



Understanding all Steps of Nipah Virus Transmission

Steve Luby, MD

Zoonoses and emergence of new infectious diseases: biology meets anthropology

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Collège de France, Paris



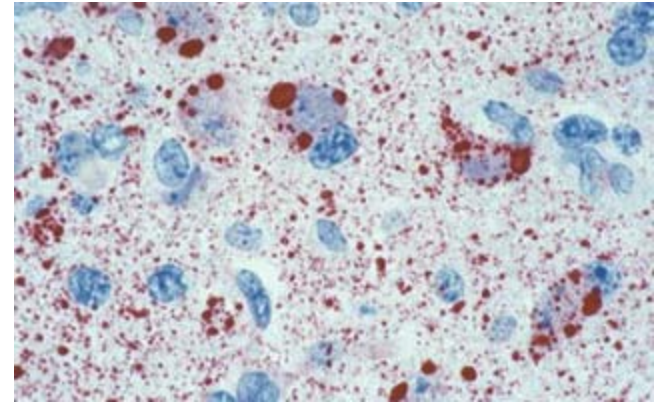
Malaysia Nipah Outbreak



- September 1998 – May 1999
- 283 human cases of acute encephalitis
 - 109 deaths
 - Case fatality rate 39%
- Paul Chua isolated a novel paramyxovirus from a patient in Kampung Sungai Nipah village

Nipah Pathology

- Causes a diffuse vasculitis
- The brain is the most severely affected organ
 - tropism to the brainstem
- Virus commonly identified in
 - lung
 - kidney



Guinea Pig Brain with NiV
From Corrie Brown, UGA

How did people contract Nipah Virus in Malaysia?

- The outbreak was concentrated among pig farmers
 - 92% of cases reported contact with pigs
- Compared to controls, persons with Nipah encephalitis were
 - 5.6 times more likely to have close contact with pigs.
 - 3.7 times more likely to have contact with sick pigs



Singapore Outbreak

March 1999

- Outbreak among 11 abattoir workers in Singapore
- 1 death
- All worked processing pigs imported from Malaysia



From where did the pigs get Nipah?

Nipah wild animal studies

- Numerous wild animals trapped and tested
- 8 different species of fruit bats sampled
 - 4 of the 8 species had antibodies against Nipah virus.
- Nipah virus isolated
 - Urine from *Pteropus hypomelanus* in Malaysia

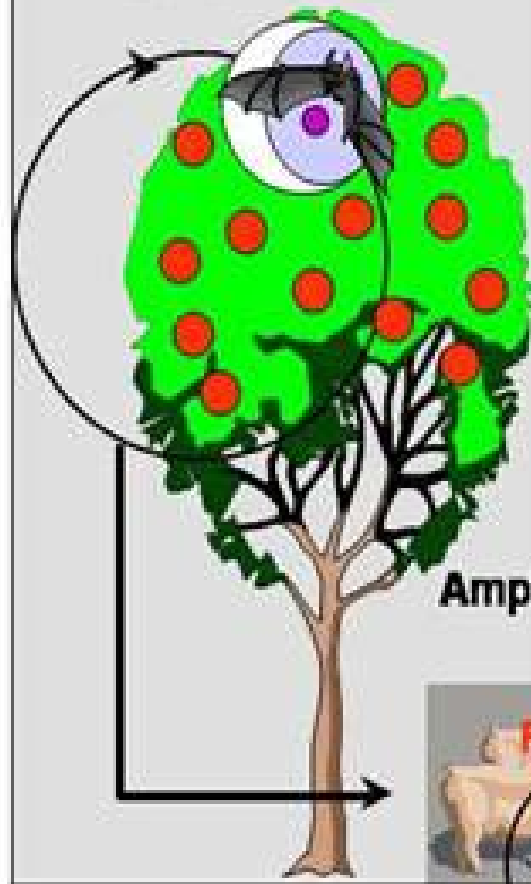


Index farm

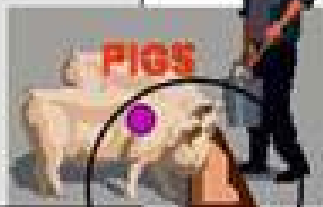
- 30,000+ pigs
- Adjacent to primary forest, fruit bat habitat
- Network of other large farms close by

Slide courtesy of Peter Daszak

**Reservoir, Amplification
And dissemination**
MEGACHIROPTERA



Amplification

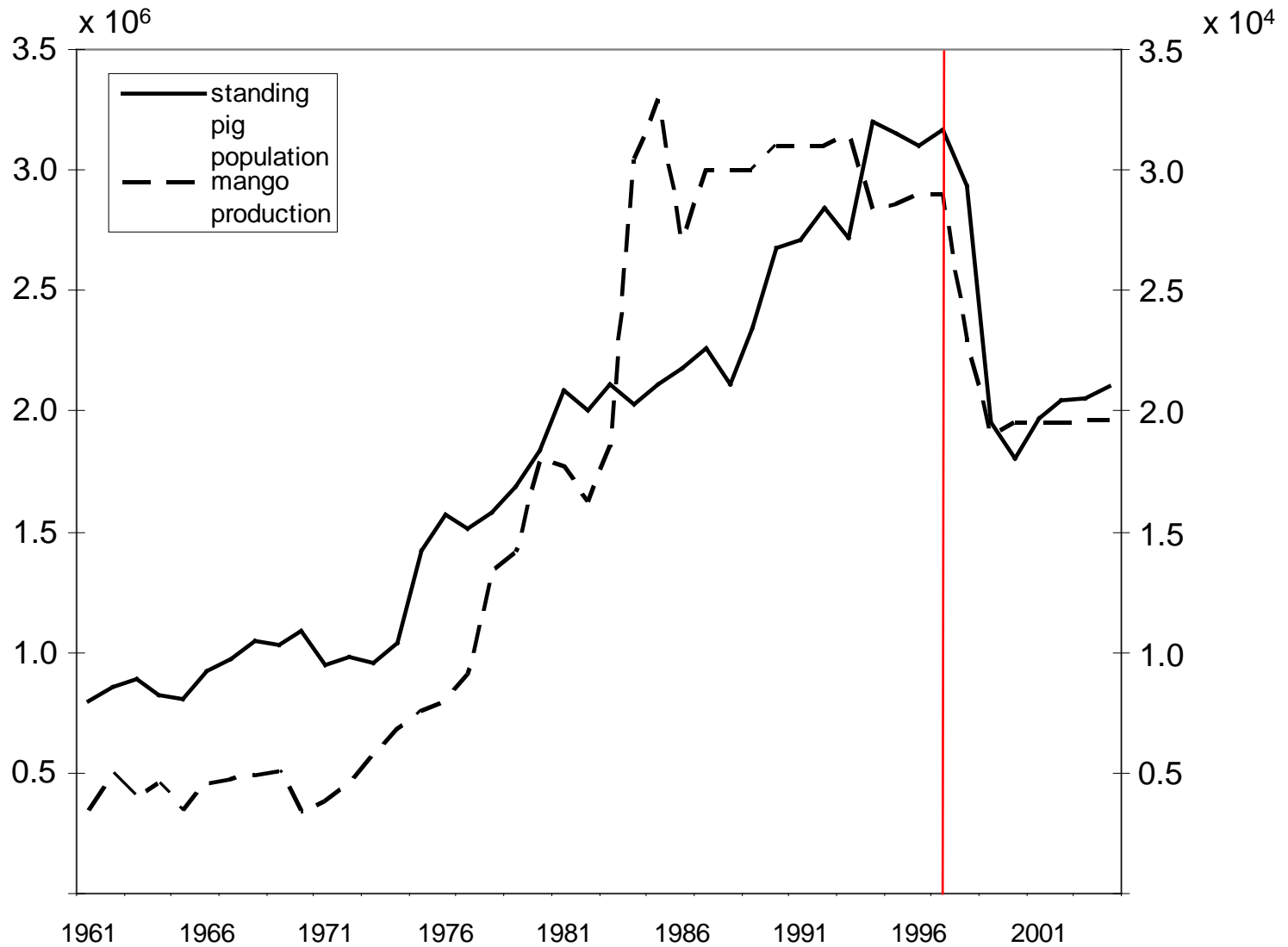


**A possible transmission
cycle for Nipah virus during
the Malaysian Singapore
outbreak in 1998-1999**



Slide: Joel Montgomery

Why did Nipah virus emerge in 1998?



Malaysia Outbreak Control

- Outbreak ceased following the culling of over 900,000 pigs
 - Fruit trees no longer permitted above pig pens
 - Pork industry decimated
- No subsequent cases of Nipah recognized in Malaysia from people or animals

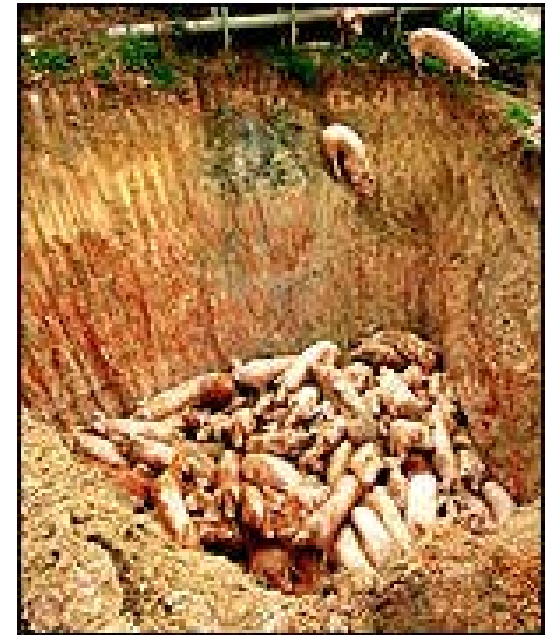
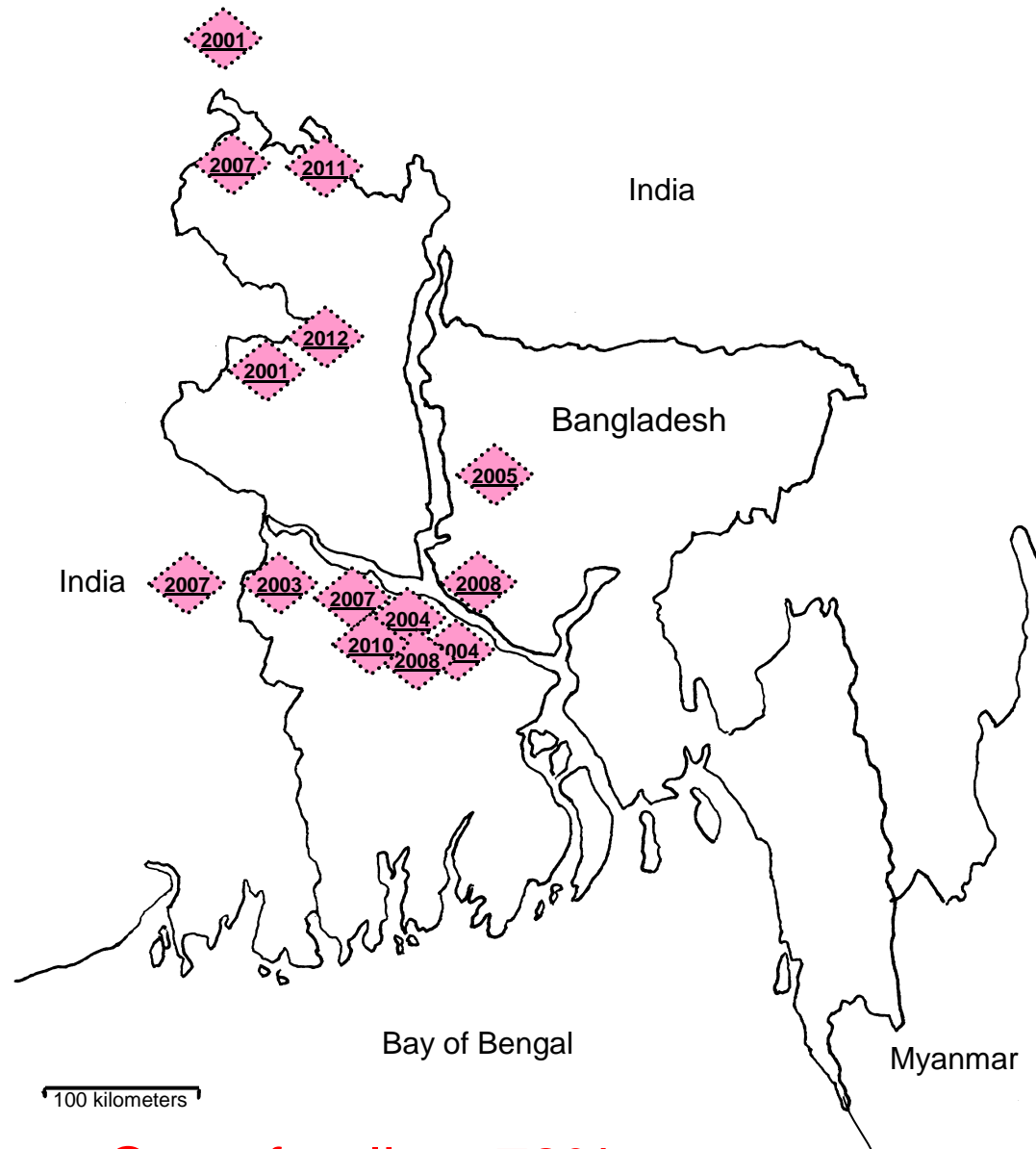


Photo: BBC News

2001		
Siliguri	66 cases	49 deaths
Meherpur	13 cases	9 deaths
2002		
No cases		
2003		
Naogaon	12 cases	8 deaths
2004		
Rajbari	31 cases	23 deaths
Faridpur	36 cases	27 deaths
2005		
Tangail	12 cases	11 deaths
2006		
No cases		
2007		
Thakurgaon	7 cases	3 deaths
Kushtia	8 cases	5 deaths
Nadia	5 cases	5 deaths
2008		
Manikgonj	4 cases	4 deaths
Rajbari	6 cases	5 deaths
2009		
Rangpur , Gaibandha, Rajbari, Niphamari	4 cases	1 death
2010		
Faridpur, Rajbairi, Gopalganj ,Kurigram	17 cases	15 deaths
2011		
Lalmonirhat, + 5 other districts	28 cases	28 deaths
2012		
Joypurhat, Rajshahi	13 cases	10 deaths
2013		
13 districts	24 cases	21 deaths
Total	290 cases	225 deaths



Case fatality : 78%

Pteropus giganteus in Bangladesh

	2004	2006	2007
Bats Tested	92	81	218
Nipah IgG+	48	15	107
% positive	52%	19%	49%



How does Nipah virus transmit from wildlife to humans in Bangladesh?

11 January 2005

- Government health workers reported that 8 previously healthy persons from Basail Upazila died within a one week period.



Case definition: Fever +

– Mental status changes

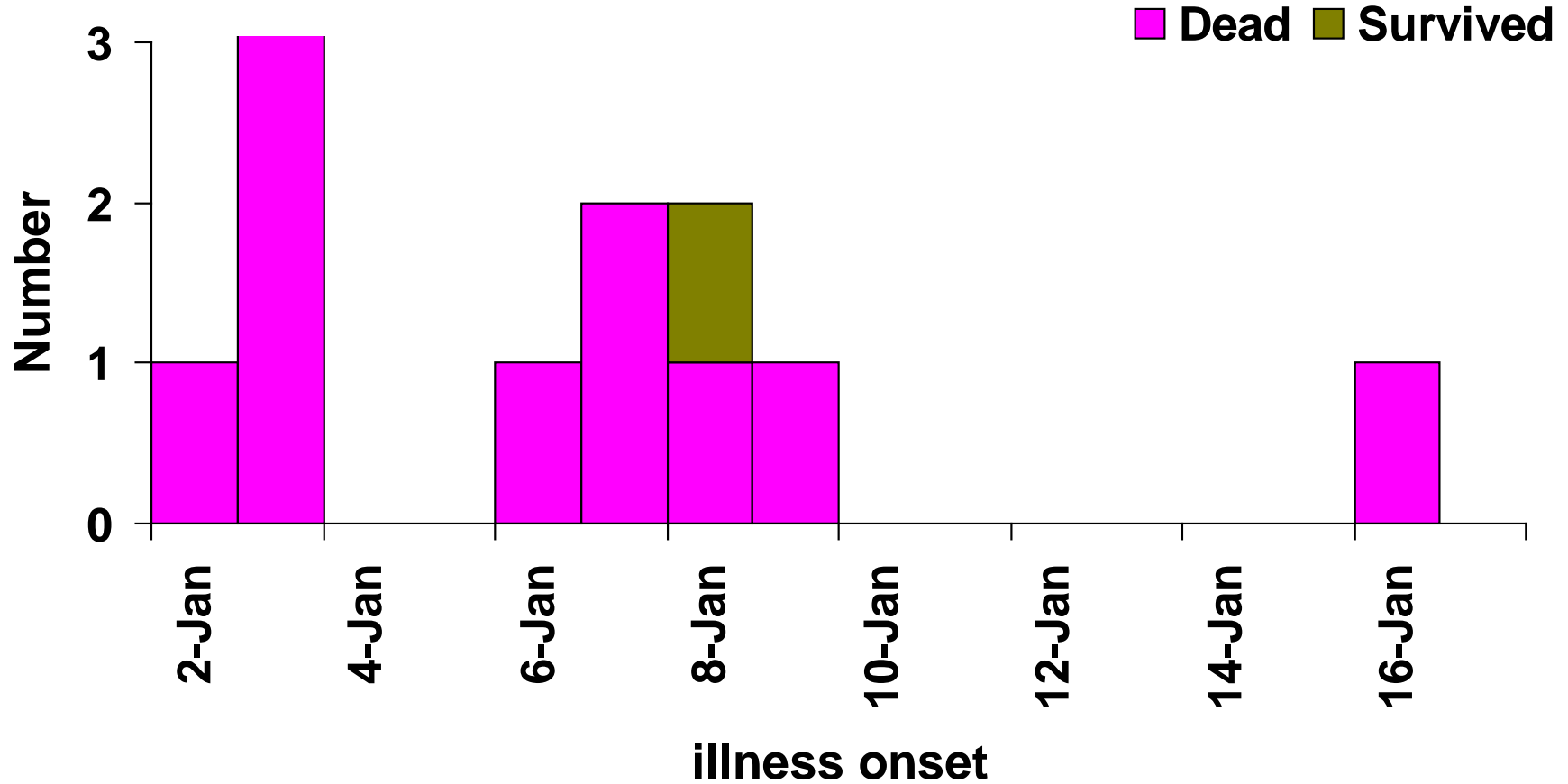
– Seizures:

12 Case-patients

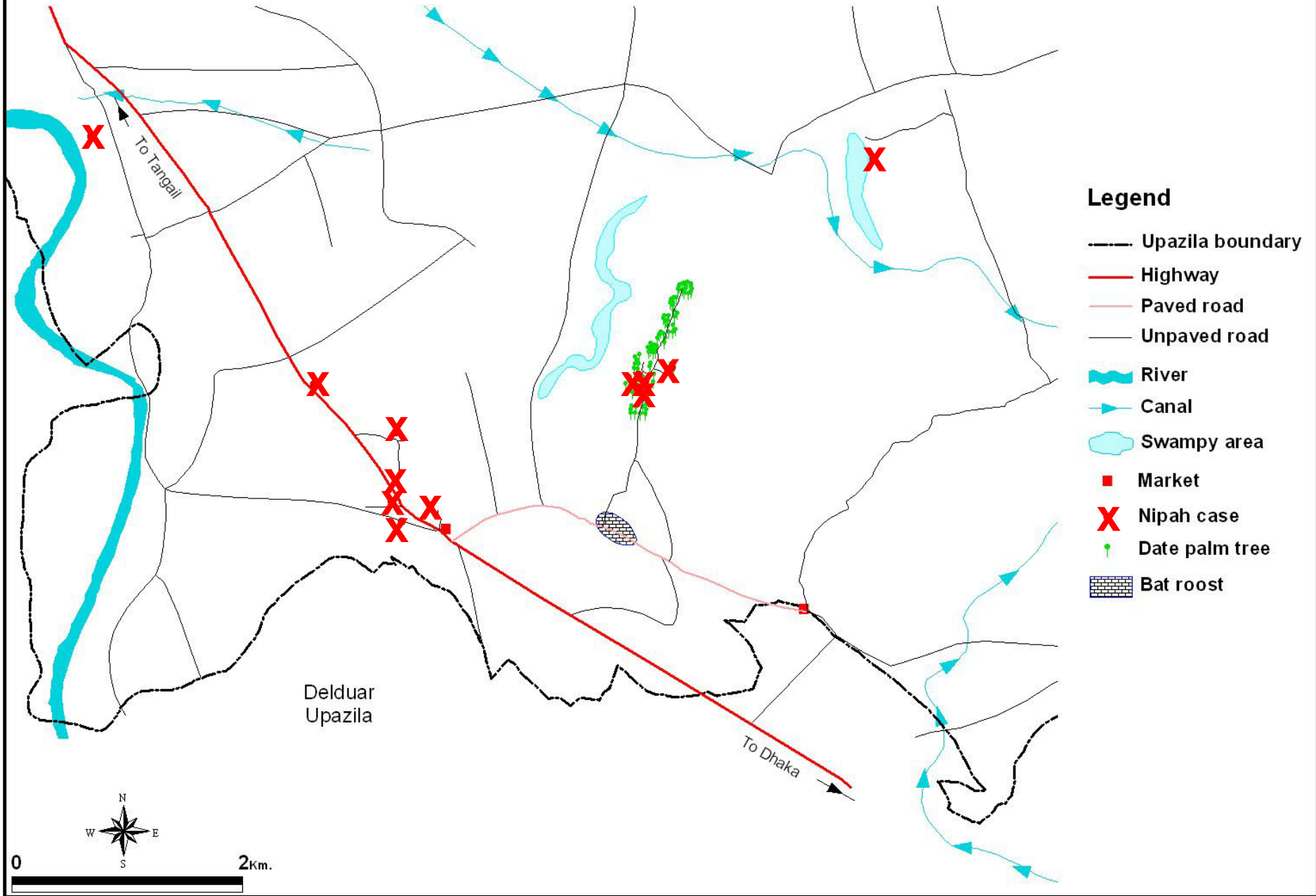
- Fever 12 (100%)
- Seizures 4 (33%)
- Unconsciousness 9 (75%)
- Headache 5 (42%)
- Vomiting 5 (42%)
- Difficulty breathing 1 (8%)
- Death 11 (92%)
- Median time from first symptom to death 4 days

Onset of illness

Tangail District, Bangladesh, 2005 (N=12)



Case location Tangail Nipah Outbreak 2005



Risk factor study

- Design: Case Control
- Cases : All 12 persons meeting the case definition enrolled
- 3 controls per case
 - Next closest house, person nearest in age
 - Proxies for persons who had died

Case Control Results

Risk factor	No. and % of cases with this risk factor	No. and % of controls with this risk factor	Odds Ratio	95% confidence limit	p-value
Physical contact with sick animal	5 (42)	5 (14)	4.4	0.9,20.4	0.09
Physical contact with sick chicken	3(25)	3(8)	3.7	0.5,24	0.16
Killed a sick animal	1(8)	2(6)	1.6	0.05,22	1.00
Ate any sick animal	1(8)	2(6)	1.6	0.05,22	1.00
Seen fruit bats during daytime	3(25)	5(14)	2.1	0.34,11	0.39
Seen fruit bats during nighttime	8(67)	13(36)	3.5	0.87,15.4	0.06
Drank raw date palm sap	7(58)	6(17)	7.0	1.6,31	0.01

Date Palm Sap Collection

- Late November through March
 - Sap harvesters cut a tap is cut into the tree
 - In the evening they place a clay pot under the tap
 - Each morning the pot is removed
 - Most sap is made into molasses
 - Some sold fresh early in the morning
 - A local delicacy



Date Palm Sap Distribution

Habla Union

- One of the fatal cases was the son of a date palm sap collector
 - drank date palm sap daily
- Heard bats in his date palm trees at night
 - Found bat excrement on his pots
- Several days prior to the outbreak he sent date palm sap to his relatives in a nearby homestead.
 - 3 cases occurred in the family



Date palm sap transmission of NIV

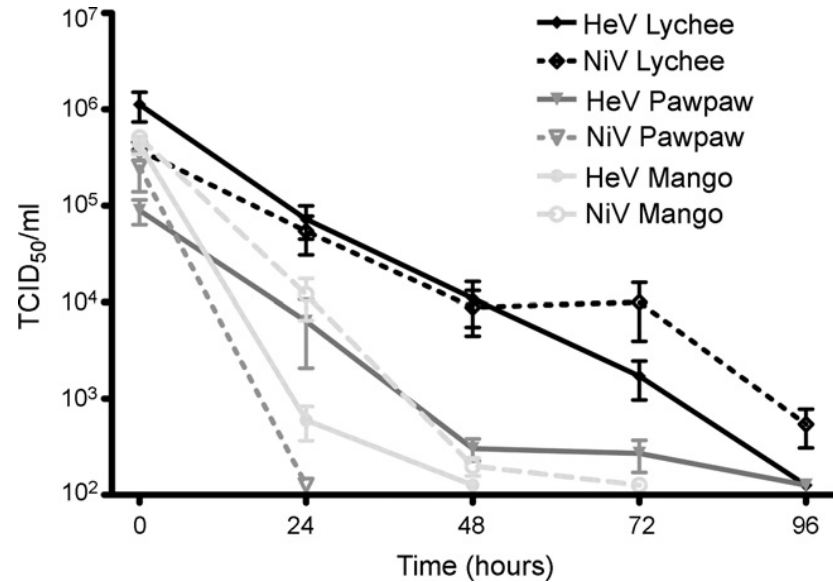
Epidemiological Evidence

Year	Location	Cases Exposed (%)	Controls Exposed (%)	Odds Ratio	95% Confidence Limit
2005	Tangail	58	17	7.0	1.6, 31
2008	Manikgonj	100	25	18	2.2, inf
2010	Faridpur	69	30	5.2	1.2, 26
2011	Lalmonirhat	68	11	17	4.0 , 70

We knew

- Pteropus bats occasionally shed Nipah virus RNA in their saliva
 - Reynes et al, Emerg Infect Dis 11: 1042-7
 - Wacharapluesadee S, et al. (2005) Emerg Infect Dis 11: 1949-51
 - Middleton DJ et al. (2007). J Comp Pathol 136: 266-72
- Date palm sap implicated in outbreak investigations
- Any sap we collected was well after the outbreak

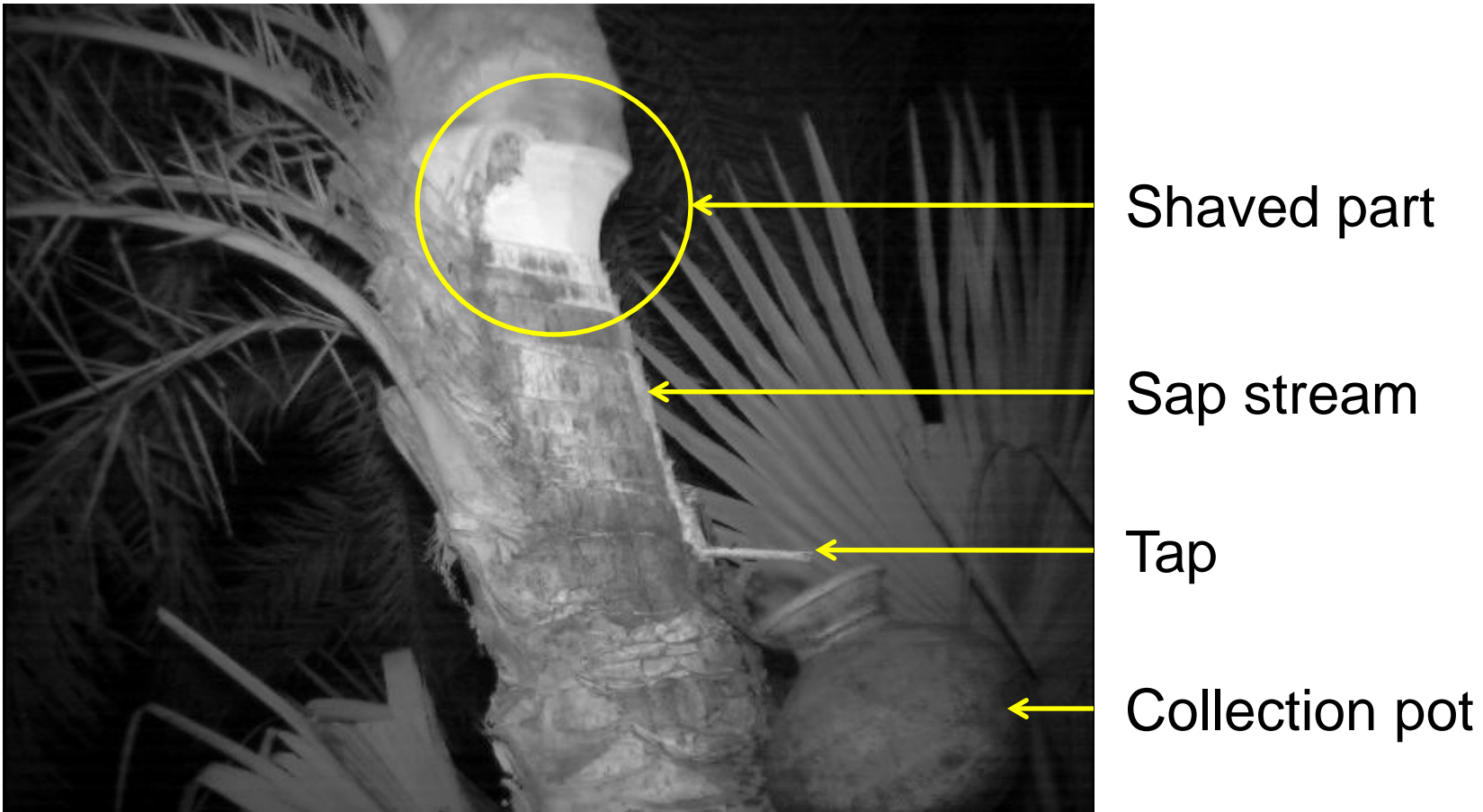
Henipavirus survival in fruit juice at 22 °C.



R. Fogarty et. al, Virus Research 132 (2008) 140–144



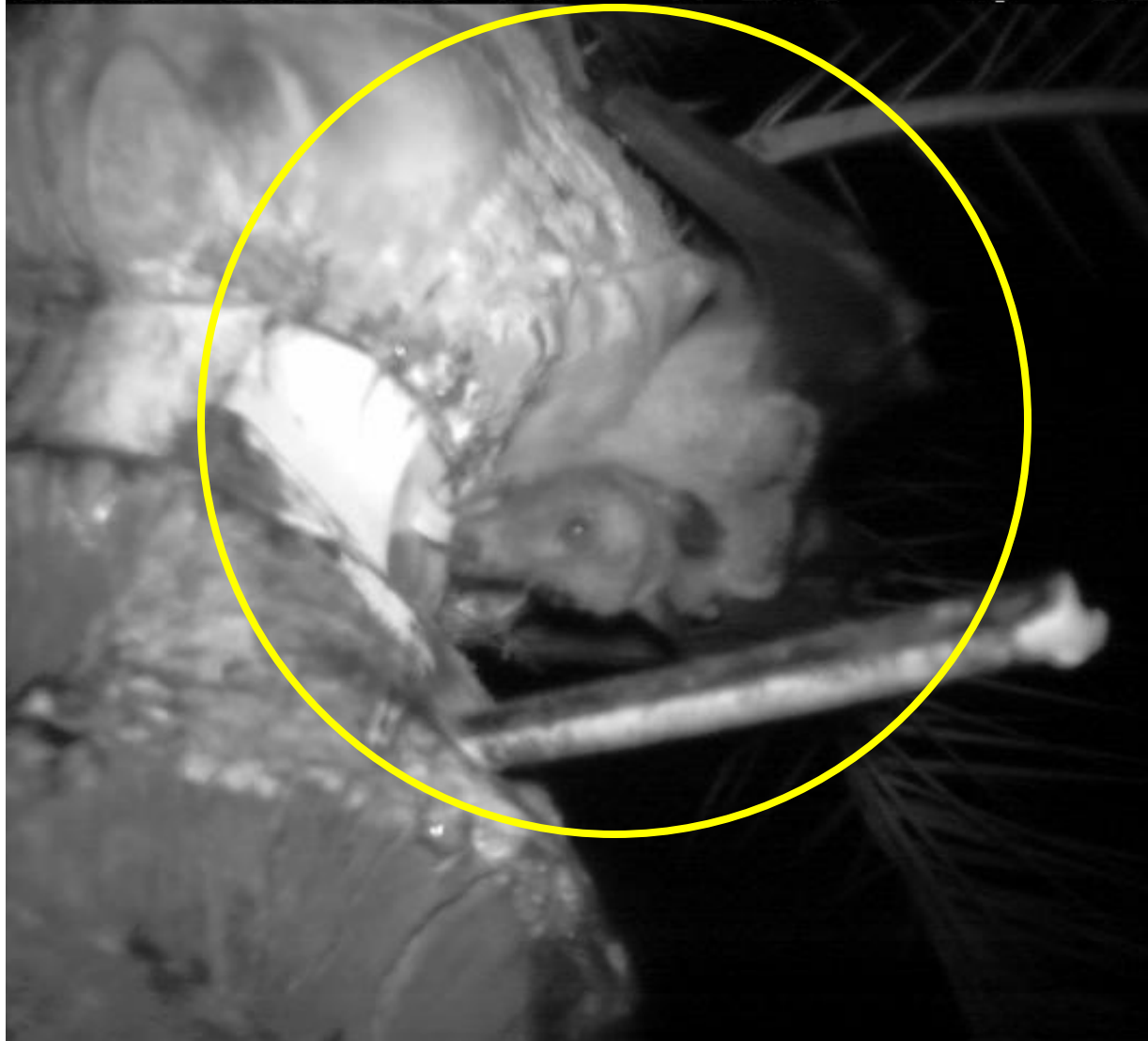
Infrared wildlife photography



Salah Uddin Khan

Manikgonj Outbreak 2008

- 7 trees where implicated date palm sap was collected
- 7 nights of observation
- Mean 15 bat visits per night
- Bats licked the sap mean 8.4 times per night
- 49% of bats were *Pteropus*



2012-02-10 4:51:45 AM M 3/3

16°C

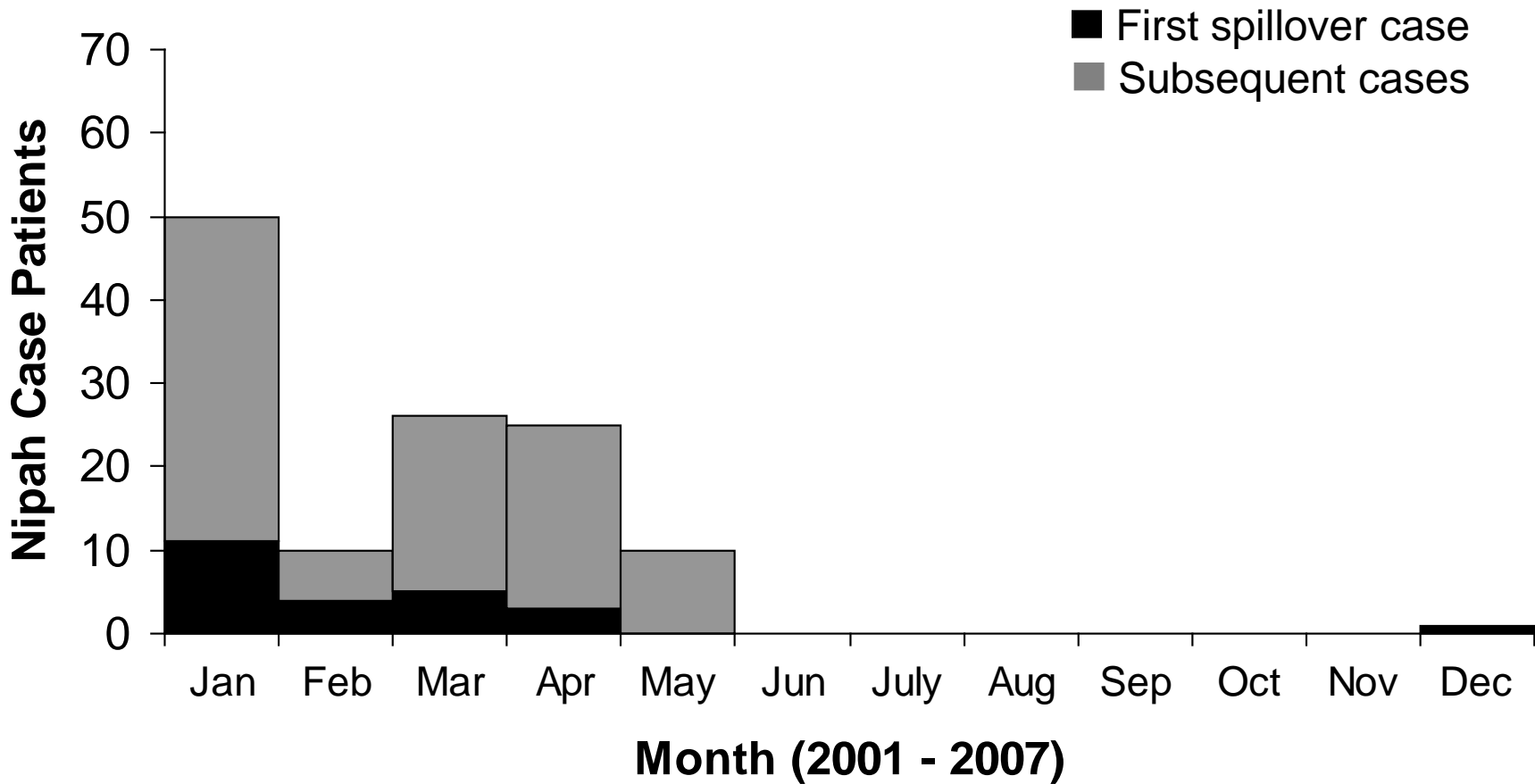


PC900 COVERT PRO



Month of Nipah illness onset

Bangladesh 2001-07



Domestic Animal Nipah Transmission in Bangladesh

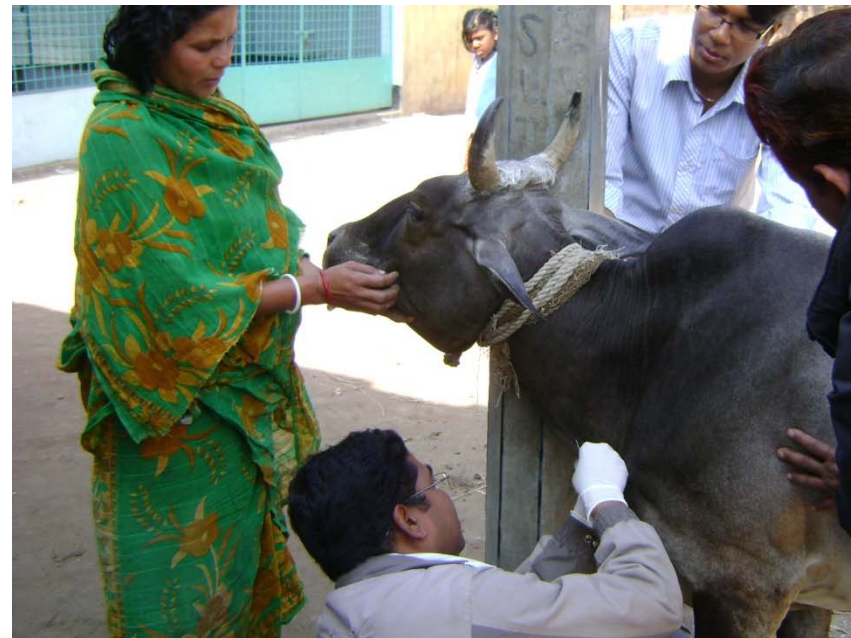
- 2001 Meherpur
 - Contact with a sick cow
 - Odds ratio 6.9 (2.2, 27.7)
- 2003 Naogaon
 - Close proximity to a pig herd
 - Odds ratio 6.1 (1.4, 25.9)
- 2004 Rajbari
 - 2 goats developed fever, difficulty walking, and died
 - 2 weeks later a child who frequently played with goats developed Nipah encephalitis



Pig herd in Bangladesh
Photo : Salah Uddin Khan

Henipah Virus infections in cattle and goats?

- Veterinary field team visited sites of 5 previous human outbreaks of Nipah virus
 - Located the bat roost closest to the highest concentration of human cases
 - Within 1000 meter radius
 - 80 cattle (400 total)
 - 80 goats (400 total)
- Administered questionnaire on exposures
- Samples sent to Australian Animal Health Laboratory for testing
 - Luminex antibody
 - against G and F protein
 - Nipah and Hendra
 - Viral neutralization



Domestic Animal Henipavirus

No. (%) Luminex
sero-positive

Nipah Hendra

Cattle (n=400) 11 (2.8) 3 (0.8)

Goat (n=400) 9 (2.3) 1 (0.3)

- All Luminex positive sera negative for viral neutralization
- Cross reactivity with an unknown henipavirus?

Cattle

Luminex henipavirus

positive

negative

odds ratio

n (%)

n (%)

(95% CI)

Fed off partially animal

eaten fruits

8 (57)

88 (23)

4.2 (1.5-11.9)

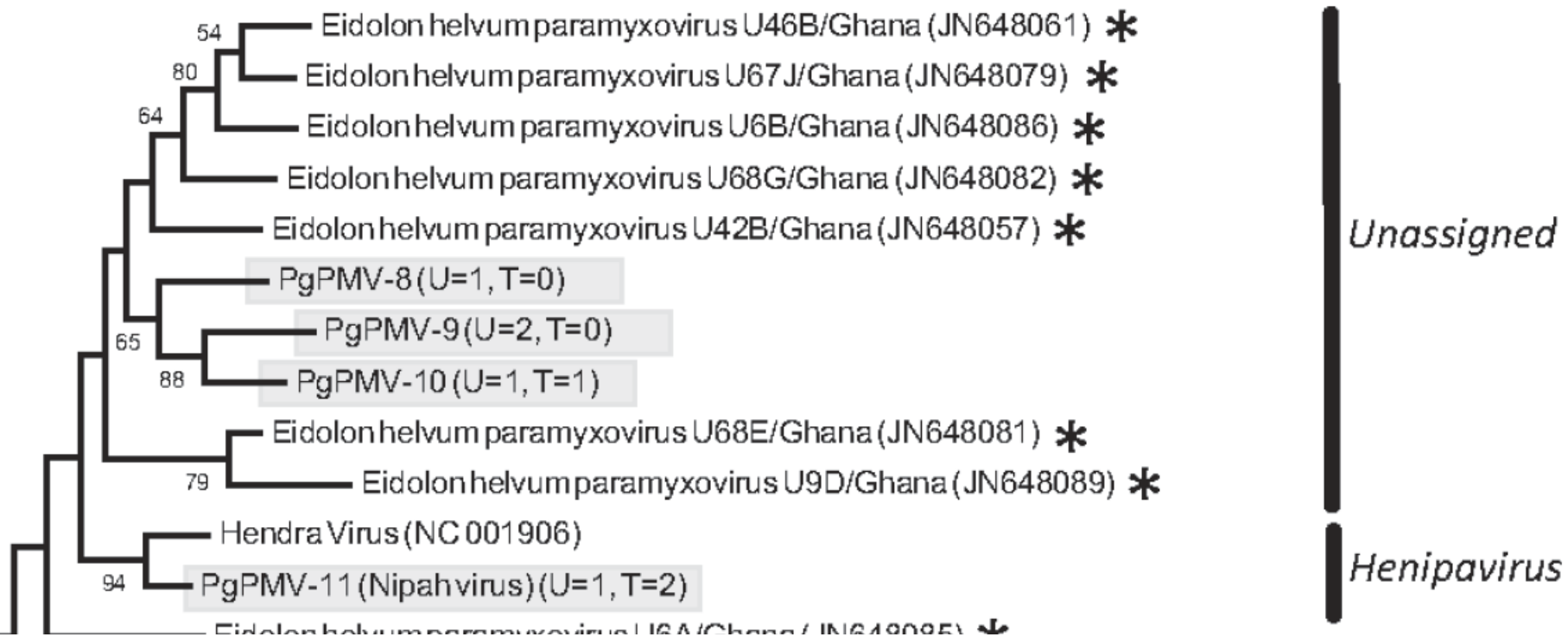
Drank raw palm juice

2 (14)

7 (2)

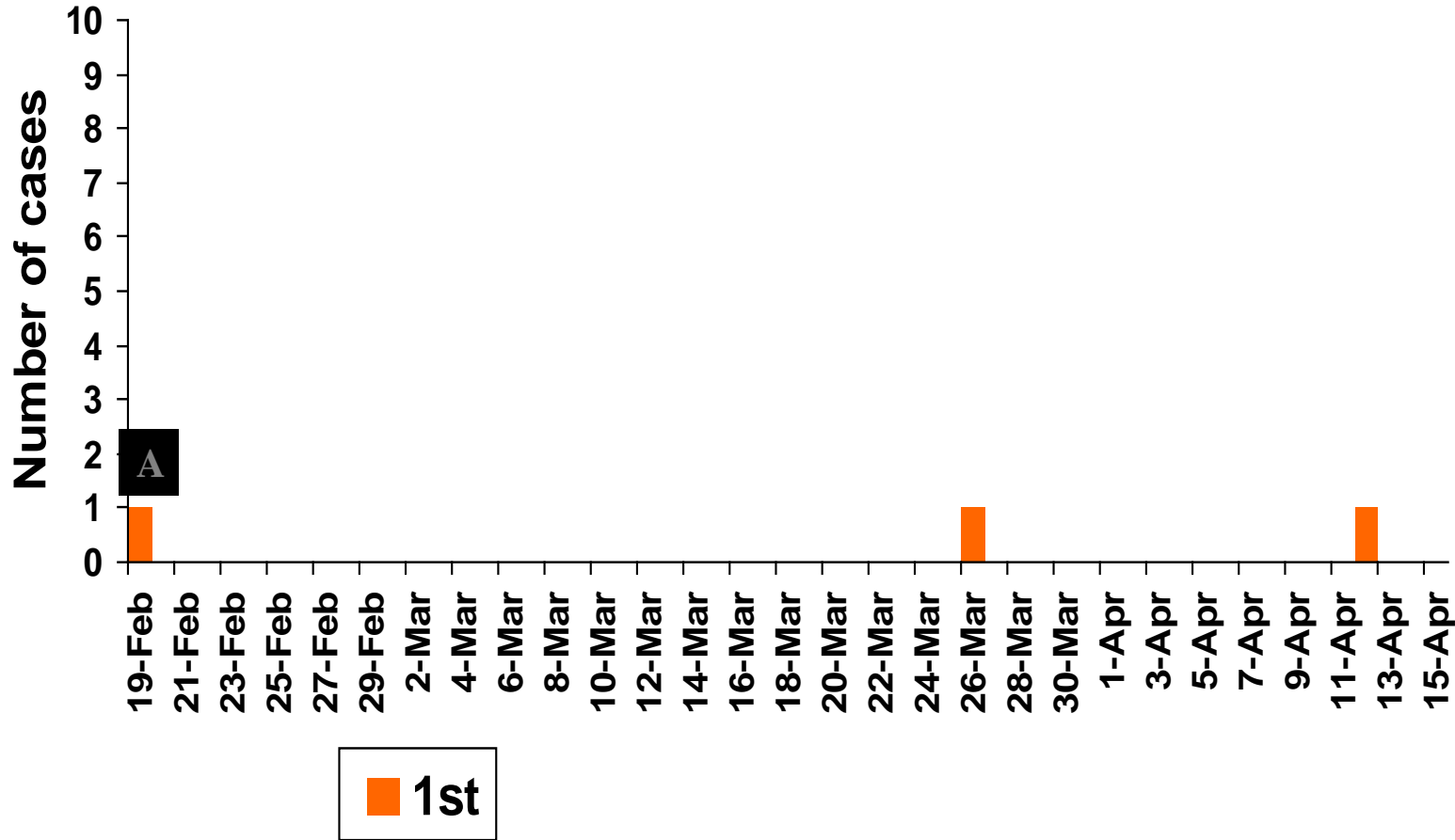
7.2 (1.9-27.7)

Novel paramyxovirus from *P. giganteus* bats in Bangladesh

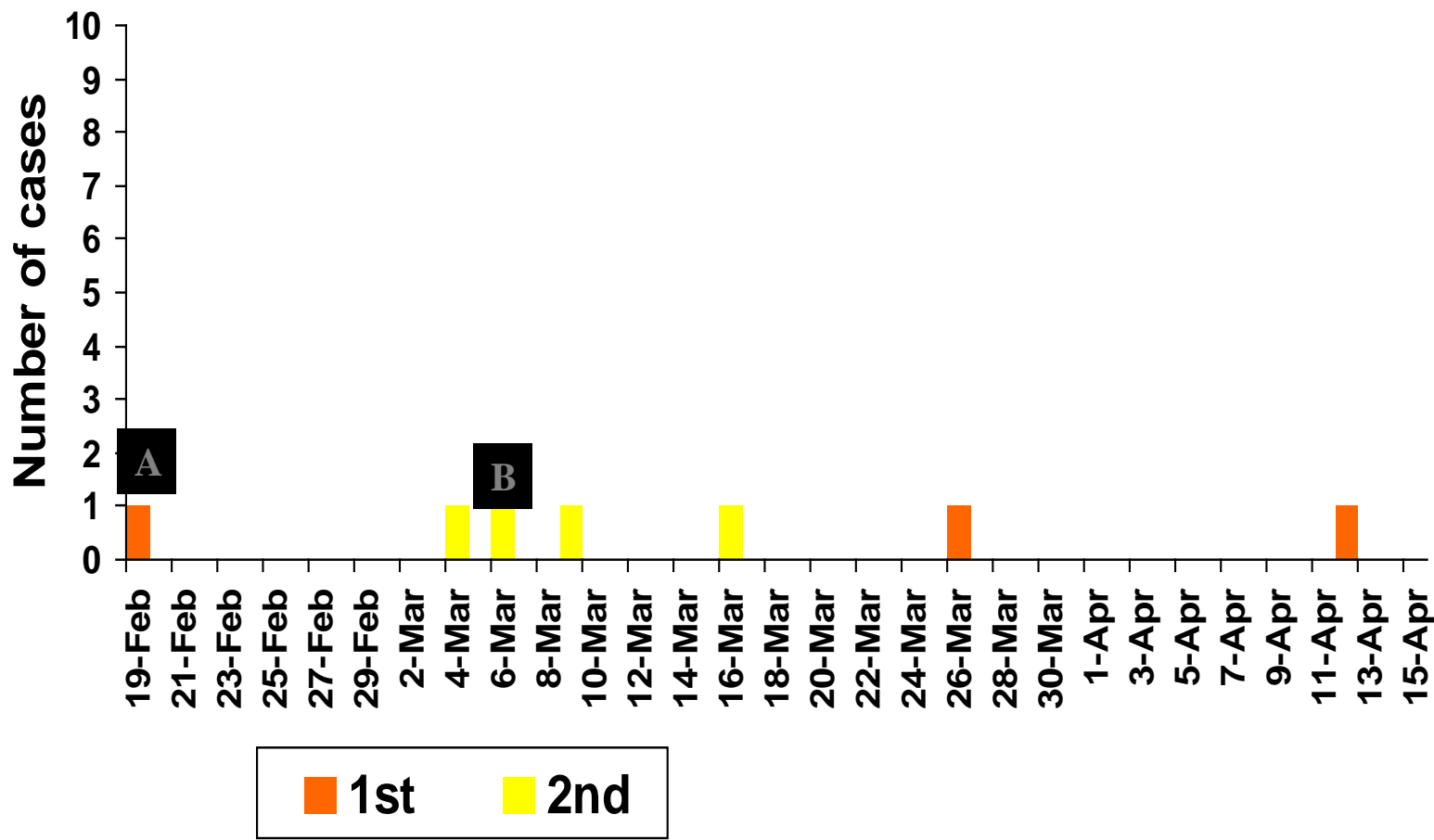


How else is Nipah virus transmitted in Bangladesh?

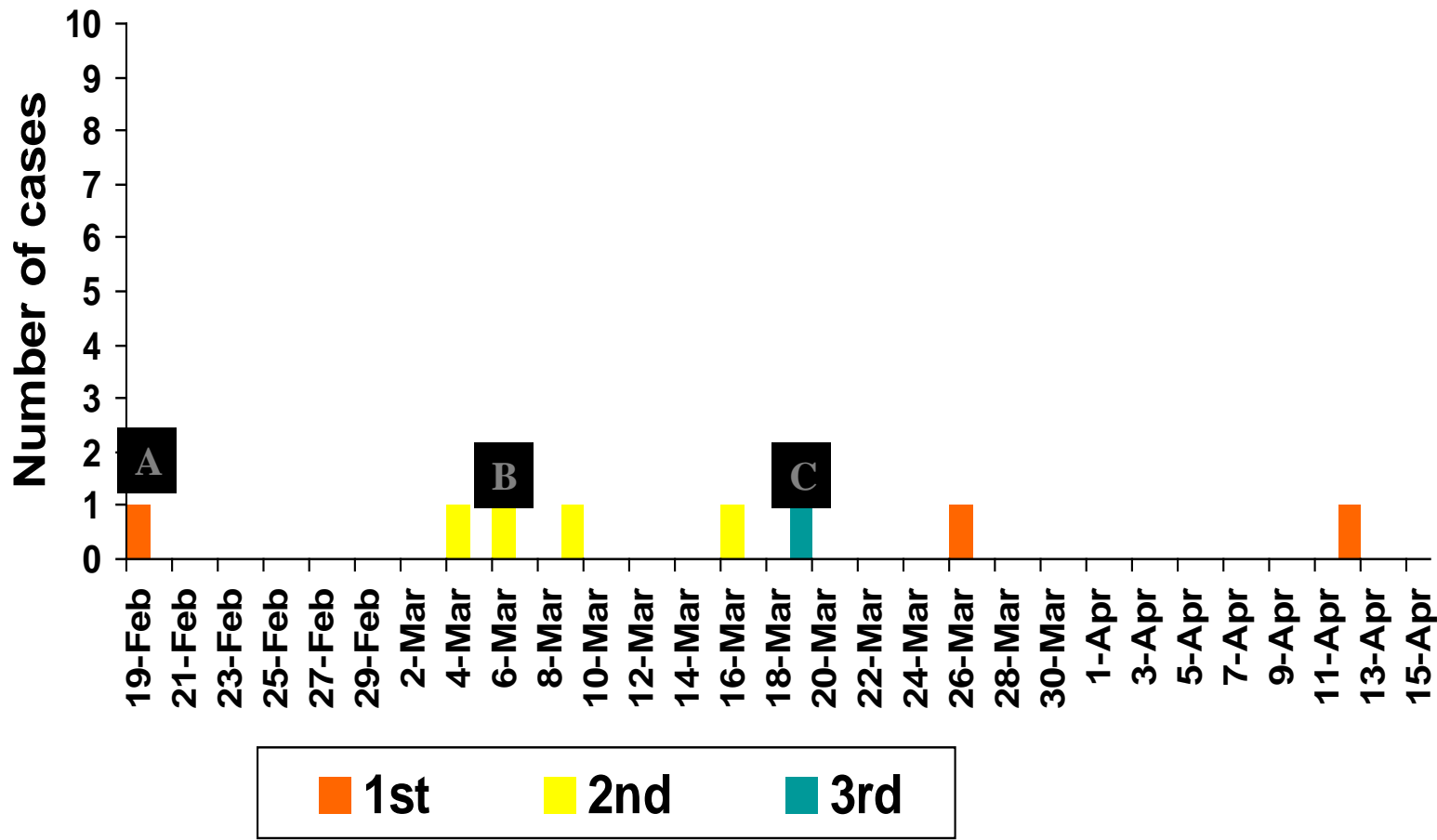
Dates of illness onset from Faridpur outbreak coded by transmission generation (N=36)



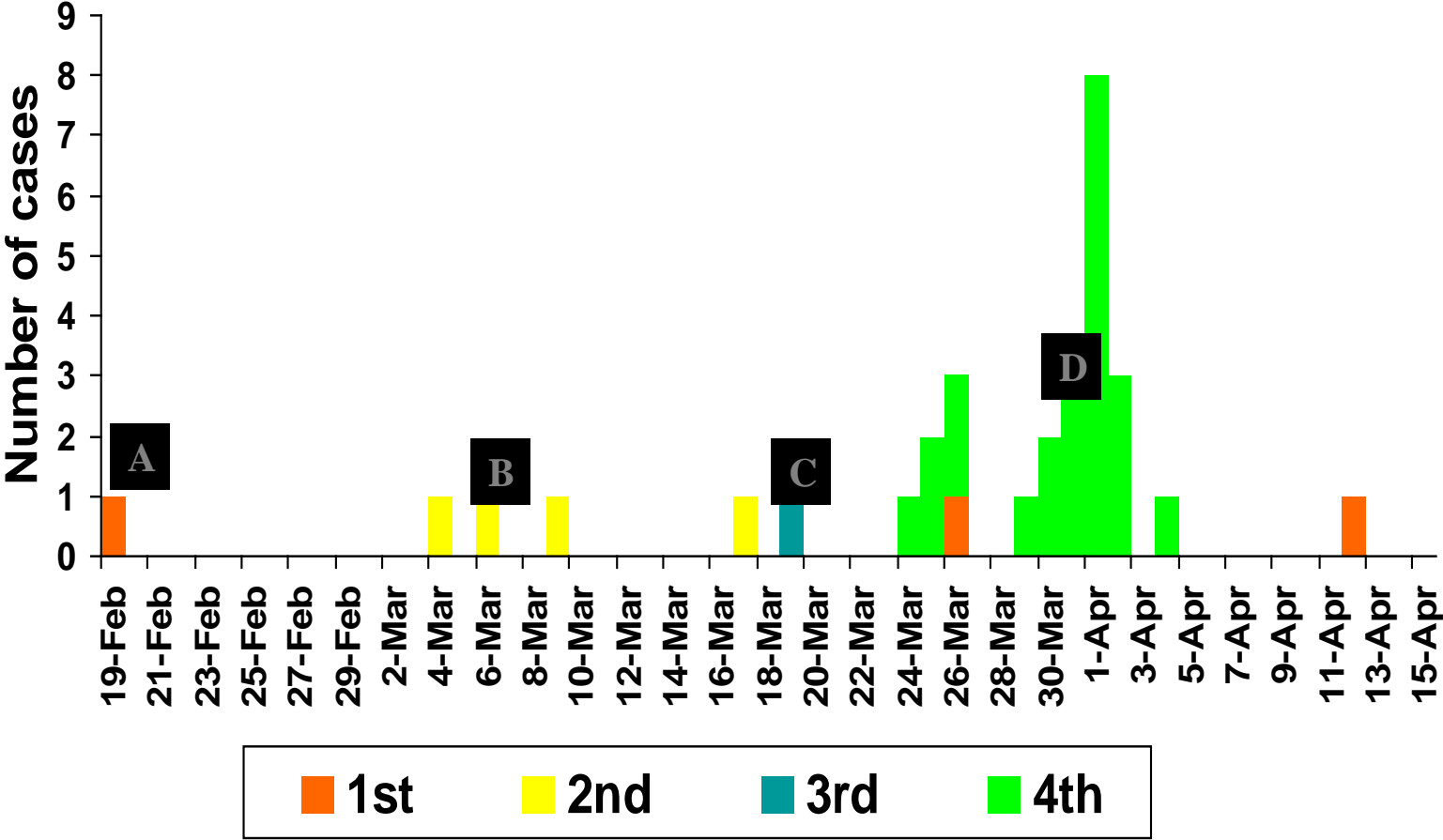
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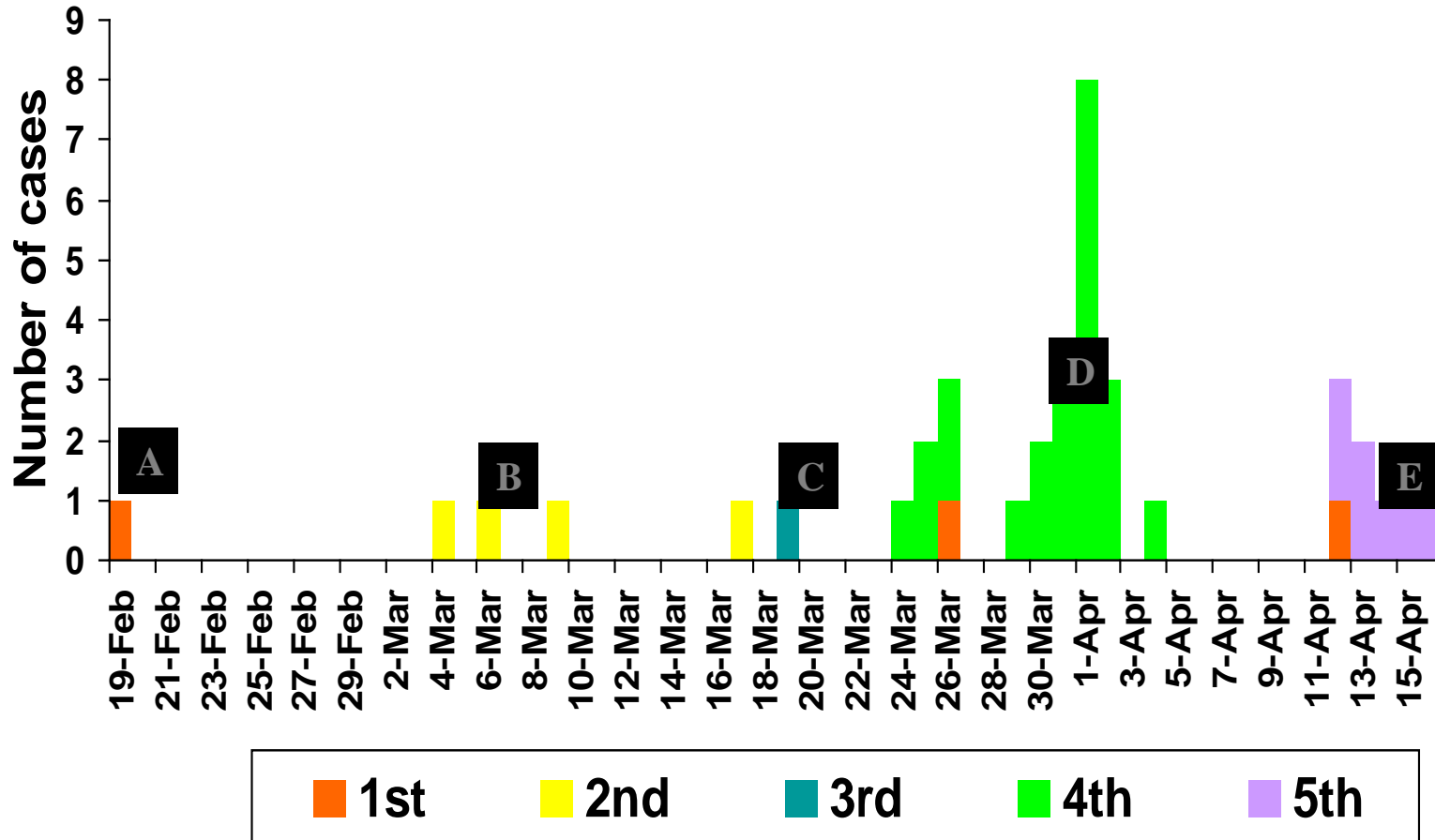
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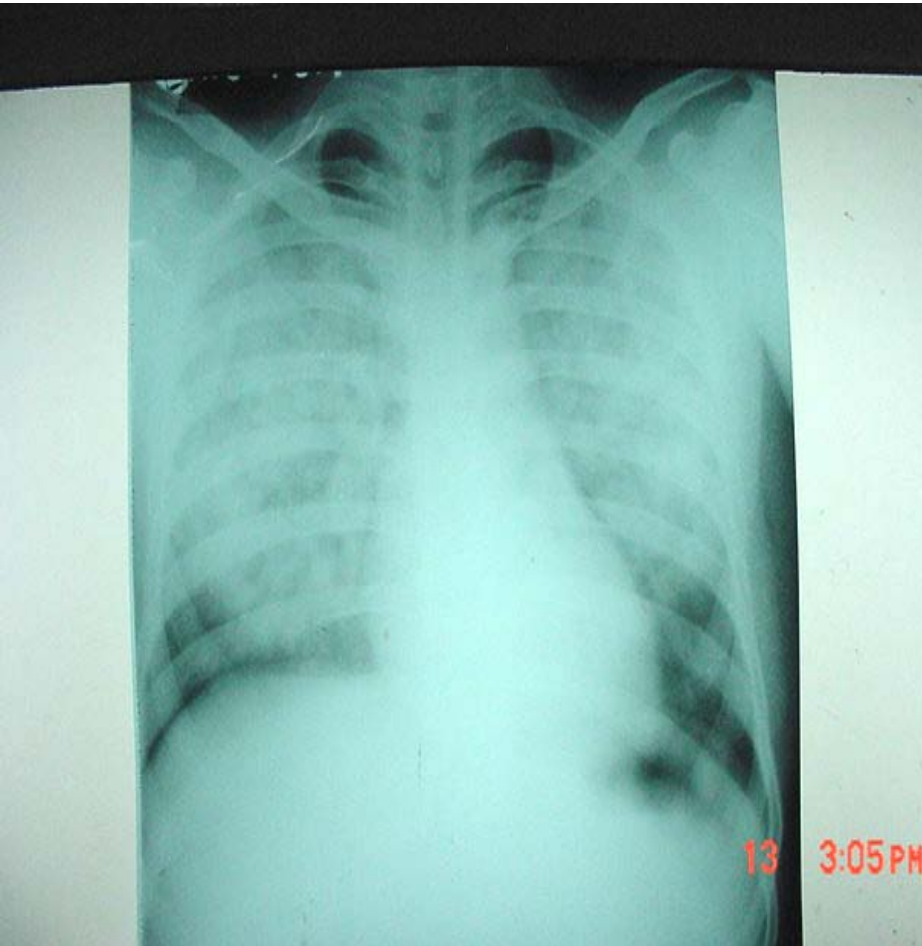
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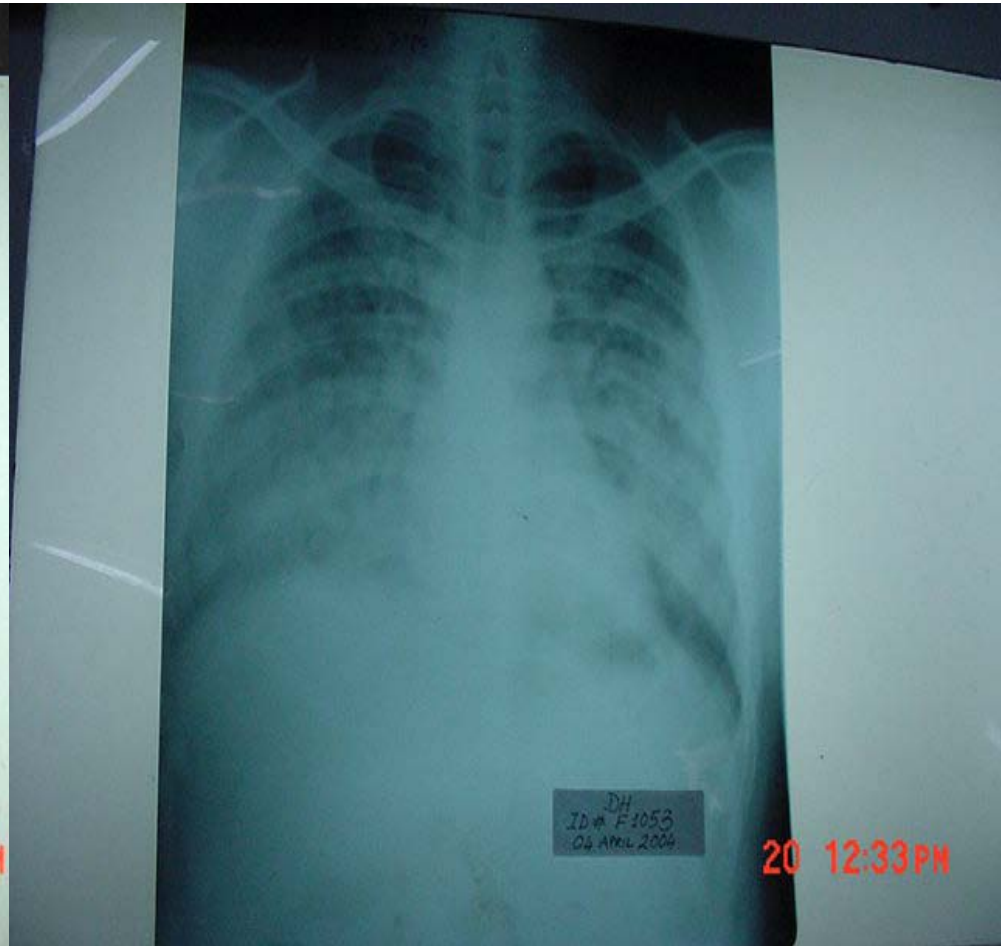
Faridpur Cohort Study

- Touching a Nipah patient who later died (RR 15.0, 95% CI 4.0, 65)
- Touching an unconscious patient (RR 4.5, 95% CI 1.7, 12)
- Touching a patient with respiratory symptoms (RR 5.0, 95% CI 2.0, 14)
- Washing hands after contact with Patient F (RR 0.20, 95% CI 0.03, 0.90)

Chest X-Rays



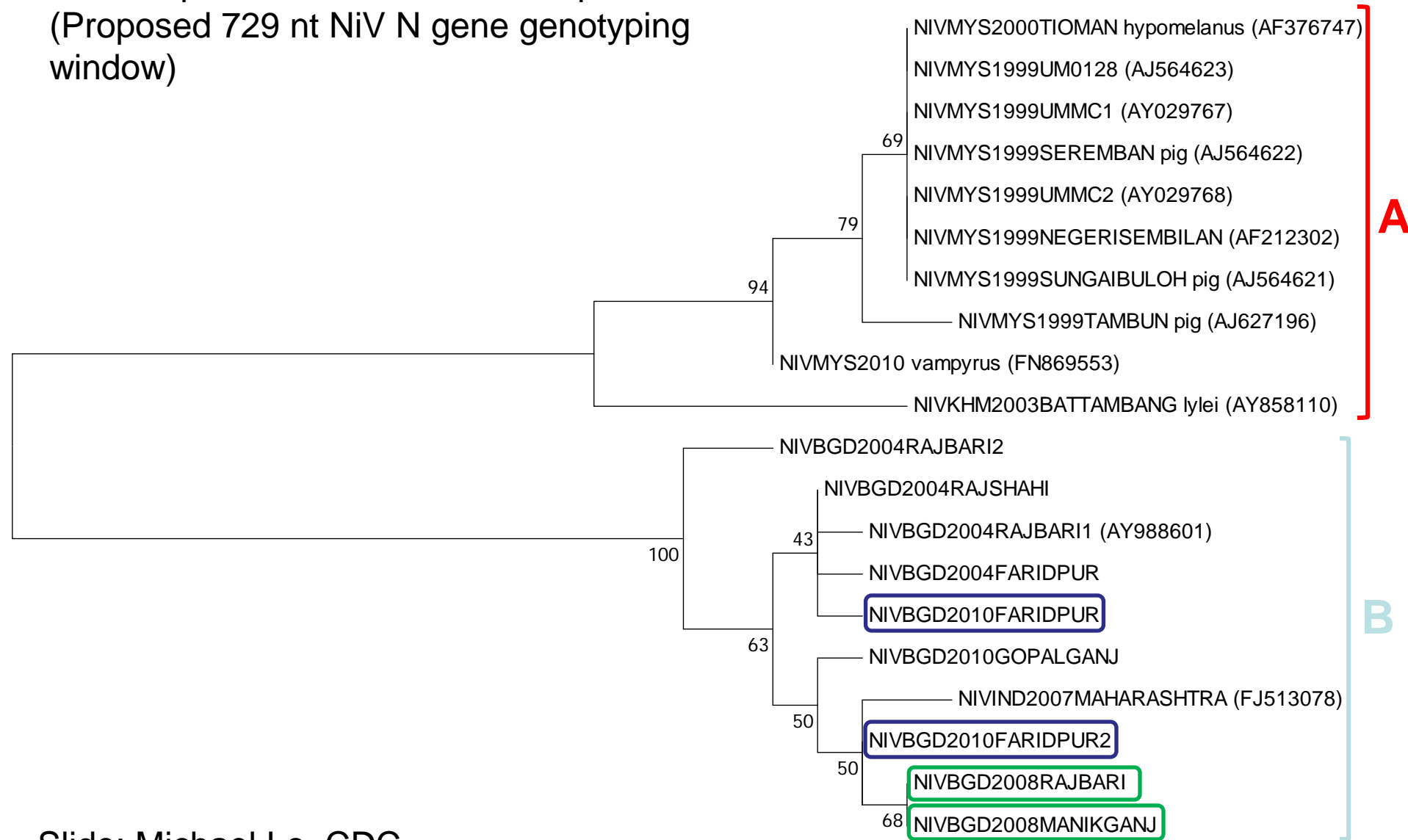
Male, 40 yrs, taken on 6th day of illness, died 2 days later



Male, 35 yrs, taken on 5th day of illness, died next day



Partial NiV N-ORF Maximum Parsimony
 Bootstrap consensus tree 1000 replicates
 (Proposed 729 nt NiV N gene genotyping
 window)



Slide: Michael Lo, CDC

Lo M, *Emerg Infect Dis*, 2012 Feb;18(2):248-55.

Phenotypic diversity of Nipah Virus

- 8 ferrets
 - inoculated with NiV strain from Bangladesh
- 7 ferrets
 - inoculated with NiV strain from Malaysia
- Mean viral RNA levels in respiratory secretions
 - 10x higher among ferrets inoculated with the Bangladesh strain



Australia Animal Health Laboratory

Anthropological Investigation

- May 2004 to January 2005
- In-depth interviews with:
 - family members in households where a Nipah case occurred
 - neighboring families
 - local health practitioners
 - hospital workers
 - date palm sap collectors
 - bat catchers

Family caregivers during Faridpur outbreak

- Families provide direct care
 - Rooted in emotional support
 - Cultural expectation to
 - maintain close physical contact during illness
 - Provide hands-on care with direct contact with patient's body fluids
- Desire for close physical contact before dying (hug to say goodbye, feed sick patient, whisper Koranic verses in ear)
- Family members and religious leaders prepare and cleanse the body, particularly the orifices, for burial

Date Palm Sap Harvesting Practices

Anthropological Investigation

- Harvesters typically tend 50 – 100 trees
 - Seasonal work
 - Share half of sap with owner
 - Earn median 5 US\$ per week selling sap
- Bats are somewhat of a nuisance
- Occasional methods to discourage bats
 - Thorns
 - Bending leaves
 - Spreading lime
 - Bamboo nets



Photo : Nazmun Nahar

Bamboo nets

- Obstructs access to jar and shaved part of the tree
- Rarely used



Photo: Nazmun Nahar

Reducing date palm sap contamination by bats a randomized controlled trial

- Selected 120 date palm sap producing trees in a village
- Randomly assigned four types of interventions to 15 trees each to cover the shaved part, sap stream, tap and collection pot:
 - bamboo skirt
 - dhoincha (local plant) skirt
 - jute stick skirt
 - polythene
- 60 trees enrolled as controls
- The controls were matched on :
 - apparent height
 - shaving pattern



Photo: Nazmun Nahar



Jute

Doincha

Bamboo

Polyethylene

Bat Visits

	Bamboo	Dhoincha	Jute	Poly ethylene	Control
Bat visits on and around tree	176	45	125	112	4630
% landed on the tree	20	18	43	11	78
Number contacting date palm sap	0	0	11	0	3556
% contacting sap	0	0	9	0	76

Sap Harvester Acceptability Trial

- Intervention:
 - Community meetings targeting 79 tree owners and 79 *gacchis*
- Baseline : No bamboo skirts used in the community
- One month after intervention
 - 34% of *gacchis* used skirts
 - 14% of tree owners used skirts

Rebeca Sultana



Photo: Jon Epstein

District Level Prevention Trial 2013

- Objective:
 - prevent human consumption of raw sap
- Site
 - Intervention in 348 villages in Rajbari District
 - Control Kushtia district
- Behavior change communication intervention
 - Posters, video documentary, 45 second television spot
 - Trained local non-government organization health communicators

নিপাহ্ রোগ থেকে পরিবারকে সুরক্ষিত রাখুন
খেজুরের কাঁচা রস খাওয়া থেকে বিরত থাকুন।

মনে রাখবেন, খেজুরের রস দিয়ে তৈরি গুড় খাওয়া নিরাপদ



বানুড় থেকে নিপাহ্ রোগ ছড়াতে পারে। রাসের বেলায় খেজুরের রসের হাড়িতে বানুড় এসে মুখ দেয়। এ রস কাঁচা খেলে তা থেকে মারাত্মক নিপাহ্ রোগ হতে পারে এবং পরিবার ও প্রতিবেশীদের মধ্যেও তা ছড়াতে পারে।

USAID FROM THE AMERICAN PEOPLE IEDCR icddr,b PREVENT Project Produced by: fhi360

Skirt message

2013/2014

কাঁচা বৃক্ষ খেতে চান
বানায় ঢাকা বৃক্ষ-ই খান



বানা হচ্ছে এক ধরনের বেড়া, যা খেজুরের রস সংগ্রহের সময় বাদুড়কে কাঁচা খেজুরের রস থেকে দূরে রাখে। যার ফলে আপনার পরিবার বাদুড়ের মাধ্যমে ছড়ানো নিপাহ রোগ হওয়ার ঝুঁকি থেকে নিরাপদ থাকে।



বাংলাদেশ সরকারের নির্দেশনা: কাঁচা রস খাবেন না

Wash your hands with soap



Before you eat



After you feed the patient



After you clean the patient



1

DO NOT

Keep your food and the patient's food in separate bowls or plates



Store the patient's food when they are finished



Eat the patient's leftovers



2

Try to sleep in a separate bed or on the floor



Otherwise, sleep with your back to the patient



Sleep face to face with the patient



3

When you hug and comfort your patient, put your head to their chest



Or, put their head to your chest



Keep your face less than 1 hand's distance from your patient's face



4

Hospital Handwashing Pilot

- Objective:
 - Pilot 2 low cost hand hygiene stations
 - Assess impact on staff and attendant handwashing
- Site
 - Gazipur District Hospital
 - Fardipur Medical College Hospital
- Behavior change communication intervention
- Measurements
 - Baseline observation
 - Process evaluation
 - Endline observation
 - In-depth interview



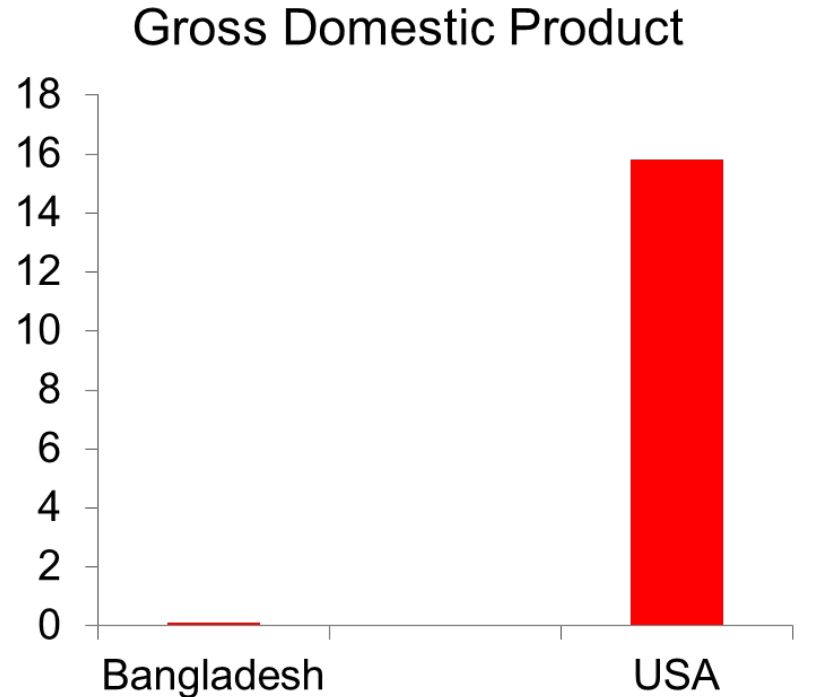
Nipah virus

- Recurrent outbreaks
- High case fatality
- Person to person transmission
- Global risk

Requires

- Global support
- Multi-disciplinary engagement
 - Government health authorities, physicians, virologists, veterinarians, anthropologists, wildlife ecologists, behavior change experts
- Multi-sector approach

Trillion US\$



Acknowledgements

- Government of Bangladesh
 - Institute for Epidemiology Disease Control and Research (IEDCR)
 - Mahmudur Rahman, Be-Nazir Ahmed, Mustak Hossein
 - Civil surgeons
 - Government Hospitals
 - Department of Forestry
- ICDDR,B
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- Centers for Disease Control and Prevention
 - Pierre E. Rollin, James A. Comer, Paul Rota, Michael Lo, Stewart Nichols, James Sejvar, Rob Breiman, Joel Montgomery
- EcoHealth Alliance
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- FHI360
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