Rabies: Recent Advances

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Fatal encephalitis

Rabies in India: Facts & Figures

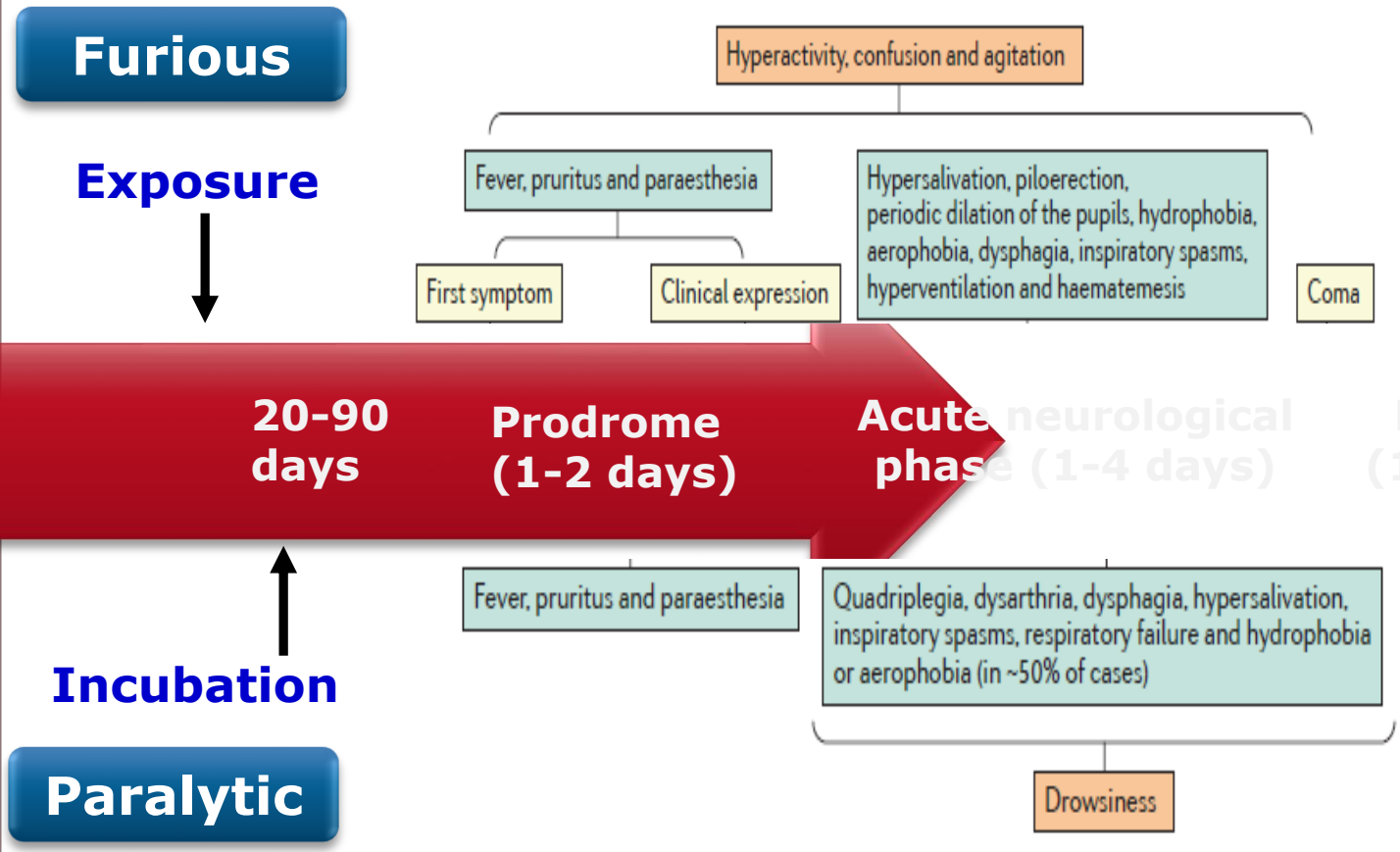
- **Highest global burden (20,000 deaths annually)**
- **>95% of human cases canine mediated; 60% victims children**
- **Endemic in all states except Andaman, Nicobar & Lakshadweep islands**
- **Estimated stray dogs: 25-30 million**
- **17.4 million animal bites annually; PEP ~4 million**
- **A dog bites a human every 2 seconds and every 30 minutes a human dies of rabies**
- **Not a notifiable disease**

Animals transmitting Rabies (India)

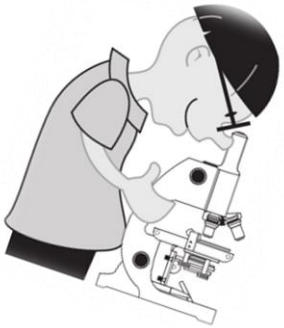
- Dogs (95% cases)
- Cats, monkeys, mongooses, wild animals
- Cattle, buffalo, horses, donkeys, pigs

- Not transmitted by
- House rats/mice, rabbits, birds, squirrels, bats

Human rabies: Clinical course



Fooks et al. Rabies. Nat Rev Dis Primers.2017;3:17091

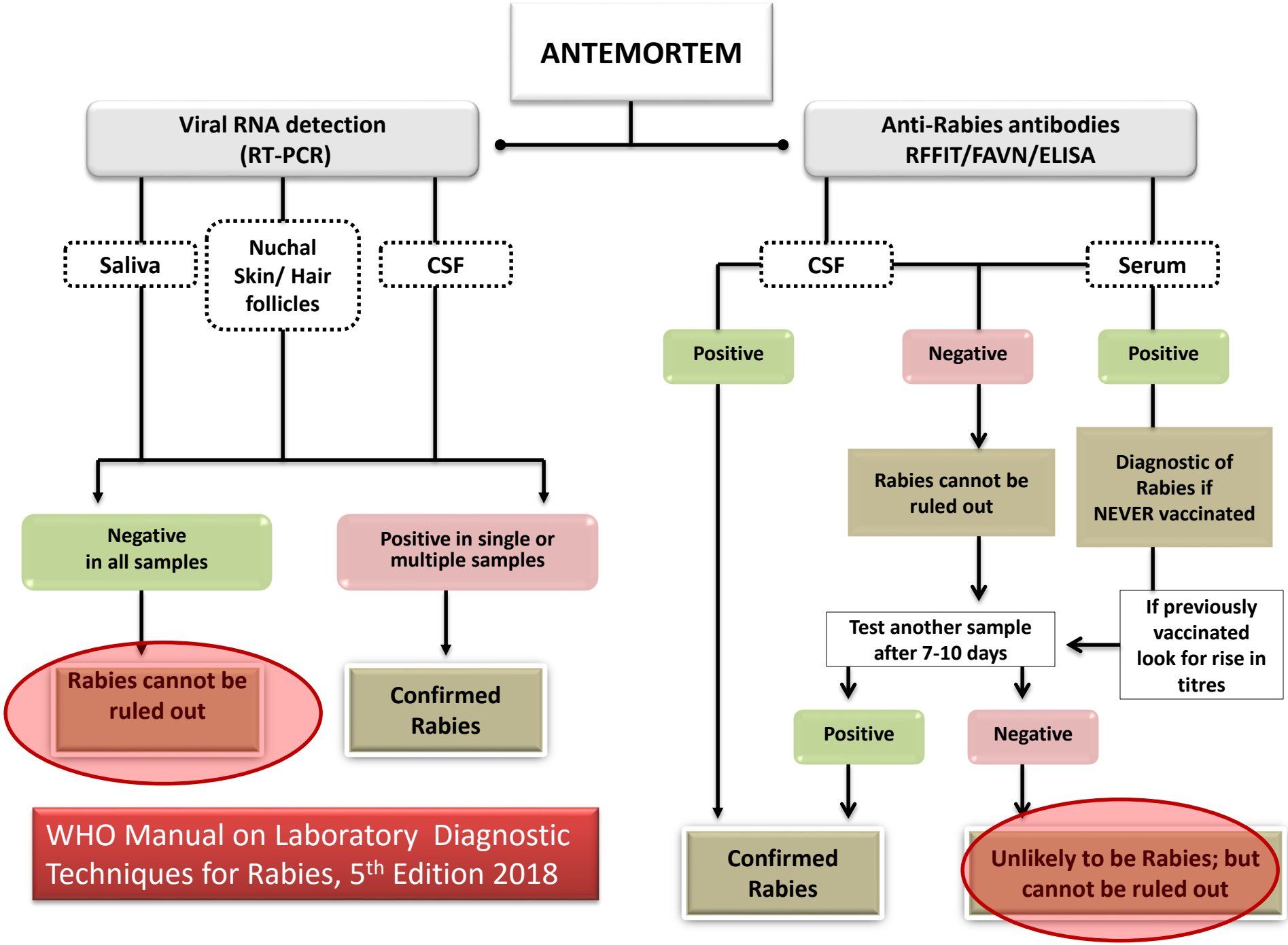


Need for Lab Diagnosis

- Early diagnosis helps avoid unnecessary tests and treatment
- Distinguish from GB syndrome/other mimics in paralytic/atypical rabies
- Patient management/Barrier Nursing
- Case closure and grief counseling
- Prophylactic vaccination to close contacts
- Characterization of causative agent
- Surveillance and estimation of disease burden

Clinical Mimics

- Guillain-Barre syndrome
- Anti-NMDA receptor encephalitis
- Psychiatric disorders
- Post-vaccinal encephalitis
- Scorpion and snake envenomation
- Cerebral malaria, herpes simplex encephalitis
- Illicit drug use
- Organophosphate poisoning


ANTEMORTEM
Viral RNA detection (RT-PCR)
Anti-Rabies antibodies RFFIT/FAVN/ELISA
Saliva
Nuchal Skin/ Hair follicles
CSF
CSF
Serum
Positive
Negative
Positive
Negative in all samples
Positive in single or multiple samples
Rabies cannot be ruled out
Diagnostic of Rabies if NEVER vaccinated
Rabies cannot be ruled out
If previously vaccinated look for rise in titres
Test another sample after 7-10 days
Positive
Negative
Confirmed Rabies
Confirmed Rabies
Unlikely to be Rabies; but cannot be ruled out
WHO Manual on Laboratory Diagnostic Techniques for Rabies, 5th Edition 2018

Obtained by craniotomy or by sub-occipital cisternal puncture, retro-orbital or a trans-nasal route.

POSTMORTEM

Brain Tissue

AVAILABLE

NOT AVAILABLE

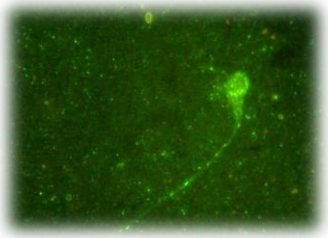
Fluorescent Antibody Test (FAT) (or PCR)

Positive

Negative

Confirmed Rabies

NEGATIVE for Rabies



Viral RNA detection (RT-PCR)

Nuchal skin

CSF

Single or both samples POSITIVE

Both samples NEGATIVE

Confirmed Rabies

Rabies cannot be ruled out

Diagnostic Challenges

- 'Gold standard'-Antigen detection by DFA in brain tissue (post-mortem)
- Obtaining consent for autopsy is a challenge
- Lab facilities for antemortem diagnosis few
- Sensitivity of antemortem diagnosis low-multiple tests on several/serial clinical samples required to confirm diagnosis
- Antemortem tests can 'rule in' Rabies but cannot 'rule out' Rabies

Human rabies: ante-mortem diagnosis

(NIMHANS 2012-2017; 267 cases)

Test	Sample	No of cases Tested	Number Positive
Real Time PCR	CSF	169	14 (8.2 %)
	Nuchal Skin	87	16 (18.4%)
	Saliva	140	28 (20%)
RFFIT (Antibodies)	CSF	189	61 (32%)

Antemortem Diagnosis in 115/267 (43%)

Approach to Rabies Post-exposure Prophylaxis (PEP)

- WOUND MANAGEMENT
- PASSIVE IMMUNIZATION (RIG)
- ACTIVE IMMUNIZATION (ARV)

Category of Exposure & PEP

Category	Type of contact with a suspect or confirmed rabid domestic or wild animal, or animal unavailable for testing	Type of exposure	Recommended post-exposure prophylaxis (PEP)
I	• Touching or feeding of animals • Licks on intact skin	**None**	**None,** if reliable case history available
II	• Nibbling of uncovered skin • Minor scratches or abrasions without bleeding	**Minor**	**Administer vaccine immediately.**
III	• Single or multiple transdermal bites, scratches or licks on broken skin • Contamination of mucus membranes with saliva (licks) • Exposure due to direct contact with bats	**Severe**	**Administer rabies immunoglobulin and vaccine immediately.**

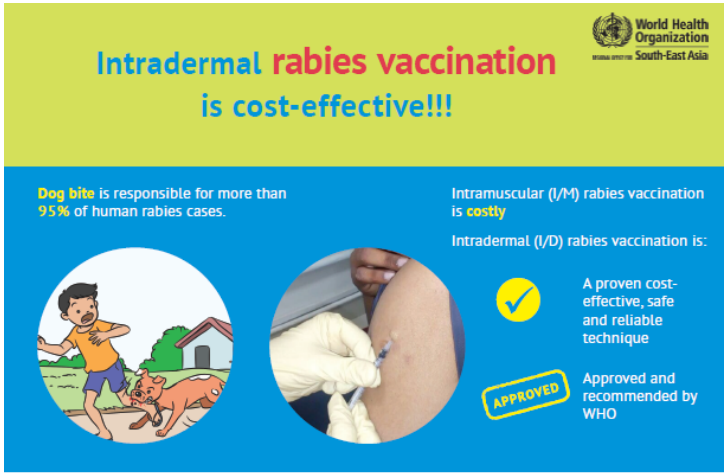
Wound Management

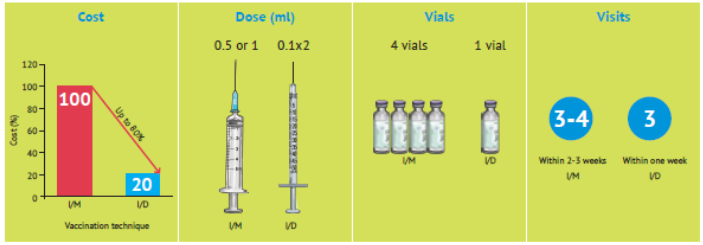
- Immediate wound care following an exposure to rabies
- Often a neglected step; when done appropriately reduces the risk (50–70%) of developing rabies

- Immediate washing and flushing with water alone or by using soap and water (running water; 10-15 minutes)
- Disinfection of the wound using povidone iodine
- AVOID covering the wound with dressings or bandages
- Suturing of the wound is usually avoided/postponed; where suturing is necessary ensure that RIG has already been applied locally
- Antimicrobials and tetanus toxoid can be administered if needed

Intradermal rabies vaccination in India
A paradigm shift

- Administering minute doses (0.1mL) of vaccine into the layers of skin
- Rational and Scientific; Highly Immunogenic, Safe and Efficacious
- Reduction in volume and costs (60-80%)
- Approved by WHO since 1992
- Used in Thailand, Philippines and Sri Lanka since 1993
- Approved by DCGI since 2006 (India)
- Implemented successfully in several states (public sector)





Use I/D schedule to improve availability, accessibility and affordability of rabies vaccine!

Post-exposure Propylaxis (PEP)

Intradermal (ID)

Route	Regimen	Days				
		0	3	7	14	28
ID	Updated Thai Red Cross					

One ID dose= 0.1 mL

Post-exposure Propylaxis (PEP)

Intramuscular (IM)

Route	Regimen	Days				
		0	3	7	14	28
IM	Essen					

One IM dose= entire vial
(0.5 or 1 mL)

Passive Immunization

- Necessary in all category III exposures (and Cat II exposures in immunocompromised individuals)
- Many PEP failures due to lack of RIG administration
- RIG administered only ONCE, preferably within 24 hrs of exposure; Can be given within 7 days of first vaccine dose
- The maximum dose is 20 IU (hRIG) and 40 IU (eRIG) per kg body weight. There is no minimum dose
- Local infiltration

Rabies monoclonal antibodies

- First mAb licensed for clinical use: Serum Institute of India
- Will help fill critical health gaps

- Concentrated product;
- Small volume (3.33 IU/kg body wt)
- rDNA technology-Less prone to availability/purity/safety issues
- Cheaper than hRIG
- No skin sensitivity testing

PEP for close contacts of patients

Pre-exposure Propylaxis (PrEP)

Route	Regimen	Days				
		0	3	7	14	21/28
IM/ID	One-site					

Advantages of PrEP?

Fewer Injections!

NO RIG

Only 2 boosters (Day 0,3) on any re-exposure

Rabies PEP Regimens

In previously immunized

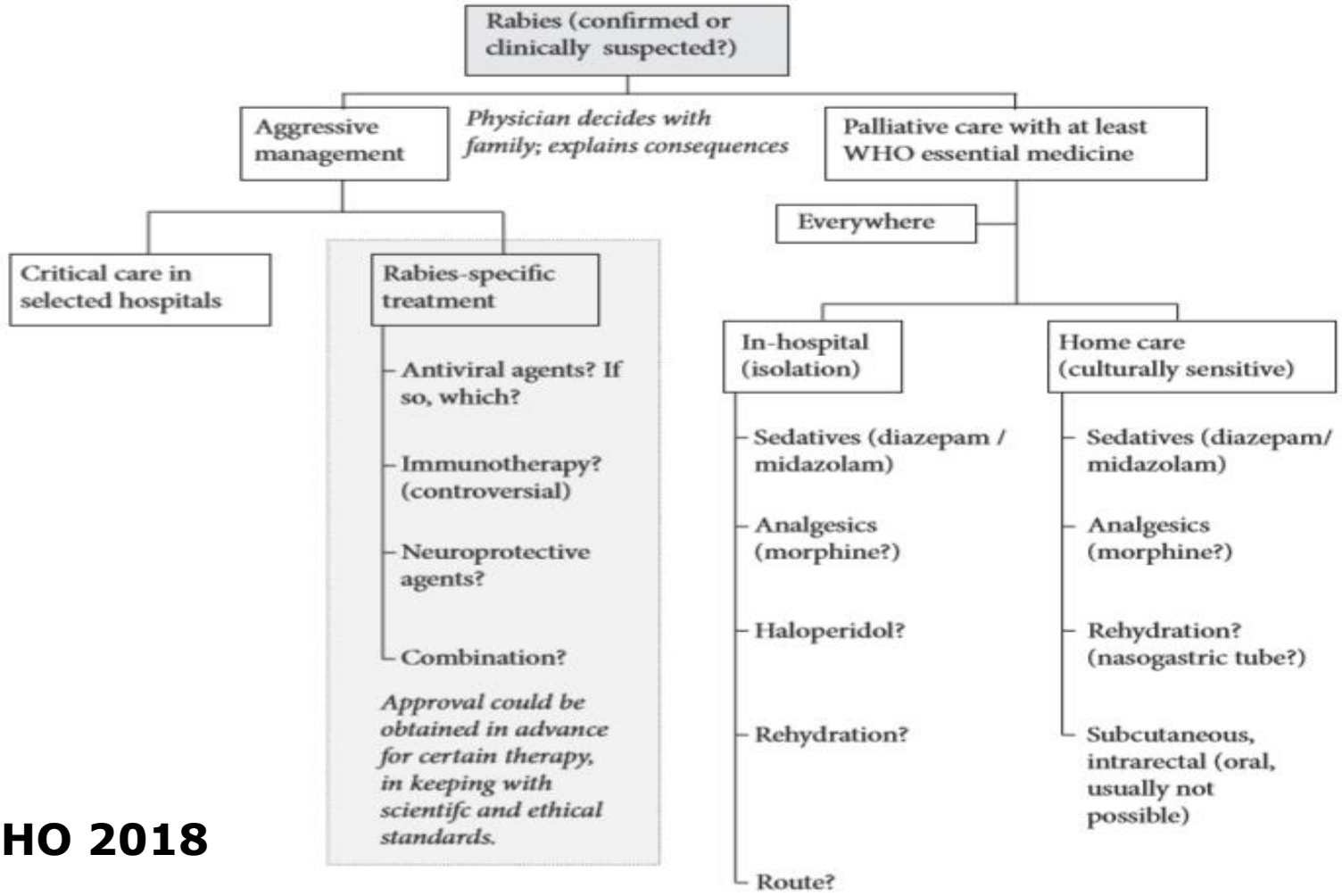
Route/Regimen	Days				
	0	3	7	14	28
1-site ID or IM					

NO RIG

- Day 0 is the day when the first dose of vaccine is administered.
- Deltoid area is the only acceptable site of IM vaccination in adults.
- In children, anterolateral aspect of thigh can be used.
- Vaccines should never be administered in the gluteal region.
- No contra-indications for rabies PEP

Management

Proposed algorithm to guide management of cases of confirmed or suspected human rabies



WHO 2018

Rabies Survivors?

Human Rabies Survivors Worldwide (1970-2014)

Country and year of disease onset	Sex and age (years) of the patient and disease outcome	Mode and site of exposure	PEP type and doses; type of RIG	Incubation period	Antibodies in CSF and serum (highest titres or concentrations recorded)	Type of antibody and method of testing	Viral material detected (sample tested)
India, 2014	Male, 6, severe sequelae*‡	Dog bite; neck and back	PCECV, 4; ERIG	~22 days	CSF (8,192); serum (>200,000)	RVNA; RFFIT	None (saliva, nuchal skin and CSF)
India, 2014	Male, 13, severe sequelae	Dog bite; right hand	PCECV, 3; none	~2 weeks	CSF (>64,000); serum (>64,000)	RVNA; RFFIT	Antigen (nuchal skin)
South Africa, 2012	Male, 4, severe sequelae	Dog bite on left ankle and scratch on forehead	Type NA, 3; none	~3–7 weeks (multiple exposures to dogs)	CSF (>13,975 IU/ml); serum (>13,975 IU/ml)	RVNA; RFFIT	None (saliva, nuchal skin and CSF)
USA, 2011	Female, 8, complete recovery§	Scratches from free-roaming, unvaccinated cats (probable source); site NA	None; none	Unknown	CSF (8); serum (160)	IgM antibody; IFA	None (saliva and nuchal skin)
India, 2011	Male, 17, severe sequelae‖	Dog bite; left calf	PCECV, 4; HRIG	~2 weeks	CSF (>8,000); serum (>16,000)	RVNA; RFFIT	None (corneal smear and nuchal skin)
India, 2010	Male, 4, severe sequelae¶	Dog bite; face	PCECV, 4; HRIG	25 days	CSF (512); serum (16,384)	RVNA; RFFIT	Antigen (nuchal skin) and RNA (nuchal skin and CSF)
Turkey, 2008	Male, 17, complete recovery#	Dog bites; left forearm and right shoulder	VCV, 1; none	~3 weeks	CSF (NA); serum (3,788)	RVNA; RFFIT	Antigen (corneal smear) and RNA (CSF and saliva)
Brazil, 2008	Male, 15, moderate sequelae	Vampire bat bite; site NA	Type NA, 4; none	~29 days	CSF (>100 IU/ml); serum (>100 IU/ml)	RVNA; RFFIT	RNA (nuchal skin hair follicles)
USA, 2004	Female, 15, mild sequelae**‡‡	Bat bite; left index finger	None; none	1 month	CSF (1,300); serum (1,604)	RVNA; RFFIT	None (saliva and nuchal skin)
India, 2000	Female, 6, severe sequelae	Dog bites; face and hands	PCECV, 3; none	20 days	CSF (312,000); serum (182,000)	RVNA; MNT	None (CSF, nuchal skin and corneal smear)
Mexico, 1992	Male, 9, severe sequelae	Dog bite; face	VCV, 3 and HDCV, 1; none	18 days	CSF (78,125); serum (134,800)	RVNA; RFFIT	None (saliva, nuchal skin and corneal smear)
USA, 1977	Male, 32, severe sequelae§§	Laboratory exposure to virus (aerosol)	None¶¶; none	~2 weeks (probable)	CSF (16,225); serum (175,000)	RVNA; RFFIT	None (nuchal skin and corneal smear)
Argentina, 1972	Female, 45, nearly complete recovery	Dog bite; left arm	SMBV, 14 and 2 boosters; none	21 days	CSF (160,000); serum (640,000)	RVNA; MNT	None (saliva, nuchal skin and corneal smear)
USA, 1970	Male, 6, complete recovery‖‖	Bat bite; left thumb	DEV, 14; none	20 days	CSF (3,200); serum (63,000)	RVNA; MNT	None (saliva, CSF, brain biopsy, corneal smear)

Fooks et al. Rabies. Nat Rev Dis Primers. 2017; 3:17091

Survival from rabies: Case series from India (2015-2017)

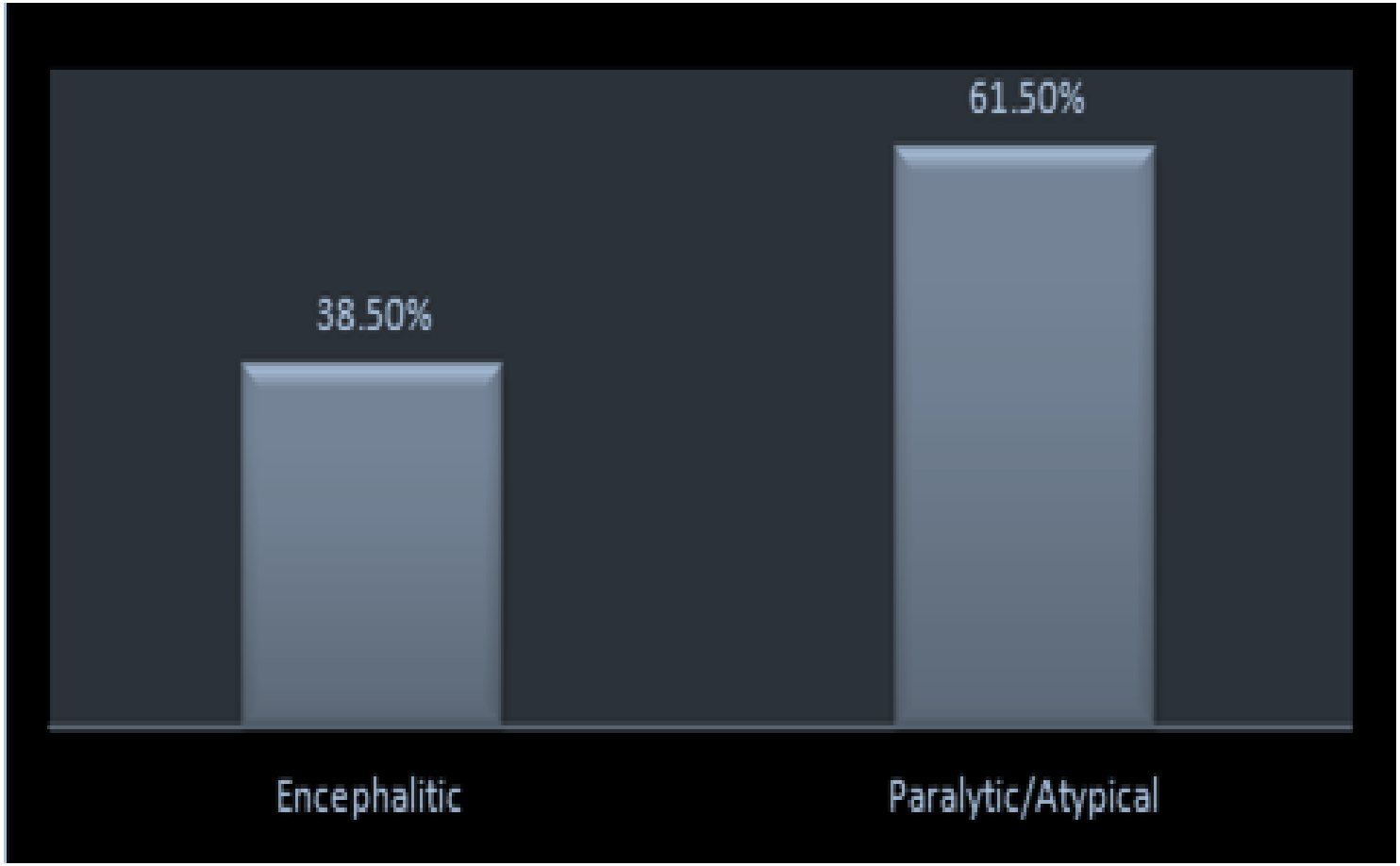
American Journal of Tropical Medicine & Hygiene (November 2018)

8 Survivors

Maharashtra (4), Karnataka (1), Andhra Pradesh (1), Telangana (1), Sikkim (1)

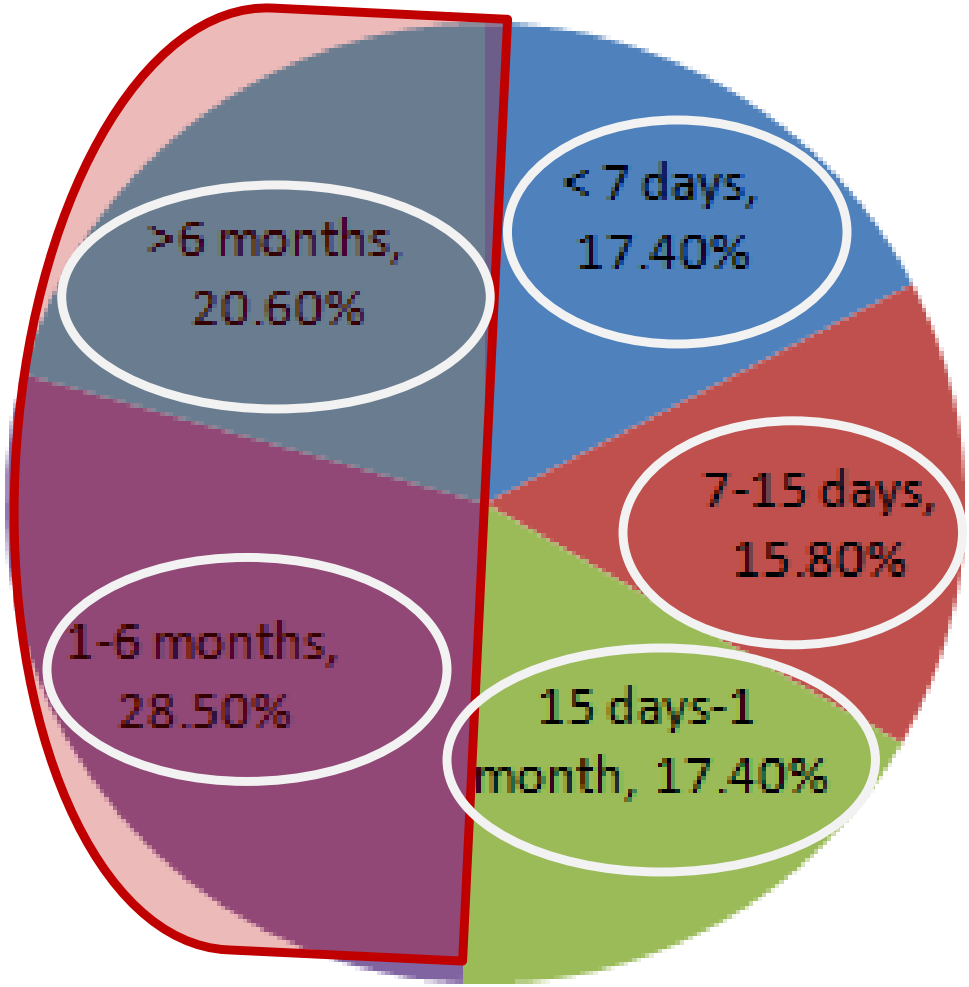
Mani et al. Am J Trop Med Hyg. 2019 Jan;100(1):165-169.

Clinical Profile-Laboratory confirmed cases 2012-2017; n=115



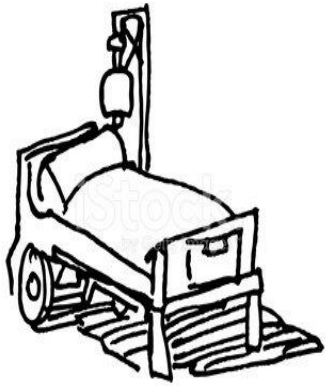
Duration of Survival (n=63)

n=31



Rabies Survivors in India: An Emerging Paradox?

- Access to advanced medical facilities: Excellent ICU care
- All had received at least partial vaccination
- 'Survival' not synonymous with 'Recovery'
- All rabies survivors in India: severe sequelae
- Long-term emotional, social and economic repercussions
- Need to explore newer therapeutic strategies
- 'Prevention' should remain primary focus



Mani RS. Human Rabies Survivors in India: An Emerging Paradox? PLoS Negl Trop Dis. 2016;10(7):e0004774.

PEP-The Alarming Statistics

- **NIMHANS (2015-2017): 65% of the patients with lab-confirmed rabies had received ARV (partial/complete with/without RIG)**
- **Isolation hospital, Rajasthan (2016-2018): 42 cases of hydrophobia; No PEP (26%), partial ARV (48%), partial ARV and RIG (26%)**
- **ID hospital, Delhi (10 years): 783 cases of hydrophobia; 32% had received ARV (with or without RIG)**

Rabies despite vaccination?

- **Deviations in PEP protocols**
  - Incorrect advice/regimen
  - Wound care Inadequate/Not done
  - Suturing of wounds without RIG
  - Delay in initiating PEP
  - Inadequate dosage of vaccine
  - Unsuitable site of vaccine administration
  - Inappropriate administration of RIG (only IM)
  - Omission of RIG even in category III exposures

- **Counterfeit vaccines/ Cold-chain lapses**
- **Vaccine/PEP failures lead to rabies and survivors (with poor functional outcomes)**

“But alas, oh ye doctors, though skilful are ye,
This potsherd of earth still a potsherd must be
Not yet hydrophobia your nostrums can cure,
His dread of the water he still must endure….”

John Edwards

(written in 1821)