Emerging Zoonoses: Nipah and Hendra viruses

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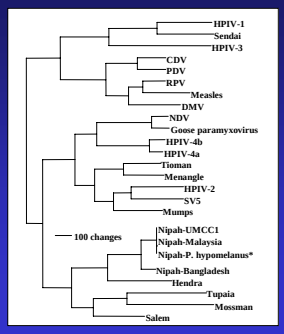
February 2010

Histogram of the phosphoprotein gene of members of the subfamily Paramyxovirinae



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Hendra and Nipah viruses

- History of previous outbreaks
- Reservoirs of viruses
- Clinical features in human
- Diagnosis and Treatment
- Transmission and Epidemiology
- Disease in horses and pigs
- Prevention and Control

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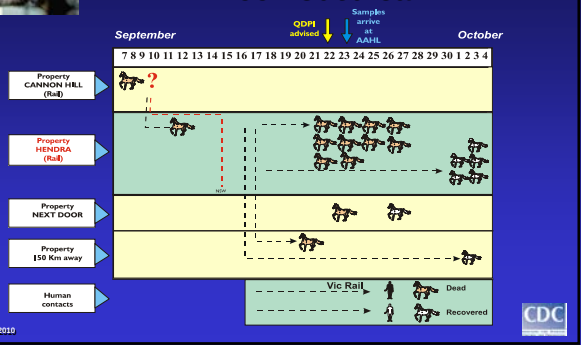
History of Hendra outbreaks - 1994 outbreak



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History of Hendra outbreaks - 1995 Mackay

- In 1995, a 36yo farmer died of severe encephalitis in Mackay, Queensland.
- Two horses died a year before of unknown infection (one of pneumonia, the other of acute neurological illness) retrospectively Hendra-confirmed.
- He had assist at their post-mortem examination and had retrospective serologic evidence of Hendra infection at that time.

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History of Hendra outbreaks

	HORSE	HUMAN	
Mackay	2	1*	August 1994
Brisbane (Hendra)	20	2*	September 1994
Cairns (Trinity Beach)	1	-	January 1999
Cairns (Gordonvale)	1	1	October 2004
Townsville	1	-	December 2004
Peachester	1	-	June 2006
Murwillimbah	1	-	October 2006
Peachester	1	-	June 2007
Cairns (Clifton Beach)	1	-	July 2007
Brisbane (Redlands)	5	2*	June 2008
Proserpine	3	-	July 2008
Cawarral	4	1*	July 2009
Bowen	2	-	Aug 2009
	43	7 (4 deaths)	

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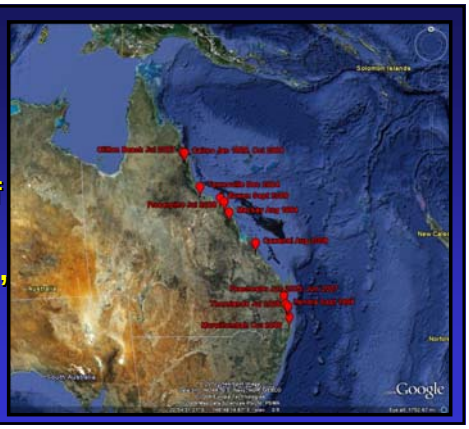
History of Hendra outbreaks, Australia



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History of Nipah outbreaks - Malaysia - 1999

Outbreak of viral encephalitis in Malaysia:

- Disease in humans (mostly pig farmers) with cases described as beginning in October 1998
- Parallel disease in pigs, but not initially reported nor well described
- Japanese encephalitis diagnosed as the etiology of the disease in humans *and pigs*
- March 1999. CSF from patients from Negeri Sembelan: yields cytopathic agent. EM--paramyxovirus like morphology on thin section. 12/13 patients positive by Hendra IgM capture. IHC on frozen brain positive for Hendra
- RT-PCR is positive with degenerate paramyxovirus P-protein primers, sequence is Hendra-like but distinct

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History of Nipah outbreaks

- In 1999, Singapore's importation of infected pigs from Malaysia. 22 human cases and one death. Of these, 12 (54±6%) were symptomatic; 9 presented with encephalitis, 2 with pneumonia and 1 with both encephalitis and pneumonia. Stopped with pig import ban from Malaysia.
- Since 2001, 10 outbreaks in Bangladesh, 2 in West Bengal, India.
- Since discovery, 480 human cases including 251 deaths

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History of Nipah Outbreaks, Bangladesh and India

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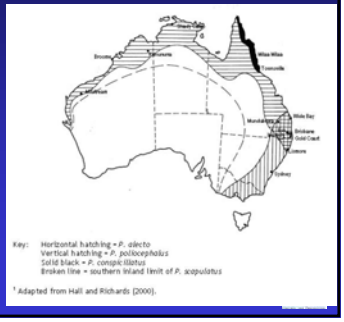
Reservoirs of viruses Hendra

- fruit bats identified as the natural host in 1996.
- antibodies in all 4 species (20-50%).
- antibodies across the geographic range.
- no attributed clinical disease in flying foxes.
- antibodies in archive samples.



† Adapted from Hall and Richards (2000).

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Reservoirs of viruses Nipah Malaysia

Species	# Tested	Nipah SNT Pos
Pteropus vampyrus	57 (28)	5
Pteropus hypomalenus	42	10
Cynopterus brachyolitis	74	0
Cynopterus horsfieldi	9	0
Rousettus amplexicaudatus	16	0
Eonycteris spelaea	74	0
Macroglosus sobrinus	4	0
Balionycterus maculata	4	0
Megaerops ecaudatus	1	0
Scotophuilus kuhli	58	0*
Rhinolophus spp.	7	0
Taphozous melanopogon	7	0
Hippeosiderus bicolor	1	0
* Toxic		

Total of ~310 bats
KB Chua has isolated Nipah virus from *Pteropus hypomalenus*

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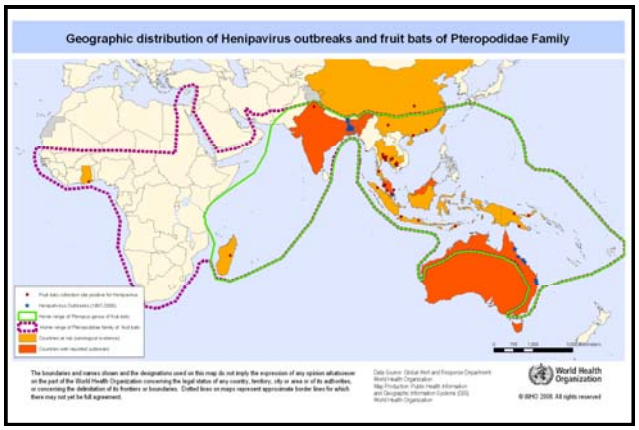

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Clinical features - Hendra

- All have unprotected contact with infected horses
- Incubation period 5-14 days
- All cases symptomatic (4/7 died)
- All start with “flu-like” syndrome: fever, headache, myalgias, sore-throat, dry cough
- Neurological manifestations indicative of bad prognosis
- Multi-organ failure and death

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Clinical features - Hendra

Mild case in a veterinarian (Hanna et al. Med J Aust 2006;562-4)

– Extensive exposure to horse’s blood & body fluids during necropsy on horse with acute febrile illness with respiratory and pre-terminal neurological manifestations

– Onset 7 days later: febrile illness with cough, pharyngitis, cervical lymphadenopathy

– Recovered ~8 days later

– Seroconversion to HeV on day 14 of illness

– No clinical evidence of relapse

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Clinical features - Hendra

33-year-old equine veterinarian (Playford et al. Emerg Infect Dis 2009 (in press)) Performed necropsy and nasal cavity lavage on infected horses (16 and 9 days previously)

Day 2 illness: Presented with “flu-like” illness, fevers, mild neutropenia & thrombocytopenia
- NPA/serum: RT-PCR-positive for HeV; – NPA: RT-PCR-negative for respiratory viruses

Days 3-4: Afebrile/improved

Day 5: Drowsy, confused, ptosis, ataxia, dysarthria
- MRI: multifocal pontine & cortical lesions
- DWI: hyperintense foci c/w infarction
- CSF: Leukocytes <5×106/L, protein 600 mg/L, HeV RT-PCRpositive
- EEG: Bilateral slow wave activity
- Commenced on iv Ribavirin (30 mg/kg, then 15 mg/kg q6h)

Days 6-31: Progressive neurological deterioration: Generalised partial tonic-clonic seizure (day 10); Ventilated (day 11); Ribavirin ceased because of haemolytic anaemia (day 16); Sluggish reactive pupils, minimal responsiveness off sedation despite seizure control (day 19 on)
- MRIs: Innumerable widespread multifocal lesions on T2 FLAIR; lesions c/w infarction on DWI
- EEGs: absent stable rhythm, periodic sharp waves, severe diffuse encephalopathy

Day 31: Death

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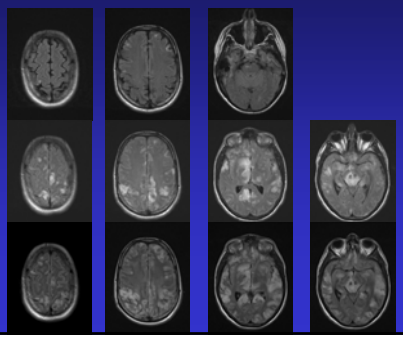
Clinical features - Hendra

Day 5

Day 18

Day 25



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Clinical features – Nipah Malaysia

- Febrile illness - 4-7 days duration
- Early respiratory signs?
- Headache, drowsiness, slurred speech, loss of cognition, coma
- Neurological signs suggest mid-brain, pons lesions
- Pathology: diffuse focal lesions of CNS
- Mortality ~36%of those hospitalized (105/285)
- There were subclinical infections

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Admission Laboratory Values

Test	Median	Range	(Normal Range)
WBC (x1000/mm3)	5.2	1.2 – 14.7	(4.5-11.0)
Platelet (x1000/mm3)	141	8 - 357	(150-400)
Creatinine (mg/dL)	0.9	0.4- 5.0	(0.7-1.5)
CSF WBC (# /cu mm)	2	0-1250	(0-10)
CSF protein (mg/dL)	67	15 - 335	(15-45)

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Clinical features of Nipah virus encephalitis
Goh et al NEJM 2000;342:1229

Clinical features at presentation (n=94)

Fever	97%
Headache	65%
Dizziness	36%
Vomiting	27%
Reduced consciousness	21%
Nonproductive cough	14%
Myalgia	12%
Focal neurological signs	10%

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Clinical features of Nipah virus encephalitis
Goh et al NEJM 2000;342:1229

Neurological characteristics (n=94)

Absent or reduced reflexes	56%
Impaired consciousness	55%
Abnormal pupils	52%
Tachycardia	39%
Abnormal doll's eye reflex	38%
Segmental myoclonus	32%
Meningism	28%
Seizures	23%
Nystagmus	16%
Cerebellar signs	9%

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Factors associated with prognosis
Goh et al. NJEM 2000;342:1229

FACTOR	DEATH (N=30)	SURVIVAL (N=64)	P VALUE
Mean age — yr	40.9	35.2	0.02
Vomiting — no. (%)	12 (40)	13 (20)	0.04
Mean lowest Glasgow Coma scores	6.8	12.8	0.005
Segmental myoclonus — no. (%)	20 (67)	10 (16)	<0.001
Abnormal doll's-eye reflex — no. (%)	26 (87)	10 (16)	<0.001
Abnormal pupils — no. (%)	29 (97)	20 (31)	<0.001
Hypertension — no. (%)	23 (77)	14 (22)	<0.001
Tachycardia — no. (%)	28 (93)	8 (12)	<0.001
Absent or reduced reflexes — no. (%)	22 (73)	31 (48)	0.02
Seizures — no. (%)	12 (40)	10 (16)	0.01
Mean AST level at admission — U/liter	87	34.4	0.001
Mean ALT level at admission — U/liter	94.2	53.6	0.006
Mean platelet count at admission — per mm3	151,000	197,000	0.005

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Relapsed and late-onset Nipah encephalitis

Chong et al Neurol J Southeast Asia 2003; 8: 109

- Relapsed encephalitis was seen in 15 (9%) of acute encephalitis survivors
- Late-onset encephalitis was seen in 10 (3.4%) of those with previous non-encephalitic or asymptomatic Nipah infection
- Mean duration from initial infection: 13 months (up to 4 ½ years)
- 3/25 patients had a second neurological episode

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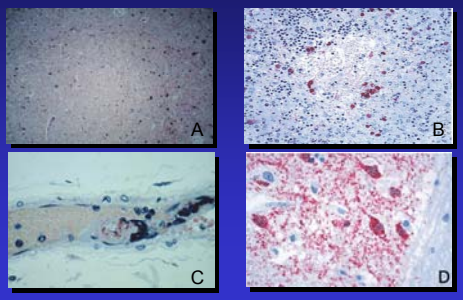
Immunohistochemistry - Nipah



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Long-term neurological and functional outcome in Nipah virus infection

Sejvar JJ et al. Ann Neurol 2007

Of the survivors of acute Nipah infection in Bangladesh

- **# 21/22** had **disabling fatigue**, with medium duration of 5 months;
- **# 3** patients continued to have **profound fatigue** 2 years after infection
- **# >50%** of those <16 years had **Behavioral abnormalities**

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Hendra and Nipah viruses

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Laboratory diagnosis "BSL-4 agent"

Sample	PCR	Isolation	IHC	Antibody
N/T Swab	+*	+*	ND	ND
Urine	+*	+*	ND	ND
Blood	+/-	-	ND	+
CSF	+	+	ND	+
Tissues	+	+	+	ND

* Positivity decrease when Ab appears

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Treatment Potential prophylactic/therapeutic modalities

– Ribavirin Nipah/Hendra
– Chloroquine
– Passive immunotherapy

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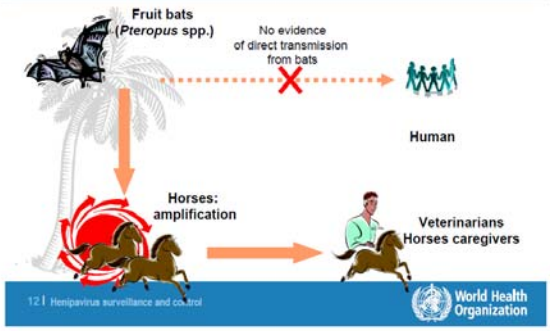
Hendra virus: transmission



Risk of spillover from bats

Probability of spillover from any given colony depends on
- the proportion of susceptible flying foxes,
- the colony size,
- the presence of infection..

plus
- the number and density of horses,
- the number and density of flying foxes,
- management of the horses,
- the virus strain/virus dose/route of infection?

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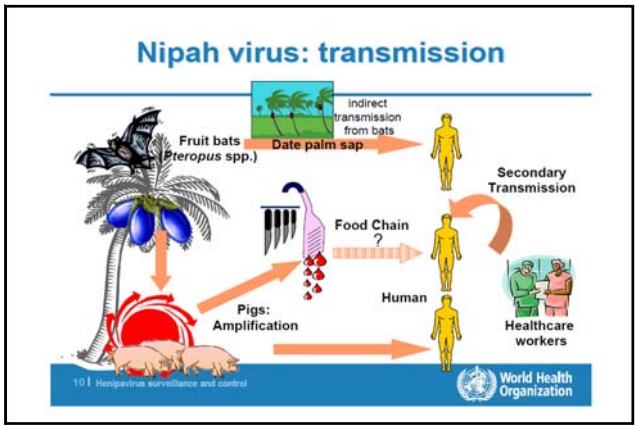
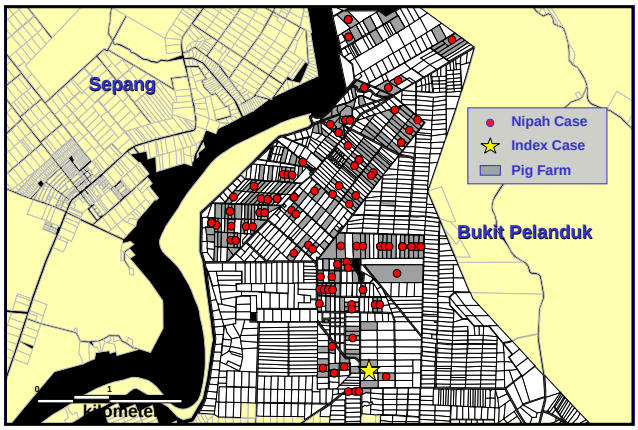
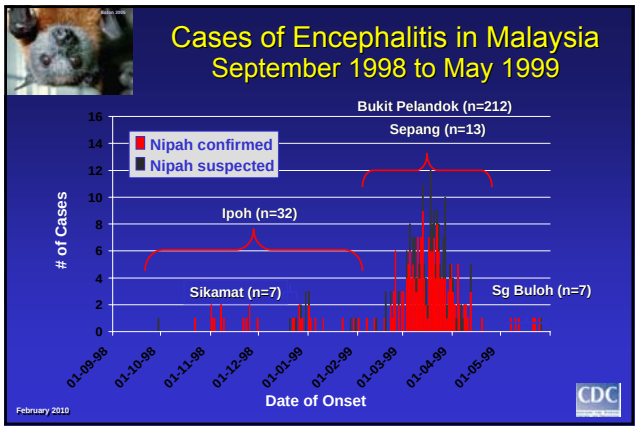

Nipah virus: transmission
indirect transmission from bats
Fruit bats (Pteropus spp.)
Date palm sap
Secondary Transmission
Food Chain ?
Human
Pigs: Amplification
Healthcare workers
10 | Henipavirus surveillance and control
World Health Organization


Sepang
Nipah Case
Index Case
Pig Farm
Bukit Pelanduk
Kilometer


Cases of Encephalitis in Malaysia
September 1998 to May 1999
Bukit Pelandok (n=212)
Sepang (n=13)
Nipah confirmed
Nipah suspected
Ipoh (n=32)
Sikamat (n=7)
Sg Buloh (n=7)
# of Cases
0
2
4
6
8
10
12
14
16
01-09-98
01-10-98
01-11-98
01-12-98
01-01-99
01-02-99
01-03-99
01-04-99
01-05-99
Date of Onset
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National Swine Surveillance

- Limited period (90 days)
- All premises sampled
  - Based on high morbidity data
  - 15 sows
  - 2 samples (at least 21 days apart)
- Abattoir sampling
- Active disease discovery
- Human case discovery
- Cull infected premises

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Results of Phase II Nat. Swine Surveillance

A total of 889 farms were tested

50 farms were found to have evidence of Nipah infection by the prearranged criteria

Farms culled

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Epidemiology Nipah Malaysia

- Spread
  - Movement of infected swine
- Transmission in swine:
  - Very transmissible in modern husbandry setting: crowding
- Virus maintenance in swine
  - Continuous transmission?
  - Persistent infections?

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Investigations Nipah Malaysia

- Risk factors:
  - Direct live infected pig contact
  - Non-encephalitic/non-clinical infections
- Virus molecular epidemiology
  - Pigs and human cases: identical sequence
- Nosocomial infections? No
- Natural reservoir?
- Other species:
  - Dogs, cats, horses: but non-spreading
  - Rodents, birds, insectivores: none or very low

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Risk factors & transmission of Nipah in Bangladesh

Year	Districts	Transmission and risk factors	Probability
2001	Meherpur	Caring or living with a case	OR 7.9; 95% CI 2.2-27.7
2003	Naogaon	Close proximity with pig herds	OR 6.1; 95% CI 1.4-25.9)
2004	Rajbari	Climbing trees	OR 8.2, 95% CI 1.25, +Inf
2004	Faridpur	Touching a Nipah patient	RR 15.0, 95% CI 4.0, 65
2005	Tangail	Drinking raw date palm juice	OR 7.0, 95% CI: 1.6-31, p<0.01
2007	Thakurgaon	Remaining in the same room with Nipah patient	OR 57.0, 95% CI: 4.4-7.44 p<0.001
2007	Kushtia	Person to person	p<0.05
2008	Manikganj and Rajbari	Drinking raw date palm juice	Adjusted OR 18, 95% CI: 2.2 - ∞, p=<0.005
		Rahman et al, 2009	

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Bangladesh Epidemiology

Person to person transmission
5 of 11 clusters, involved ranging from 1 to 5 generations
Study conducted to reduce the risk of Nipah virus transmission
- Nipah virus isolated from saliva and urine
- Nipah infection associated with close contact of patients
- Hand washing is protective

Superspreaders

Palm sap transmission
Understand date palm sap collection
- Explore existing techniques to interrupt bats in accessing date palm sap

Photo: Nazmun Nahar

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Hendra disease in horses

Respiratory HeV
- Peracute or acute illness
- Frothy nasal discharge
- Facial oedema
- Body temperature > 40 C
- Elevated heart rate (>90 beats/minute)

Neurological HeV (seen recently in Australia)
- Mild focal neurological signs, including muscle twitching
- Ataxia
- Head tilt, facial nerve paralysis
- Elevated body temperature
- Neurological signs may resolve

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Nipah disease in swine

- Febrile respiratory disease predominates
  - Labored or forced breathing
  - "One-mile" cough
- CNS disease much rarer than in man
- Sudden death/neurological disease in sows and boars, some abortions reported
- Mortality 1-3%, morbidity: ~100%
- Post-mortem changes primarily in lung, some CNS

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1. Control in domestic animals

- Routine cleaning & disinfection of pig farm/horse stable is expected to be effective in preventing infection
- Reducing the risk of bat-to-domestic animal transmission:
  bat proof buildings, bat exclusion strategy, fruit tree removal…
- Outbreak suspected:
  Quarantine animal premises
  ± euthanasia or culling of infected animal(s)
  Restrict/ ban animals movements
- Establish active animal health surveillance system for early warning for veterinary and human public health authorities.

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2. Reducing risk of infection in people

- Reduce risk of bats-to-human transmission:
  Protect collection process of date palm juice (bamboo)
  Wash & peel fruits thoroughly
- Reduce risk of human-to-human transmission:
  Avoid or minimize physical contact with ill patient
  Hand hygiene + use of personal protective equipment (PPE)
- Reduce risk of domestic animal-to-human transmission:
  Avoid or minimize contact with ill or dead pig, horse
  Hand hygiene + use of personal protective equipment (PPE)
  Particularly important in veterinary practices (care, necropsies)

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Social Mobilization and Communication

- Prevention: what should be the key messages:
  - Exposure to bats,
  - Exposure to sick animals,
  - Home care,
  - Funerals?
- Guidelines/trainings for specialized categories
  - Health care workers
  - Veterinarians
  - Farmers
  - Wildlife experts

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