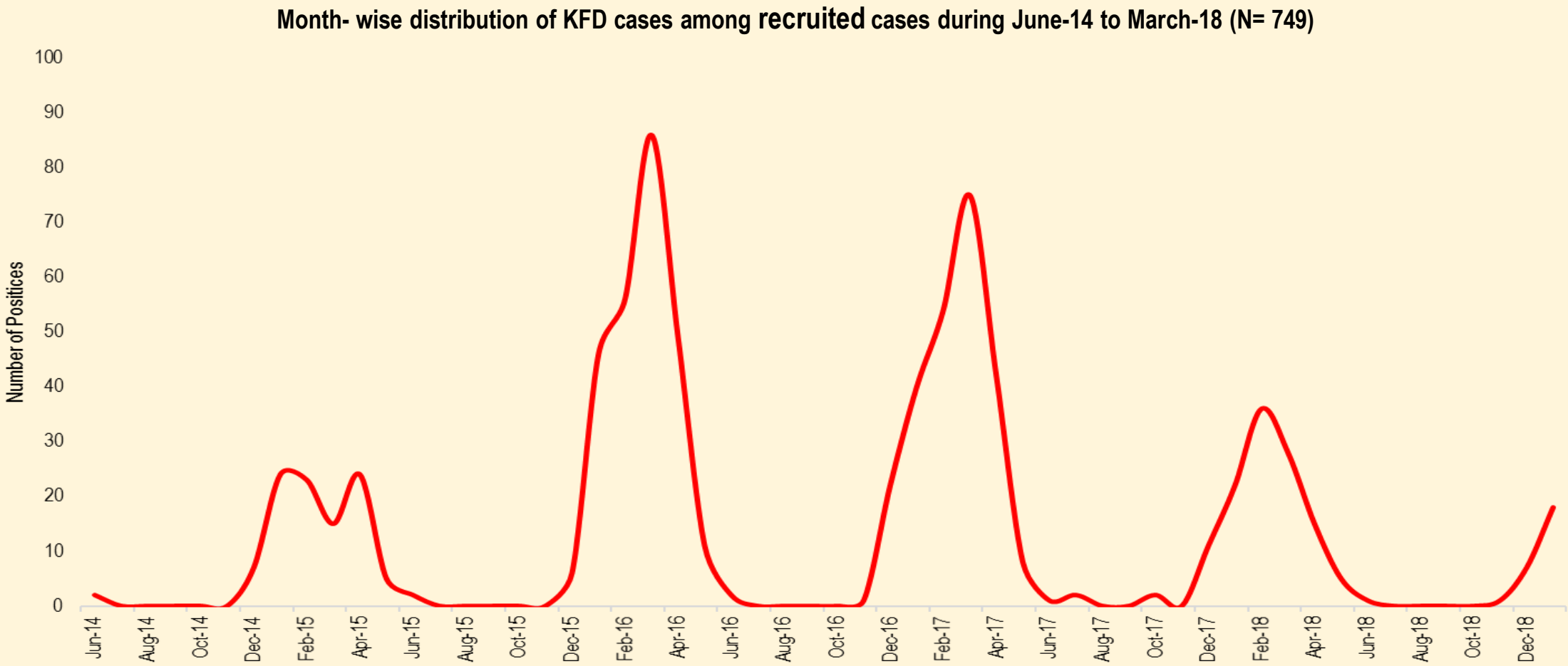
Age distribution of the KFD positive cases (n = 723)



Unpublished data

MANIPAL
ACADEMY of HIGHER EDUCATION
(Deemed to be University under Section 3 of the UGC Act, 1956)

Seasonality of KFD, June 2014- Jan 2019



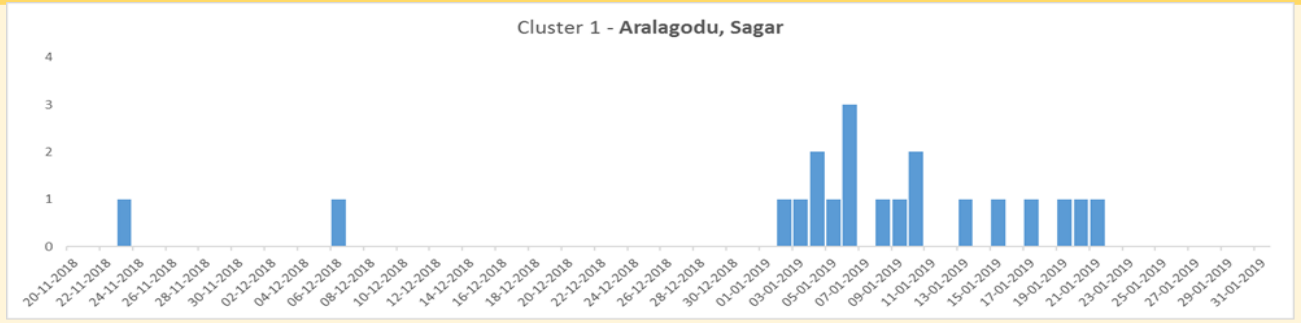
Unpublished data

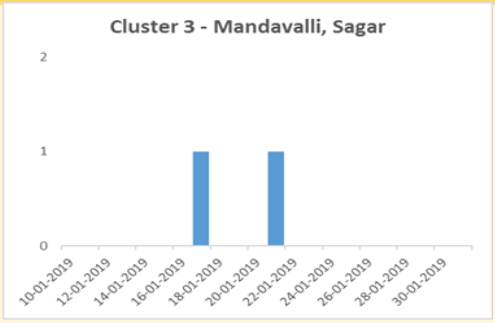
KFD- Nov 2018- May 2019 season

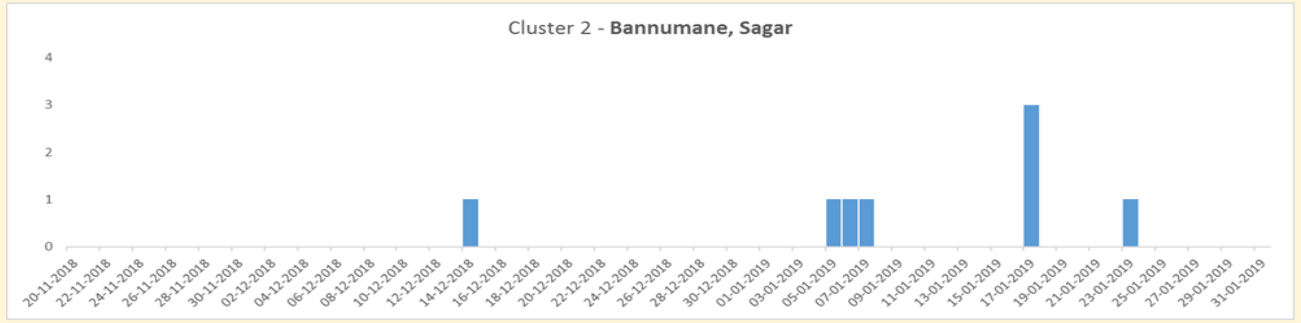
- Active in western ghat regions of
- Karnataka (sagara, thirthahalli, Bairakoppa)
- Kerala (Wayanad)
- Tamilnadu (Nilgiri)
- Goa (Valpoi)
- Maharashtra (Sindhudurg)

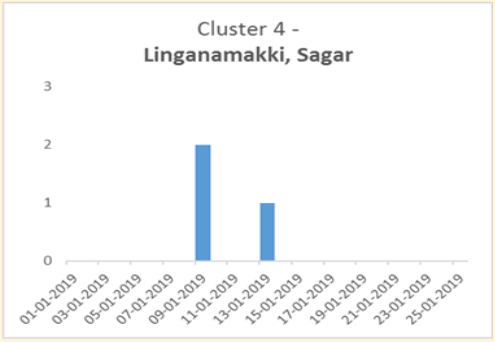
MANIPAL ACADEMY of HIGHER EDUCATION
(Deemed to be University under Section 3 of the UGC Act, 1956)

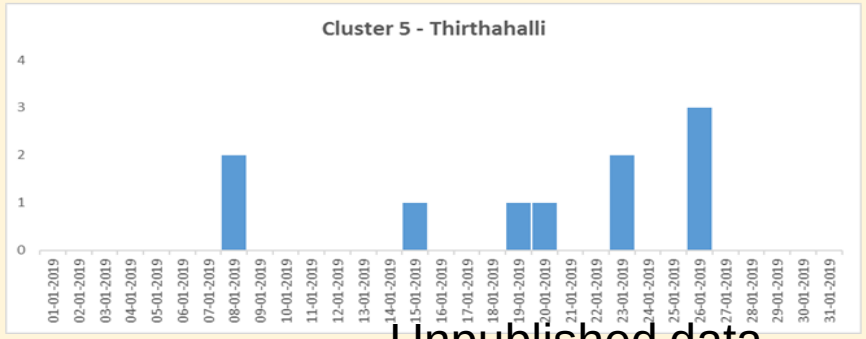
KFD- 2019 situation in Karnataka – It is not a single outbreak but multiple outbreaks (Nov – June)











Unpublished data

Clinical Manifestations of KFD (2014-18) (n=723)

Clinical features upon presentation	KFD confirmed cases (n=723)	
	N	%
Fever	723/723	100
Myalgia	637/723	88
General weakness	622/723	86
Nausea/vomiting	365/619	60
Abdominal pain	211/723	30
Diarrhoea	177/723	24
Prostration	102/561	18
Bleeding manifestations	**16/598**	**3**
Altered sensorium/ Seizures	9/702	1

Case fatality – 10/723 (**1.4%**)

Unpublished data

Laboratory Investigations (N=723)

Lab parameters	KFD confirmed cases (n=723) N	%
Total WBCs		
Leukopenia (< 4000 cells/µl)	486 / 584	**83**
Platelets		
Thrombocytopenia <150,000/µl	372 / 593	**63**
Liver functions tests		
Elevated Aspartate aminotransferase (AST) >40 IU	304 / 390	**78**
Elevated Alanine aminotransferase (ALT) >40 IU	184 / 392	**47**
C-reactive protein		
≤ 6 mg/dl	297 / 331	**90**

Unpublished data

Major Risk Factors for KFD

Risk Factor	Adjusted OR (95%CI)
Going to forest	5.6 (4-7.9)
Exposure to ticks	2.7 (2.6-5.3)

Unpublished data

Ecology of KFDV, Karnataka, India
- Dry leaves from forest floor in cattle shed

Unpublished data

Ecology of KFDV, Kerala, India
- Living in coffee plantation on forest fringe

Unpublished data

MANIPAL
ACADEMY of HIGHER EDUCATION
(Deemed to be University under Section 3 of the UGC Act, 1956)

Ecology of KFDV, Goa, India
- Cashew plantation within forest

Unpublished data

Ecology of KFDV, Tamilnadu, India
- Cardamom plantation –forest fringe

Unpublished data

MANIPAL
ACADEMY of HIGHER EDUCATION
(Deemed to be University under Section 3 of the UGC Act, 1956)

Ecology of KFDV, Aralagodu, Karnataka, India - Aracanut plantation –forest fringe

Unpublished data

KFD Vaccination

- Vaccine developed in early 1960s
- Chick embryo fibroblast vaccine – Formalin inactivated
- Efficacy is around 30%- Yearly vaccination required
- URGENT NEED FOR A VACCINE

KFD vaccination	Vaccinated (at least 1 dose) N (%)	Not vaccinated N (%)
KFD Positive (n=702)	127 (18)	576 (82)
KFD Negative (n=37,223)	1019 (3)	36,206 (97)

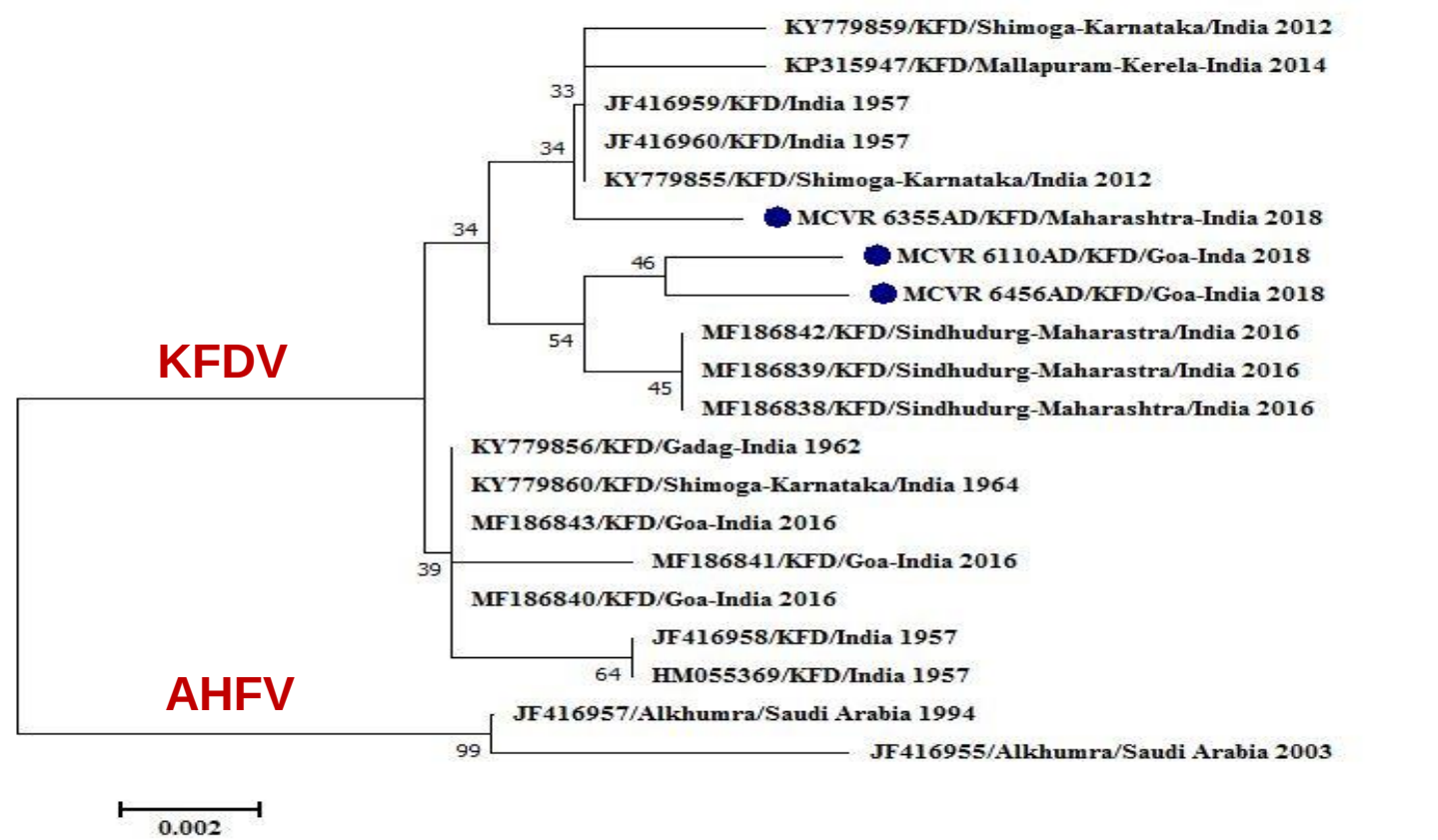
Unpublished data

Immune Response During KFDV Infection

- Marked leukopenia
- Increased CD8 T cells
  - 40-60% were activated (Majority proliferating Ki67^{+})
  - Expressed high levels of Granzyme B but not Perforin
- Moderate increase in the activated CD4 T cells
- Very few cases had demonstrable B cell activation (In spite of 12 cases with history of receiving 1-2 doses of KFD vaccine)
- Antibody-secreting cells (Plasmablast) were seen only in few cases
- Antibody (IgM and IgG) detectable only after 10 days POI (Viremia viral RNA in blood) up to 10 days POI
- **Consistent with antigen activation via the T-cell receptor** (Ki67^{+} CD8 T Cells had CD45RA low, Bcl-2low, and PD-1high)

Unpublished data

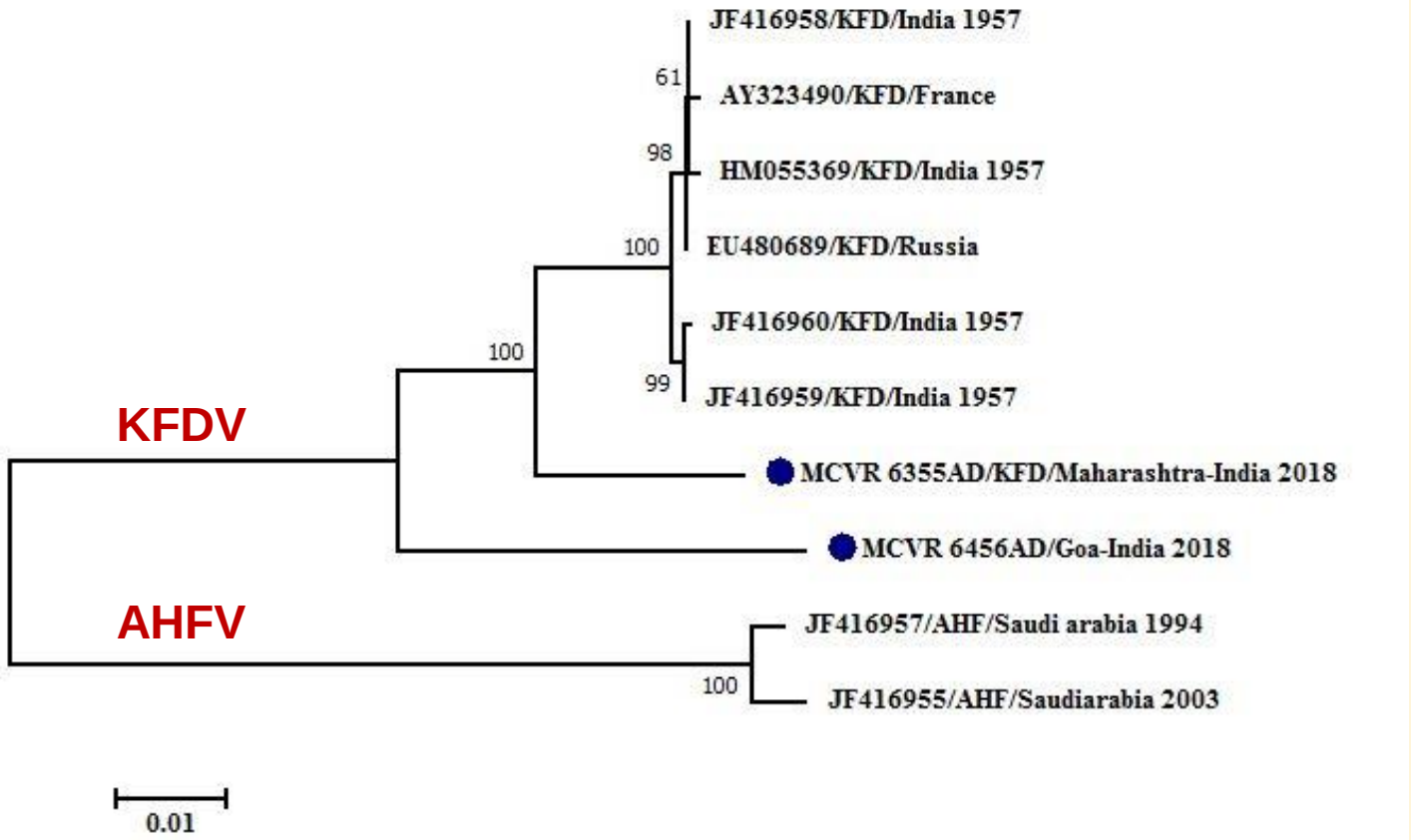
Phylogenetic Analysis of the Envelope Gene of KFDV



Neighbor-joining method with MEGA version 7 software. Bootstrap probabilities of each node were calculated with 1000 replicates

Unpublished data

Phylogenetic Analysis of the Complete Genome of KFDV



Maximum likelihood method with MEGA version 7 software. Bootstrap probabilities of each node were calculated with 1000 replicates

Unpublished data

KFD - Summary

- KFD is not restricted to the Shimoga forest region but is now detected along the entire Western Ghat region of India
- We recorded cases without confirmed forest incursion
- Need for research to elucidate actionable risk factors
- KFD has more diverse clinical presentation than previously observed
- Urgent need for a point of care diagnostics
- Need for research to understand pathogenesis
- Urgent need for an effective vaccine – Suitable candidate

Unpublished data

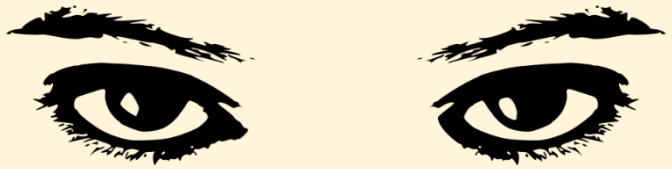
VHF - Diagnostic challenges

- Risk group 3 and 4 organisms
- Acute cases
- Preferred diagnostic assays: Nucleic acid detection and (Antibody detection)
- Limited availability of assays and access
- Non availability of point of care tests
- Referral testing – Turn around time
- Change in strategy - Need for reducing the risk – removing hazard – Inactivation of samples

Hospital and laboratory biosafety – What is required?

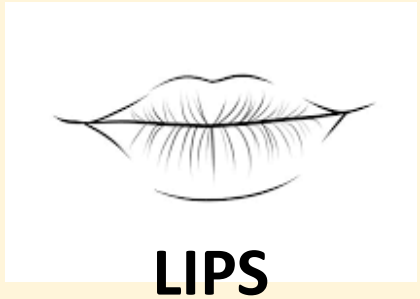
- Microbiological / Virological risk assessment
- Biosafety containment based on the risk assessment
- Use of appropriate risk reduction activities
- Follow good Clinical / laboratoty practices and procedures (GCPP / GLPP)
- Training (frequent) and administrative controls and auditing
- Use of appropriate PPEs and Engineering controls
- Need locally sustainable relevant solutions
- Increased awareness and continuing education

Personal Protective Equipment (PPE)

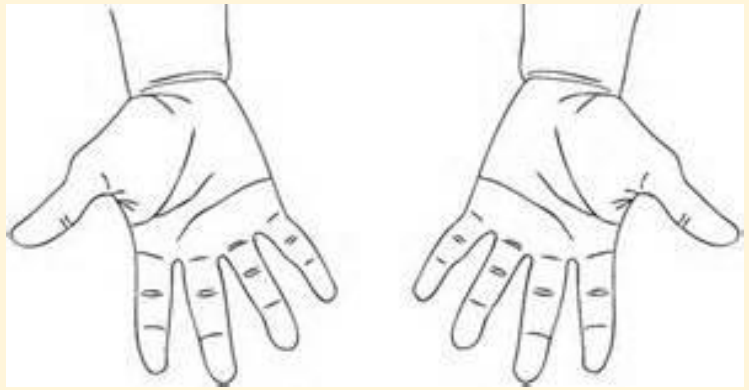


EYES

NOSE



LIPS



HANDS

You must ALWAYS protect these areas of the body!

Personal Protective Equipment (PPE)

Face Shield

Gloves

Face Mask

Gown

PPE is specialized clothing or equipment worn by health care workers to protect against germs

Laboratory Biosafety- How to practice in daily work?

- Good Clinical practices and attitude
- Administrative procedures
- Engineering controls and PPE

- PPE is the least protective to ensure biosafety
- **Your good practices are the best way to ensure biosafety**

- Make biosafety / personal safety a culture
- Make biosafety practices a behavior

Preparedness in the hospital

- Clear plan and SOPs in place – including reporting channel
- Who is responsible?
- Quick risk assessment in the case of an event
- Availability of PPE and other stocks (regular and in emergency)
- Mock drills
- Refresher training
- Administrative and engineering controls
- Awareness
- All HCWs are important – Preparedness is as good as the weakest link in the chain.
- Need special programs to train different categories of HCWs
- Administrative and financial support.

EBOLA – CUBE – Bio secure workspace – a sustainable solution

www.who.int

Conclusion

- Infectious Diseases will continue to emerge, re-emerge and spread.
- Human-induced environmental changes, inter- species contacts, altered social conditions, demography and medical technology affect microbes' opportunities
- Most Haemorrhagic viral diseases cause nosocomial transmission
- We need to learn to live with it and be prepared to face the challenge

Safety first, work next!

MANIPAL
ACADEMY of HIGHER EDUCATION
(Deemed to be University under Section 3 of the UGC Act, 1956)

Acknowledgements

- Ministry of Health and Family Welfare, Govt of India
- Ministry of Health and Family Welfare, Govt of Kerala Karnataka, Goa, Maharashtra and Tamilnadu.
- Indian Council of Medical Research, New Delhi
- National Centre for Disease Control, New Delhi
- National Institute of Virology, Pune
- Centres for Disease Control and Prevention (CDC), Atlanta, USA –
- Manipal Academy of Higher Education (Deemed to be University)
- Manipal Institute of Virology Team

MANIPAL
ACADEMY of HIGHER EDUCATION
(Deemed to be University under Section 3 of the UGC Act, 1956)

Thank You

Follow us on twitter @MCVRMU

Manipal Institute of Virology,
Manipal Academy of Higher Education, Manipal, India
virology@manipal.edu, www.manipal.edu/dvr