NIPAH....
Guidance on clinical care and Infection control Practices

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NIPAH VIRUS INFECTION

- Human Nipah virus (NiV) -first recognized - 276 reported cases in Malaysia and Singapore -from September 1998 to May 1999.
- In India – 5 outbreaks - 2001 and 2007 two outbreaks -West Bengal, neighbouring Bangladesh.
- 2018-kozhikode,2019-one case .2021-one
- Large fruit bats of *Pteropus* genus - natural reservoir
- Circumstantial evidence of human-to-human transmission in India in 2001.
- In Siliguri, 33 health workers and hospital visitors became ill ? nosocomial infection.
- Tend to occur in a cluster or as an outbreak.

Epidemiology

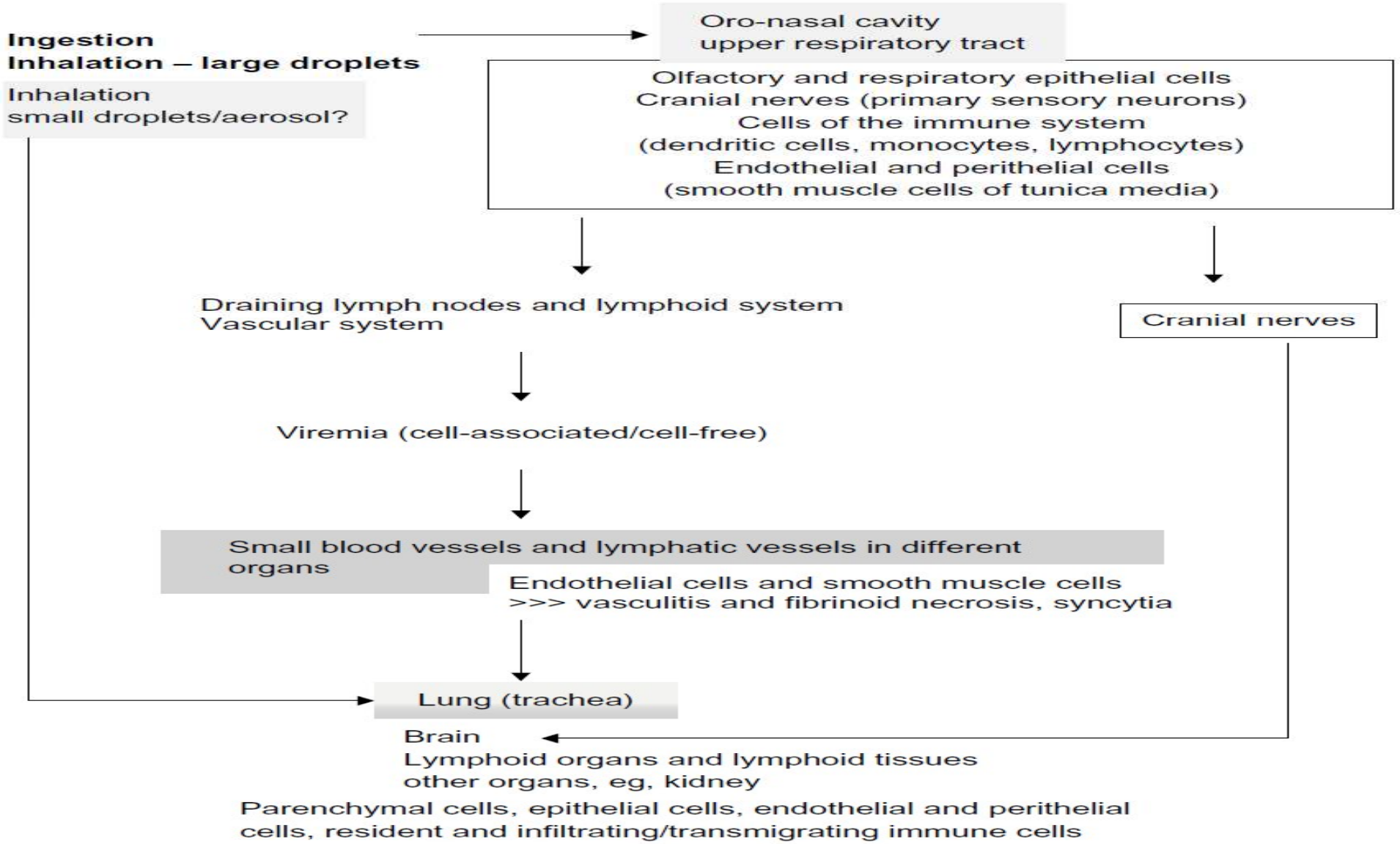
- **Agent:** NiV is a highly pathogenic paramyxovirus
- **Natural Reservoir:** Large fruit bats of *Pteropus* genus. Presumably, pig may became infected after consumption of partially bat eaten fruits that dropped in pigsty.
- **Seasonality** was strongly implicated in NiV outbreaks in Bangladesh and India. All of the outbreaks occurred during the months of winter to spring (December-May). Now 2 cases in September.
- **Incubation period:** varies from 4-21 days. In the Kozhikode outbreak, average incubation period was 10 days.

Nipah virus dynamics in bats and implications for spillover to humans

Jonathan H. Epstein,[a,1] Simon J. Anthony,[b,2] Ariful Islam,[a] A. Marm Kilpatrick,[c] Shahneaz Ali Khan,[a,d]

- Outbreaks in *Pteropus* bats are driven by increased population density, loss of immunity over time, and viral recrudescence, resulting in multiyear interepizootic periods.
- Can shed virus at any time of year, highlighting the importance of routes of transmission to the timing and location of human NiV outbreaks.

PATHOGENESIS



Modes of Transmission

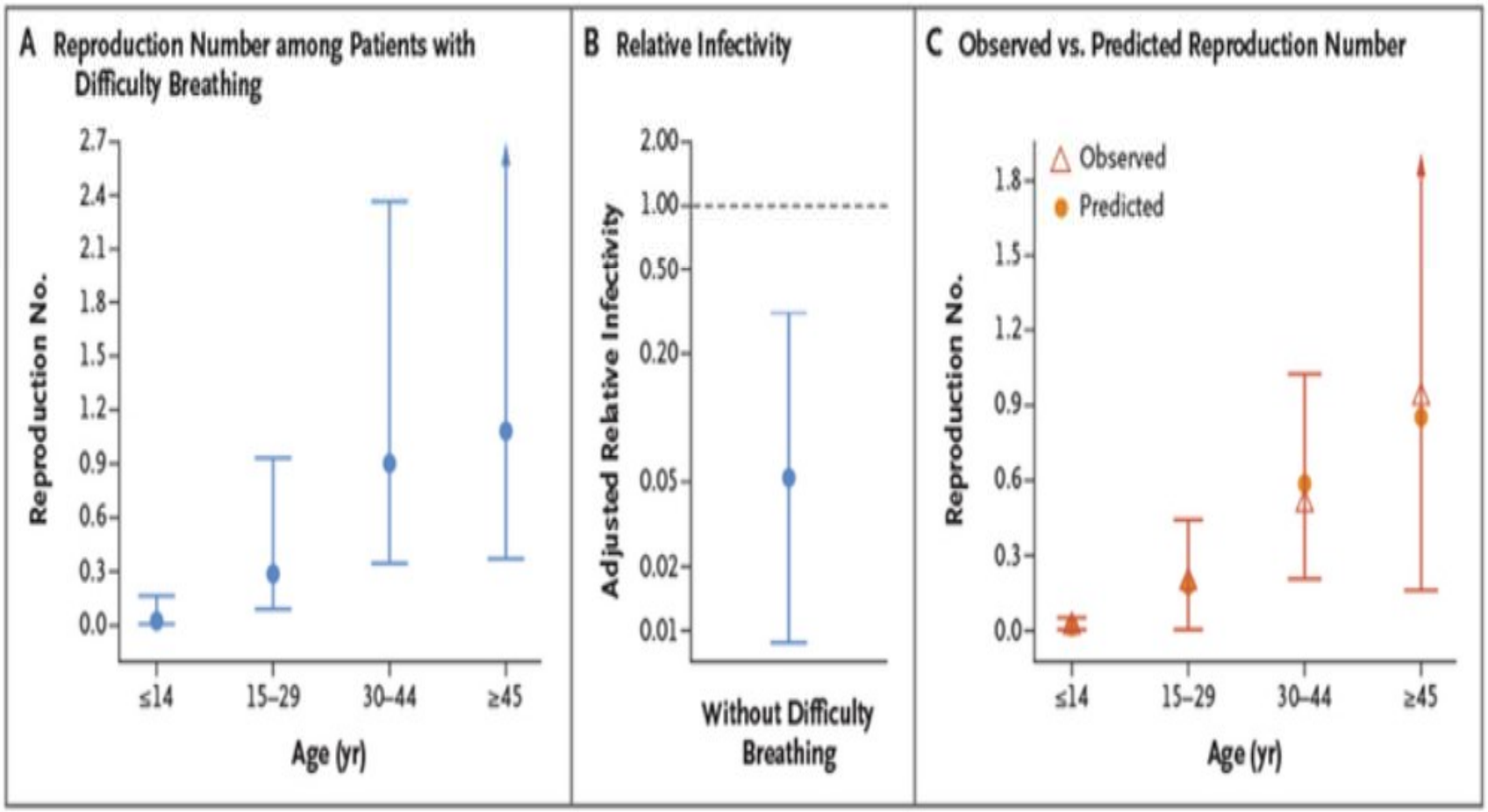
- Transmission of Nipah virus to humans may occur after

1. Direct contact with infected bats, infected pigs [Malaysia], or from other Nipah virus infected people.
2. Indirect contact—drinking date palm sap [Bangladesh], horse meat [Phillipines].

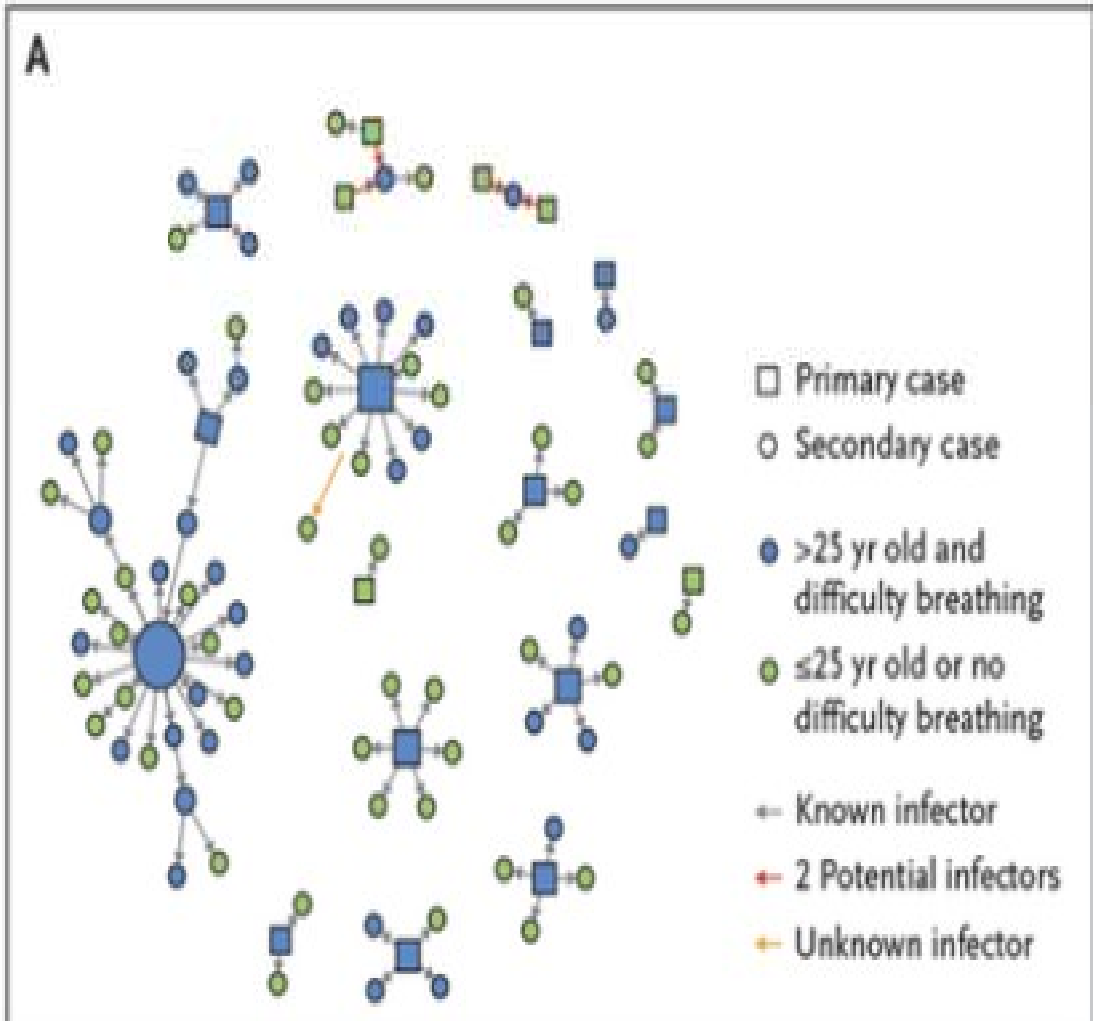
- In recent outbreak…direct spread from index patients to others by contact and droplet spread.

Transmission of Nipah Virus — 14 Years of Investigations in Bangladesh

Birgit Nikolay, Dr.rer.nat, Henrik Salje, Ph.D., M. Jahangir Hossain, M.B., B.S., A.K.M. Dawlat Khan,



N Engl J Med. Author manuscript; available in PMC 2019 Nov 9.

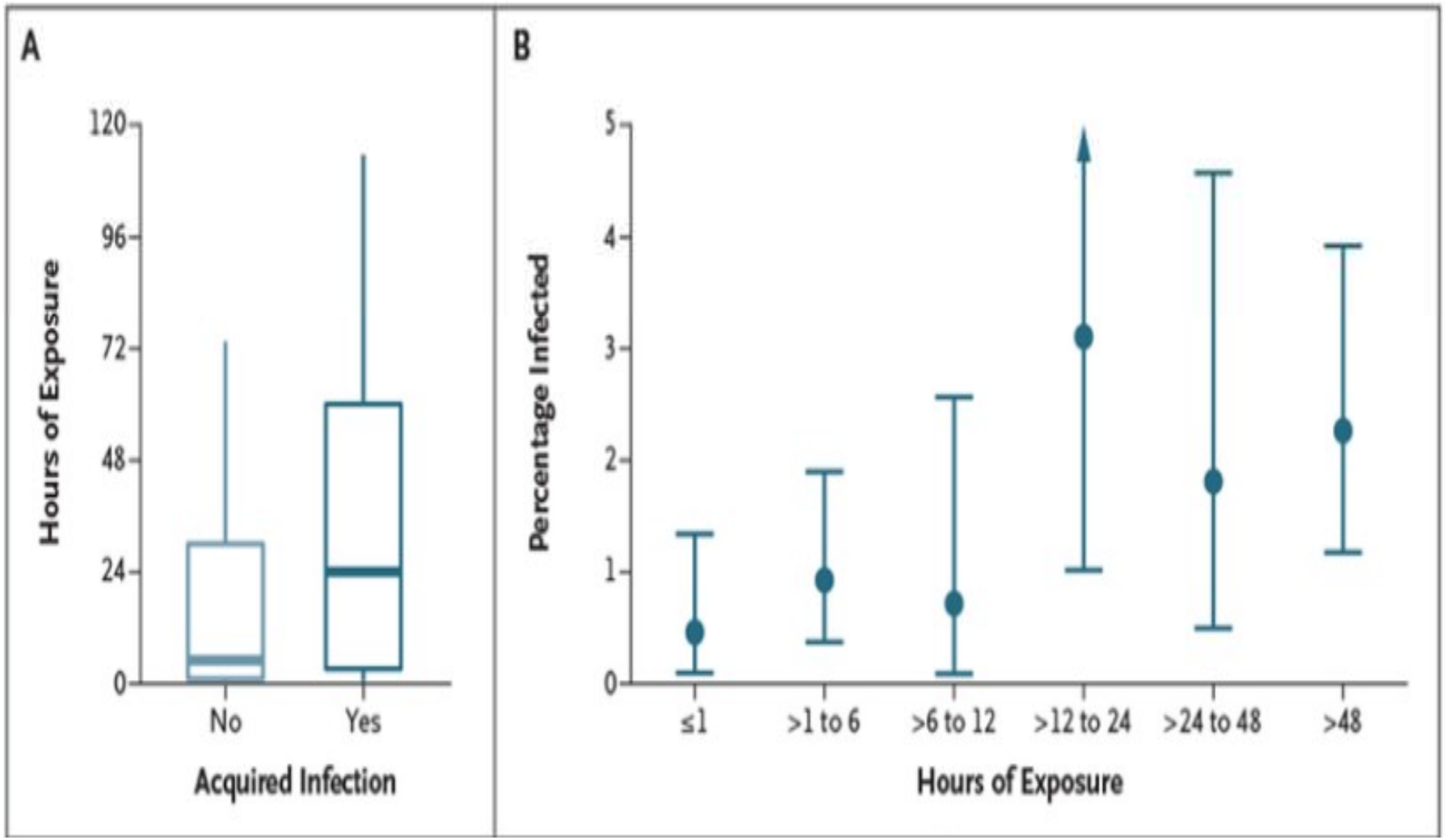


•The number of secondary cases per case patient was highly overdispersed:

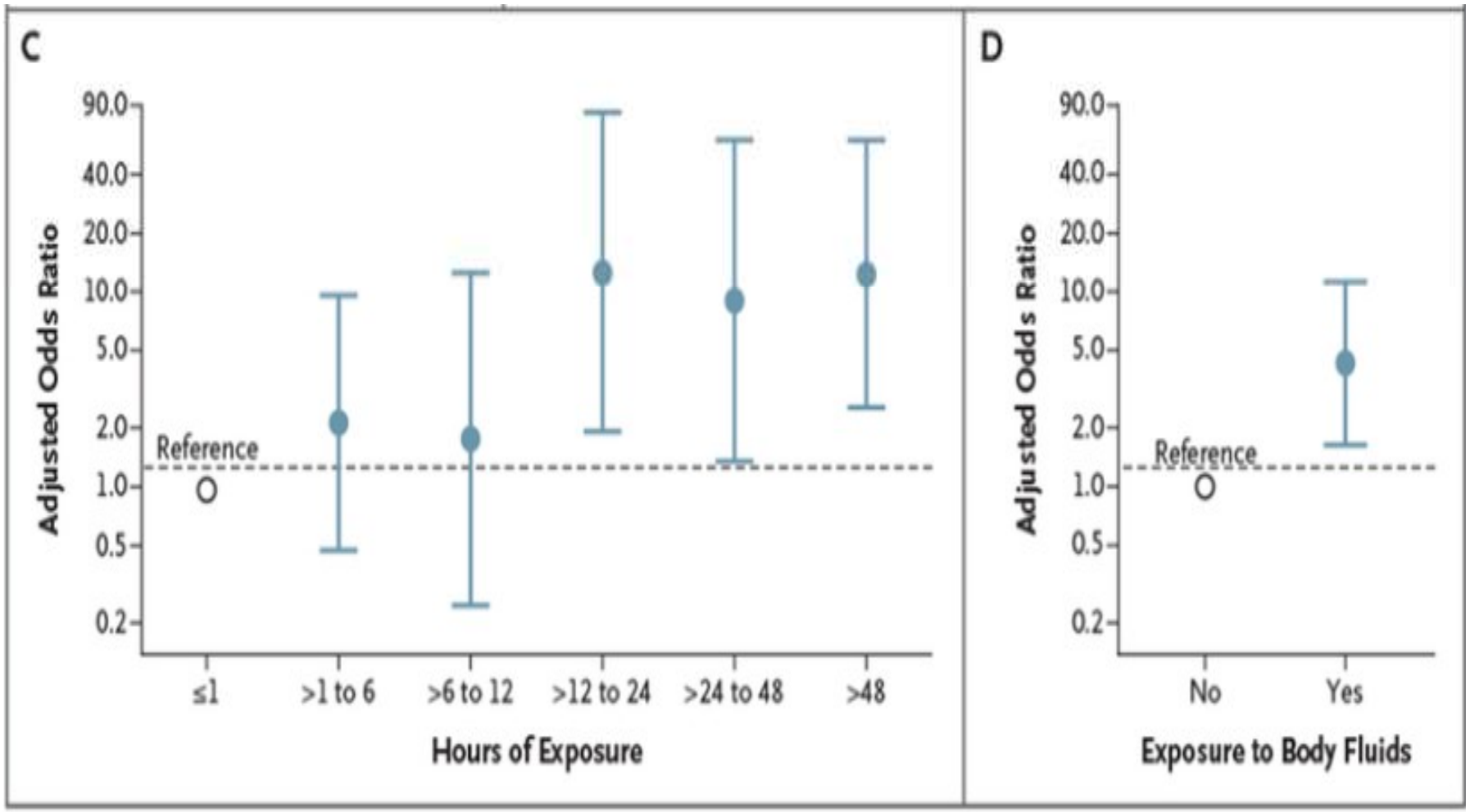
•5% of case patients (12 of 248) were responsible for 86% of transmission events (68 of 79)

•. A total of 9% of case patients (22 of 248) transmitted Nipah virus.

Predictors of acquiring infection



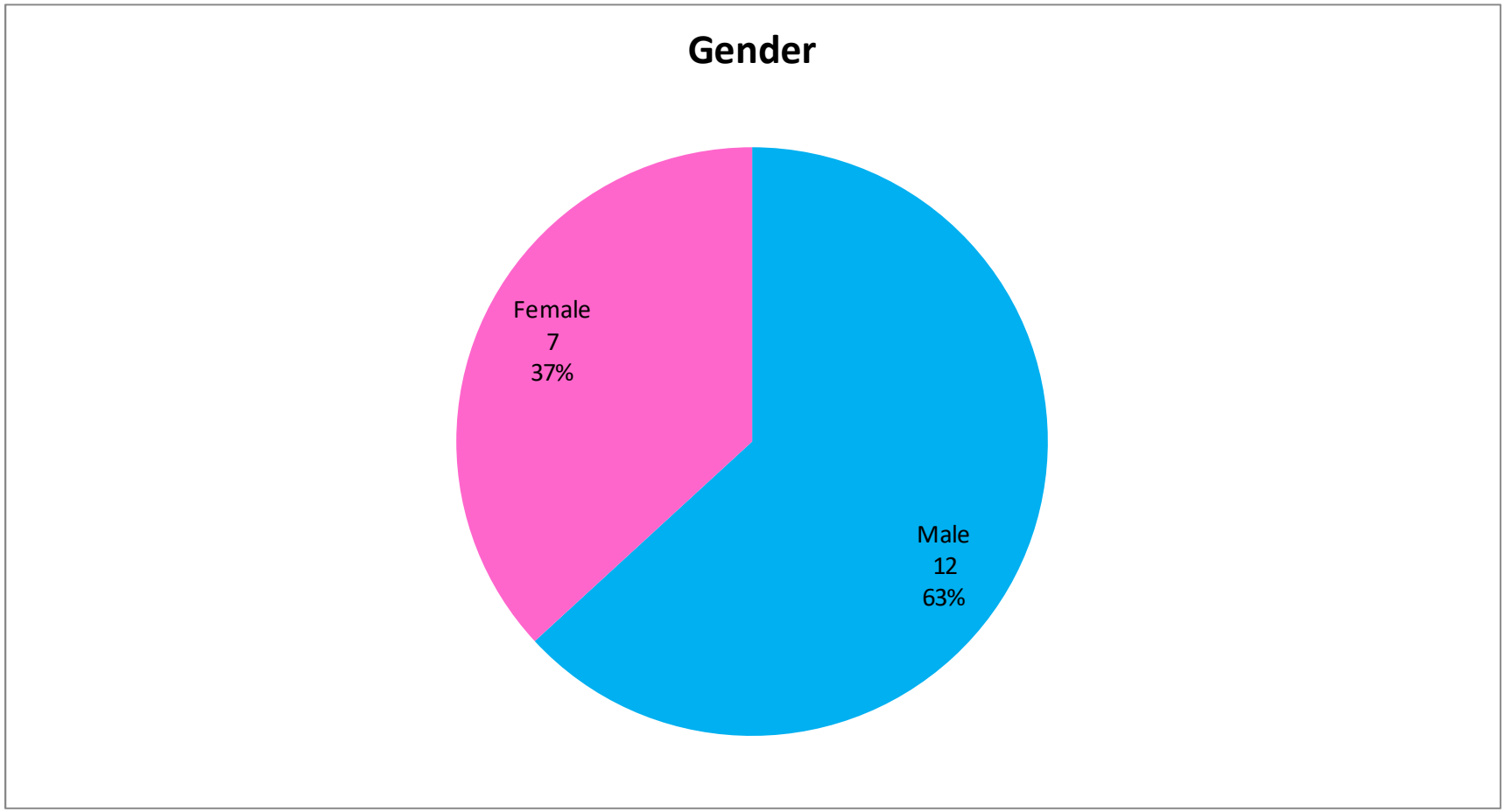
Predictors of acquiring Infection



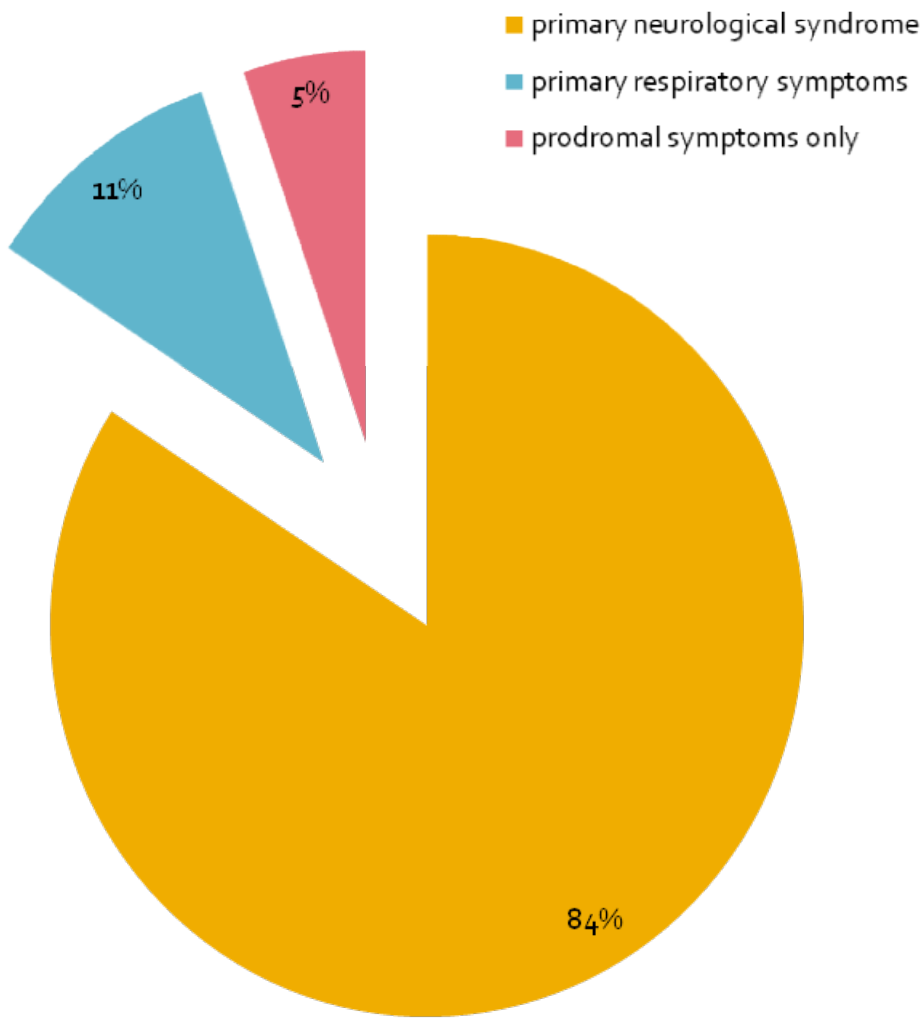
Clinical features

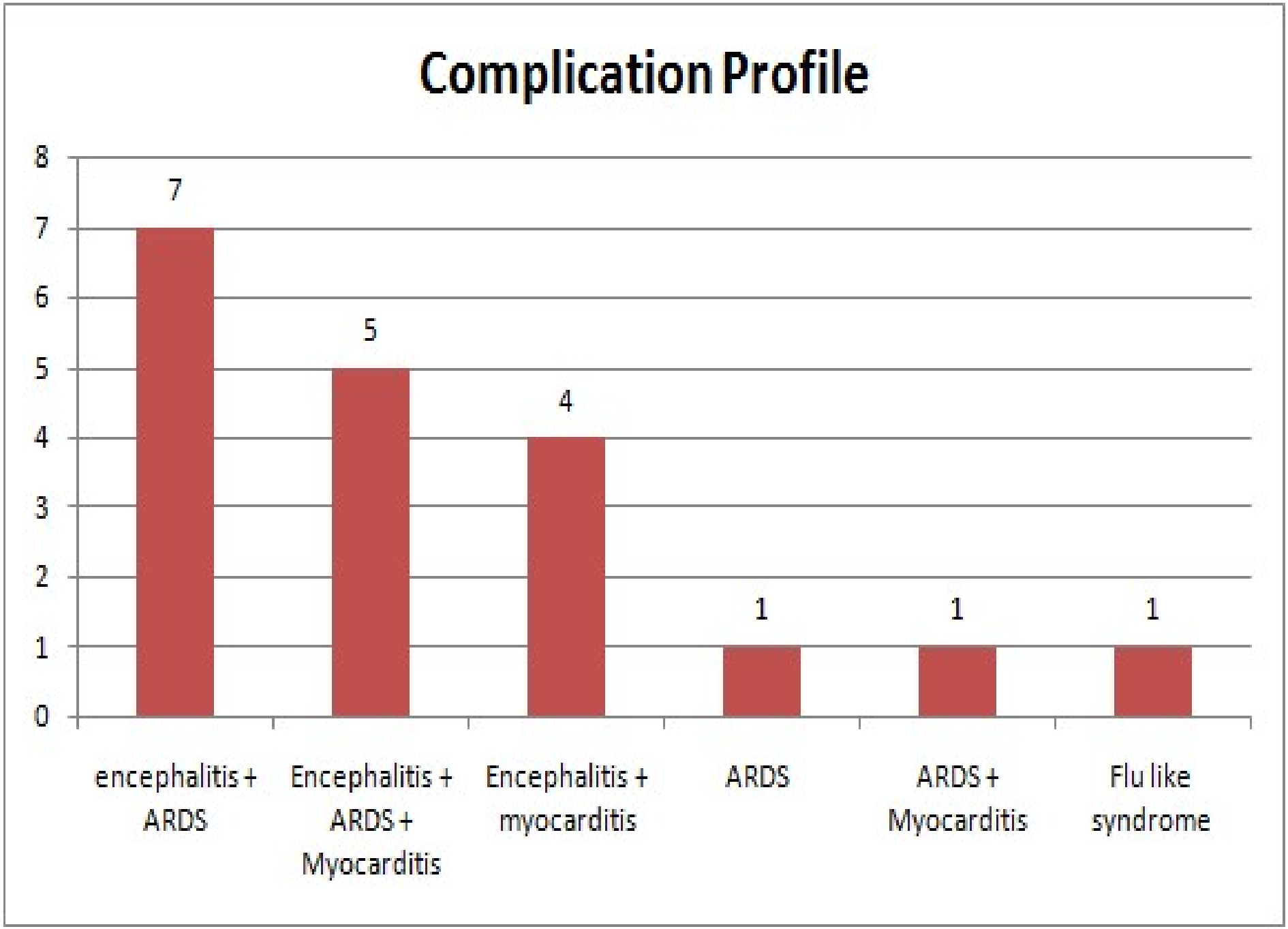
- Fever, Altered mental status, Severe weakness, Headache, Respiratory distress, Cough, Vomiting, Muscle pain, Convulsion, Diarrhoea
- Pulmonary Neurological syndrome.
- Flu like syndrome+ encephalitic syndrome.

Gender Distribution [2018-Kozhikode]

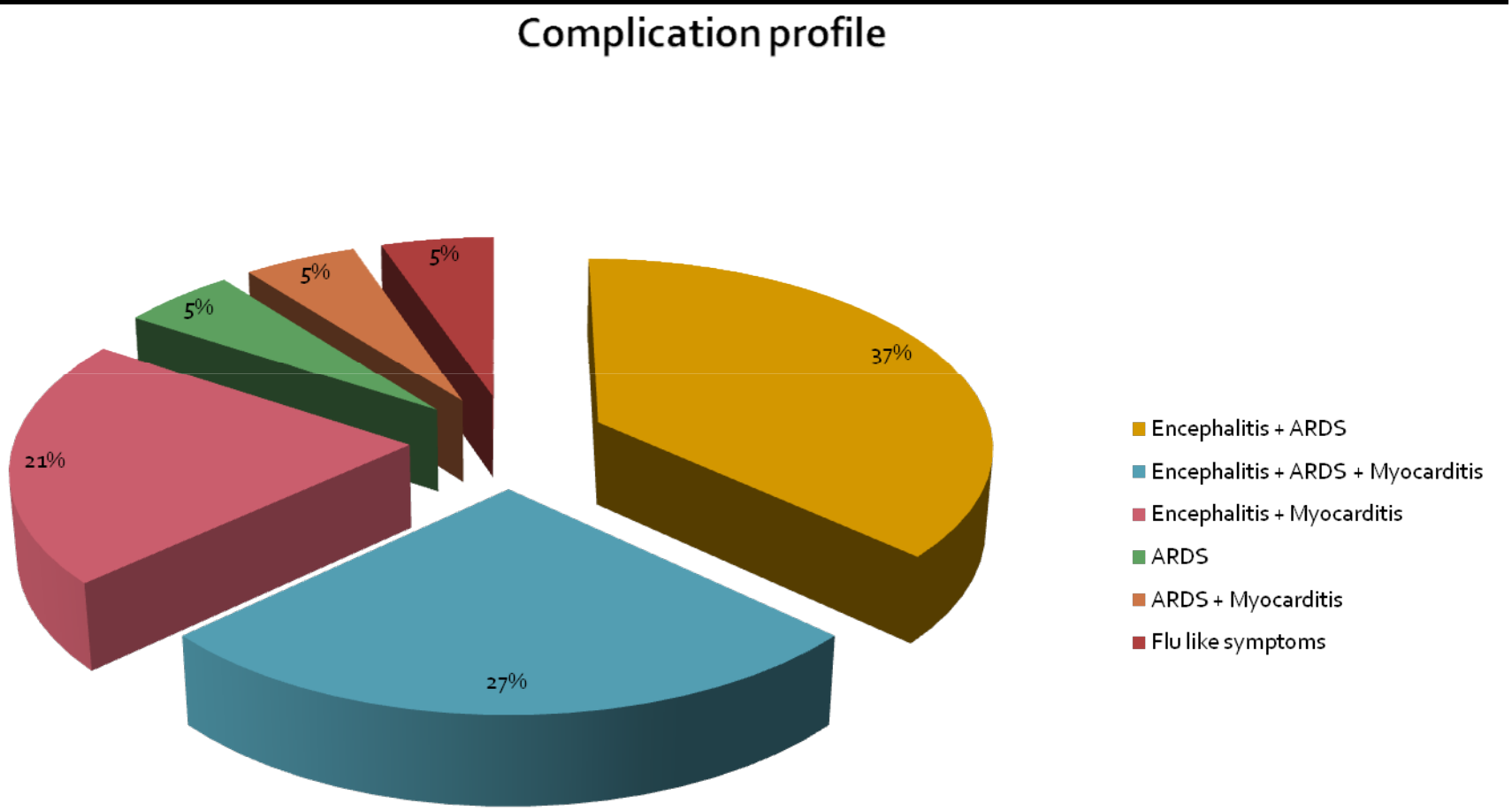


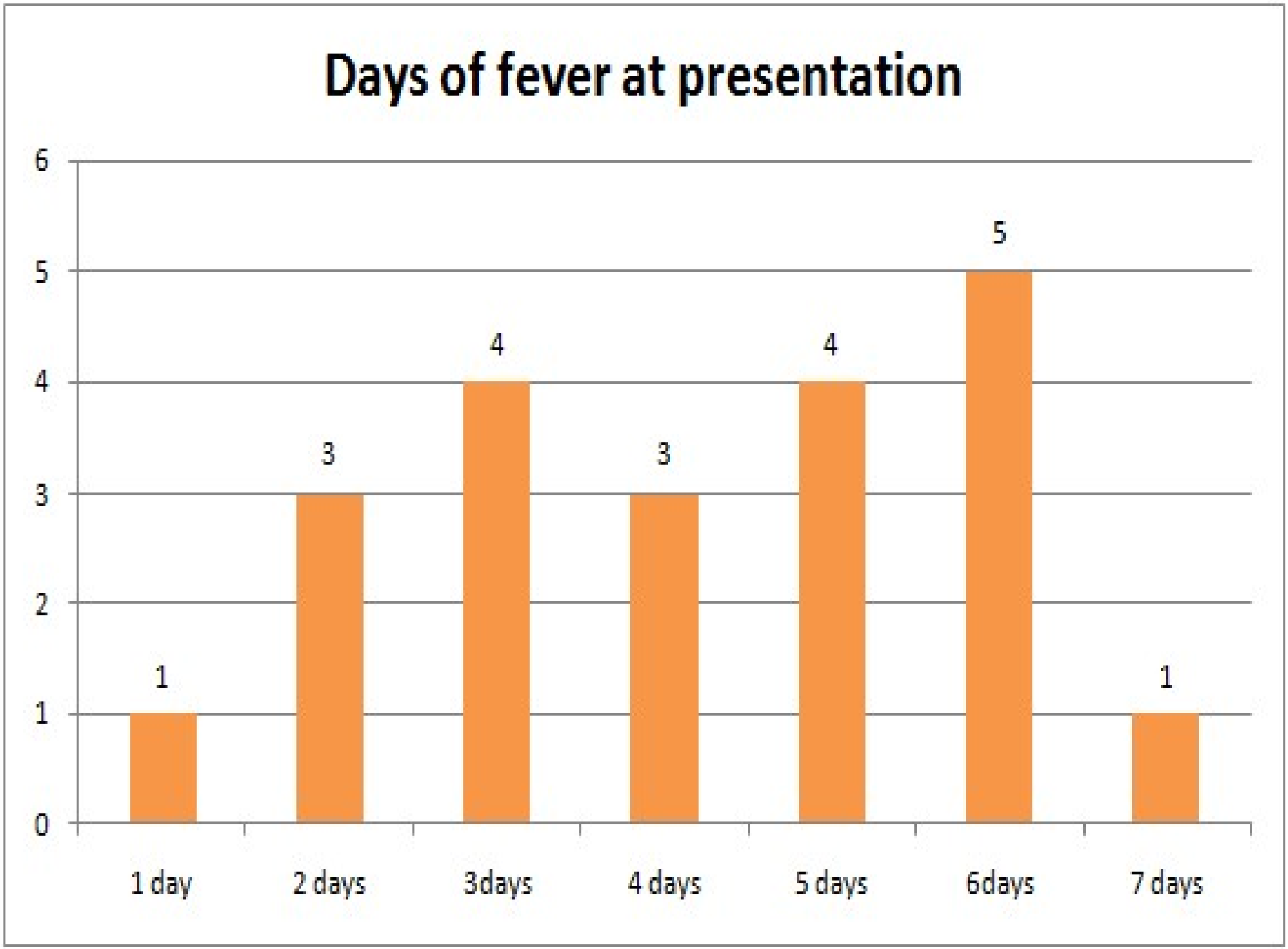
MODE OF PRESENTATION

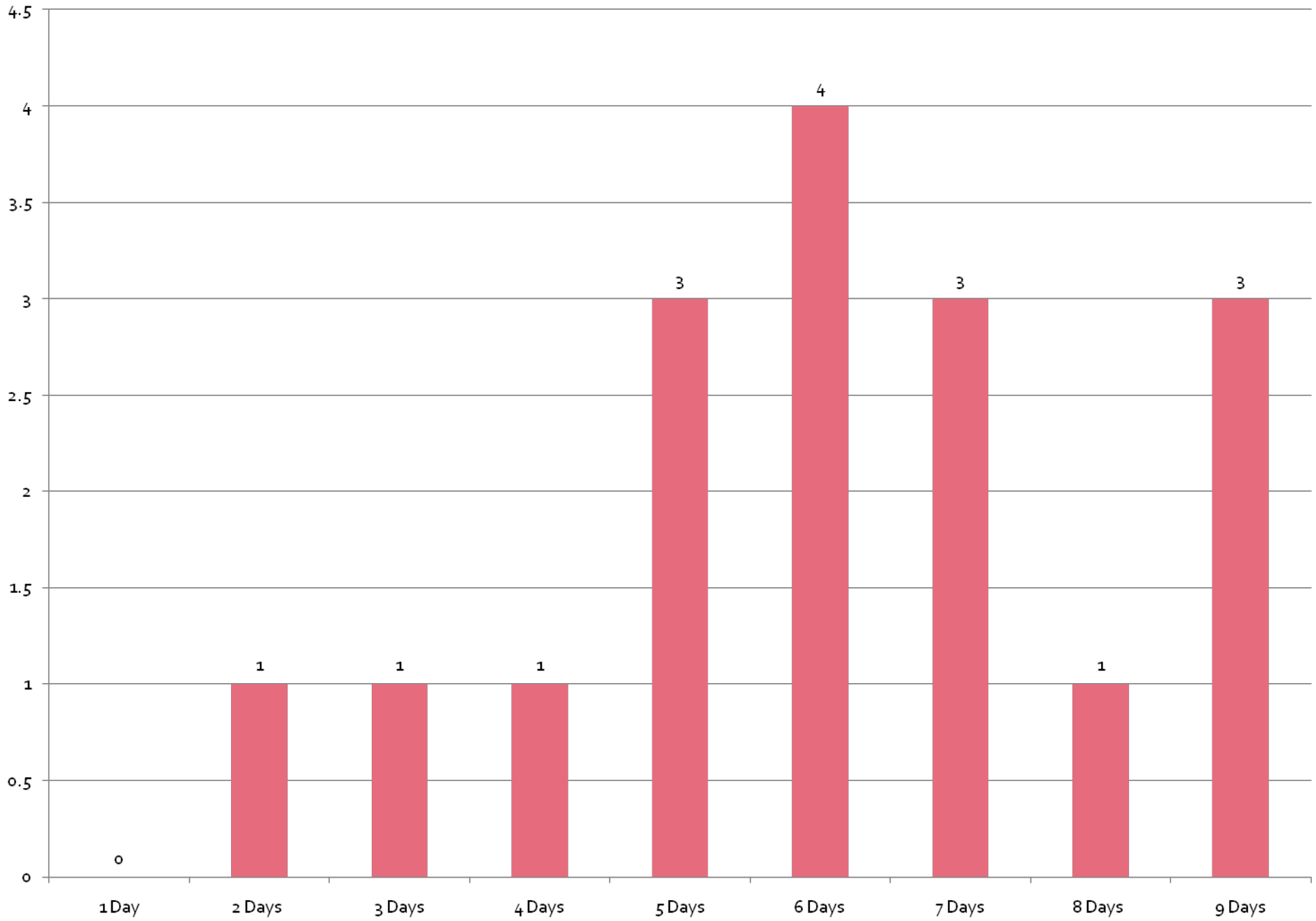


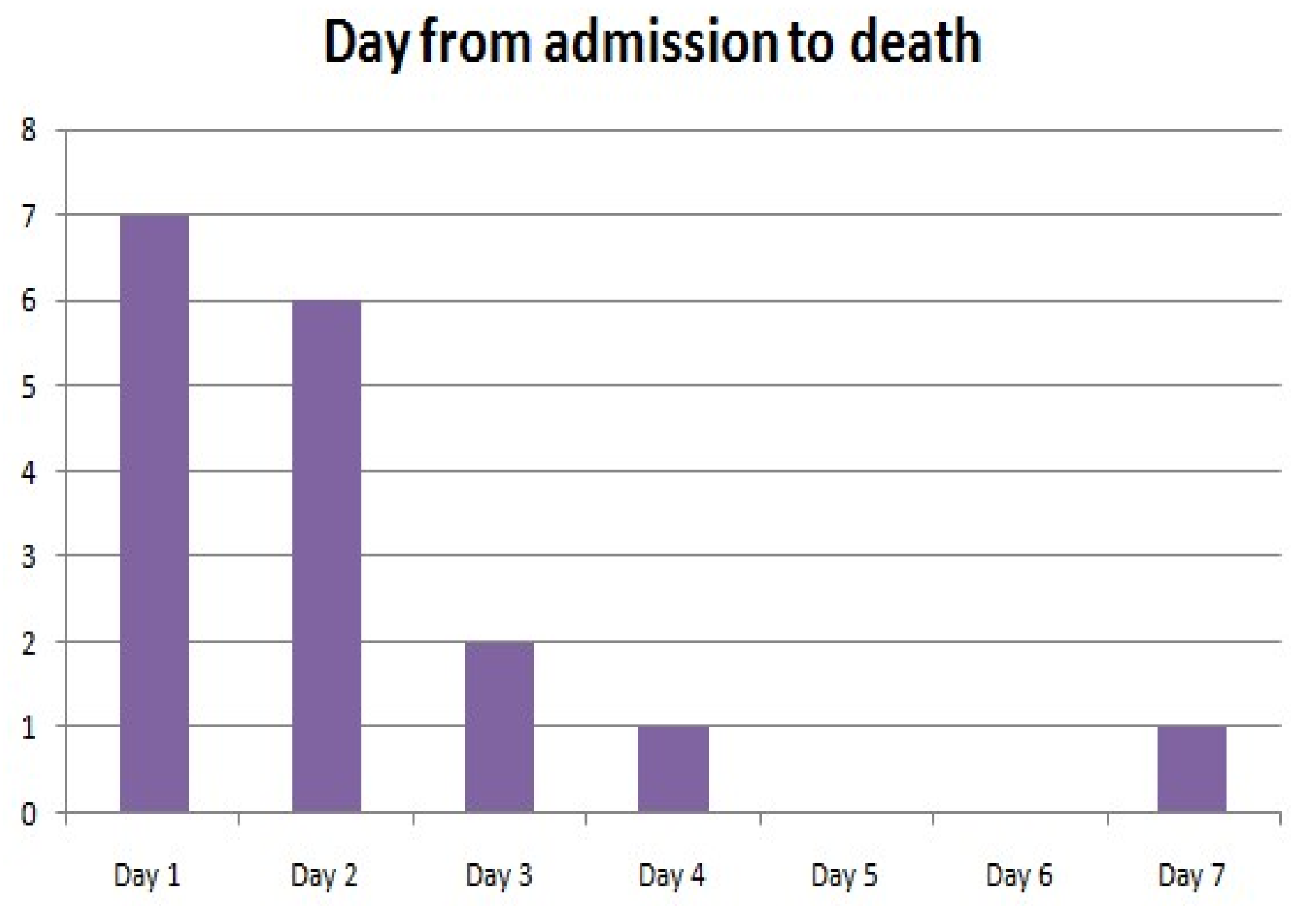

Complication Profile
8
7
6
5
4
3
2
1
0
7
5
4
1
1
1
encephalitis + ARDS
Encephalitis + ARDS + Myocarditis
Encephalitis + myocarditis
ARDS
ARDS + Myocarditis
Flu like syndrome

Complication profile




Days of fever at presentation
6
5
4
3
2
1
0
1
3
4
3
4
5
1
1 day
2 days
3days
4 days
5 days
6days
7 days


Day from onset of fever to death
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
0
1
1
1
3
4
3
1
3
1 Day
2 Days
3 Days
4 Days
5 Days
6 Days
7 Days
8 Days
9 Days


Day from admission to death
8
7
6
5
4
3
2
1
0
Day 1
Day 2
Day 3
Day 4
Day 5
Day 6
Day 7

S No	Symptom	Percentage
1	Fever	100%
2	Headache	94.73%
3	Fatiguability	94.73%
4	Cough	73.68%
5	Sorethroat	52.63%
6	Vomitting	73.68%
7	Diarrhoea	10.5%
8	Breathlessness	78.94%
9	Alteration of sensorium	84.2%
10	Seizures	36.84%
11	Myoclonus	10.5%
12	Vasomotor dysautonomia	52.63%
13	Neurologic deficit	26.3%
14	Bilateral ptosis and opthalmoplegia	26.3%
15	Neck stiffness	10.5%

S no	Parameter	Value
1	Mean Hb	13.27 gm/dl
2	Mean TC	5616 cells/mm3
3	Mean Polymorph %	81.44 %
4	Mean Lymphocyte %	12.06%
5	Mean Platelet count	1.38 lakh / mm3
6	Mean ESR	19
7	Mean Bilirubin	0.8 mg/dl
8	Mean SGPT	41.9 U /l
9	Mean SGOT	55.36 U /L
10	Mean Urea	21 mg/dl
11	Mean Creatinine	1.05 mg/dl

Suspected Nipah case

- Person from a area/ locality affected by a Nipah virus disease outbreak who has:
  - Fever with new onset of altered mental status or seizure and/or
  - Fever with severe headache and/or
  - Fever with Cough or shortness of breath

Probable case

Suspect case-patient/s who resided in the same village where suspect/confirmed case of NIPAH were living during the outbreak period and who died before complete diagnostic specimens could be collected.

OR

Suspect case-patients who came in direct contact with confirmed case-patients in a hospital setting during the outbreak period and who died before complete diagnostis.

Confirmed case

Suspected case who has laboratory confirmation of Nipah virus infection either by:

- Nipah virus RNA identified by PCR from respiratory secretions, urine, or cerebrospinal fluid.
- Isolation of Nipah virus from respiratory secretions, urine or cerebrospinal fluid.

Definition of a Contact:

A Close contact is defined as a patient or a person who came in contact with a Nipah case (confirmed or probable cases) in at least one of the following ways.

- Was admitted simultaneously in a hospital ward/ shared room with a suspect/confirmed case of NIPAH
- Has had direct close contact with the suspect/confirmed case of NIPAH during the illness including during transportation.
- Has had direct close contact with the (deceased) suspect/confirmed case of NIPAH at a funeral or during burial preparation rituals
- Has touched the blood or body fluids (saliva, urine, vomitus etc.) of a suspect/confirmed case of NIPAH during their illness
- Has touched the clothes or linens of a suspect/confirmed case of NIPAH

These contacts need to be followed up for appearance of symptoms of NiV for the longest incubation period (21 days).

Risk stratification of contacts

Risk Stratification of Contacts

RISK CATEGORY	DESCRIPTION
High risk	1. Any contact with body fluids (blood, urine, saliva etc) of a confirmed case of Nipah 2. Any contact with body fluids of a probable case who died without a lab confirmation of Nipah 3. Spend time in close proximity or in closed space for more than or equal to 12 hrs
Low risk	Any other contact such as touching, contact with clothes or linen or any other item used

Follow-up Action

RISK CATEGORY	Follow-up Action
High risk	Asymptomatic- Home quarantine with active follow up for fever, by health workers using telephone, twice a day for 21 days Symptomatic (fever)- Immediate admission in designated isolation ward with ICU facility
Low risk	Asymptomatic- Home quarantine and follow up for fever by telephone. Symptomatic (fever)- Immediate admission in designated isolation facility

Diagnosis

- Laboratory diagnosis of a patient with a clinical history of NiV can be made during the acute and convalescent phases of the disease by using a combination of tests.

- Nipah virus is classified internationally as a biosecurity level (BSL) 4 agent. In India, testing facility is available at NIV, Pune.

- For Kerala—MCH Calicut, NIV Alappuzha

Management

- Nipah –necrotising vasculitis with predeliction especially for brain and lung .
- In the 2018 outbreak,myocarditis was also present in 51% of patients.
- Fibrinoid necrosis in kidneys also observed.

Treatment measures

- Treatment - largely supportive consisting of
  - Anticonvulsants
  - Treatment of secondary infection
  - Mechanical ventilation and rehabilitation
- Malaysia outbreak- empiric treatment with ribavirin (broad spectrum and ability to cross the blood-brain barrier)
- In an open-label trial of ribavirin- a reduction in mortality observed (54% in control vs 32% treatment) (Chong *et al.*, 2001)
- Malaysia outbreak- Mortality rate: ~ 40%
- Bangladesh and India- Mortality rate ~ 70%
- Greater involvement of respiratory tract in Bangladesh & India outbreak
- Differences in pathogenicity between Clade 1 [B] and Clade 2 [M]

TREATMENT

- Currently there is no known treatment or vaccine available for either people or animals. Ribavirin, an antiviral may have a role in reducing mortality among patients with encephalitis caused by Nipah virus disease.

- RIBAVIRIN HAS NO ROLE IN PROPHYLAXIS.

Annals of NEUROLOGY
An Official Journal of the American Neurological Association and the Child Neurology Society

Brief Communication

Treatment of acute Nipah encephalitis with ribavirin

Heng-Thay Chong MRCP, Adeeba Kamarulzaman FRACP, Chong-Tin Tan FRCP, Khean-Jin Goh MRCP, Tarmizi Thayaparan MRCP, Sree Raman Kunjapan MRCP, Nee-Kong Chew MRCP, ... See all authors

First published: 06 June 2001 | https://doi.org/10.1002/ana.1062 | Cited by: 81

Nipah virus, a newly identified paramyxovirus caused a severe outbreak of encephalitis i Malaysia with high fatalities. We report an open-label trial of ribavirin in 140 patients, with 54 patients who were managed prior to the availability of ribavirin or refused treatment as control. There were 45 deaths (32%) in the ribavirin arm; 29 deaths (54%) occurred in the control arm. This represents a 36% reduction in mortality ($p = 0.011$). There was no associated serious side effect. This study suggests that ribavirin is able to reduce the mortality of acute Nipah encephalitis.

Journal of General Virology (2010), **91**, 765–772 DOI 10.1099/vir.0.017269-0

Combined chloroquine and ribavirin treatment does not prevent death in a hamster model of Nipah and Hendra virus infection

Alexander N. Freiberg,[1] Melissa N. Worthy,[1] Benhur Lee[2,3,4] and Michael R. Holbrook[1,5,6]†

Hendra virus (HeV) and Nipah virus (NiV) are recently emerged, closely related and highly pathogenic paramyxoviruses that cause severe disease such as encephalitis in animals and humans with fatality rates of up to 75 %. Due to their high case fatality rate following human infection and because of the lack of effective vaccines or therapy, they are classified as Biosafety Level 4 pathogens. A recent study reported that chloroquine, an anti-malarial drug, was effective in preventing NiV and HeV infection in cell culture experiments. In the present study, the antiviral efficacy of chloroquine was analysed, individually and in combination with ribavirin, in the treatment of NiV and HeV infection in *in vivo* experiments, using a golden hamster model. Although the results confirmed the strong antiviral activity of both drugs in inhibiting viral spread *in vitro*, they did not prove to be protective in the *in vivo* model. Ribavirin delayed death from viral disease in NiV-infected hamsters by approximately 5 days, but no significant effect in HeV-infected hamsters was observed. Chloroquine did not protect hamsters when administered either individually or in combination with ribavirin, the latter indicating the lack of a favourable drug–drug interaction.

Clinical Manifestations of Nipah Virus–Infected Patients Who Presented to the Emergency Department During an Outbreak in Kerala State in India, May 2018

Radhakrishnan Chandni,[1] T. P. Renjith,[1] Arshad Fazal,[1] Noufel Yoosef,[1] C. Ashhar,[1] N. K. Thulaseedharan,[1] K. P. Suraj,[1] M. K Sreejith,[1] K. G. Sajeeth Kumar,[1] V. R. Rajendran,[1] A. Remla Beevi,[2] R. L. Sarita,[3] Attayur P. Sugunan,[4] Govindakarnavar Arunkumar,[5] D. T. Mourya,[6] and Manoj Murhekar[7]

- The outbreak of NiV disease in Kozhikode in May 2018 presented as encephalitis, acute respiratory distress and myocarditis or combinations of these.

- Ribavirin therapy was tried but no evidence for its benefit could be obtained.

Therapeutic Treatment of Nipah Virus Infection in Nonhuman Primates with a Neutralizing Human Monoclonal Antibody

Thomas W. Geisbert[1,2,*,†], **Chad E. Mire**[1,2,*], **Joan B. Geisbert**[1,2], **Yee-Peng Chan**[3], **Krystle**

exposure before animals show signs of disease. We assessed the efficacy of a fully human monoclonal antibody, m102.4, at several time points after virus exposure including at the onset of clinical illness in a uniformly lethal nonhuman primate model of NiV disease. Sixteen African green monkeys (AGMs) were challenged intratracheally with a lethal dose of NiV, and 12 animals were infused twice with m102.4 (15 mg/kg) beginning at either 1, 3, or 5 days after virus challenge and again about 2 days later. The presence of viral RNA, infectious virus, and/or NiV-specific immune responses demonstrated that all subjects were infected after challenge. All 12 AGMs that received m102.4 survived infection, whereas the untreated control subjects succumbed to disease between days 8 and 10 after infection. AGMs in the day 5 treatment group exhibited clinical signs of disease, but all animals recovered by day 16. These results represent the successful therapeutic in vivo efficacy by an investigational drug against NiV in a nonhuman primate and highlight the potential impact that a monoclonal antibody can have on a highly pathogenic zoonotic human disease.

Remdesivir (GS-5734) protects African green monkeys from Nipah virus challenge

Michael K. Lo[1], Friederike Feldmann[2], Joy M. Gary[1], Robert Jordan[3,*], Roy Bannister[3],

- 8 Animals were inoculated with a lethal dose of Nipah virus, and a once-daily intravenous remdesivir treatment was initiated 24 hours later and continued for 12 days.
- Mild respiratory signs were observed in two of four treated animals, whereas all 4 control animals developed severe respiratory disease signs. In contrast to control animals, which all succumbed to the infection, all remsdesivir-treated animals survived the lethal challenge, indicating that remdesivir represents a promising antiviral treatment for Nipah virus infection.
- Remdesivir—was studied against NiV-B: where as Favipiravir tried against NiV-M

Favipiravir (T-705) protects against Nipah virus infection in the hamster model

Brian E. Dawes[1], Birte Kalveram[1], Tetsuro Ikegami[1,2,3], Terry Juelich[1], Jennifer K. Smith[1], Lihong Zhang[1], Arnold Park[4], Benhur Lee[4], Takashi Komeno[5], Yousuke Furuta[5] & Alexander N. Freiberg[1,2,3]

Nipah and Hendra viruses are recently emerged bat-borne paramyxoviruses (genus *Henipavirus*) causing severe encephalitis and respiratory disease in humans with fatality rates ranging from 40–75%. Despite the severe pathogenicity of these viruses and their pandemic potential, no therapeutics or vaccines are currently approved for use in humans. Favipiravir (T-705) is a purine analogue antiviral approved for use in Japan against emerging influenza strains; and several phase 2 and 3 clinical trials are ongoing in the United States and Europe. Favipiravir has demonstrated efficacy against a broad spectrum of RNA viruses, including members of the *Paramyxoviridae*, *Filoviridae*, *Arenaviridae families*, and the *Bunyavirales* order. We now demonstrate that favipiravir has potent antiviral activity against henipaviruses. *In vitro*, favipiravir inhibited Nipah and Hendra virus replication and transcription at micromolar concentrations. In the Syrian hamster model, either twice daily oral or once daily subcutaneous administration of favipiravir for 14 days fully protected animals challenged with a lethal dose of Nipah virus. This first successful treatment of henipavirus infection *in vivo* with a small molecule drug suggests that favipiravir should be further evaluated as an antiviral treatment option for henipavirus infections.

Contents lists available at ScienceDirect

Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral

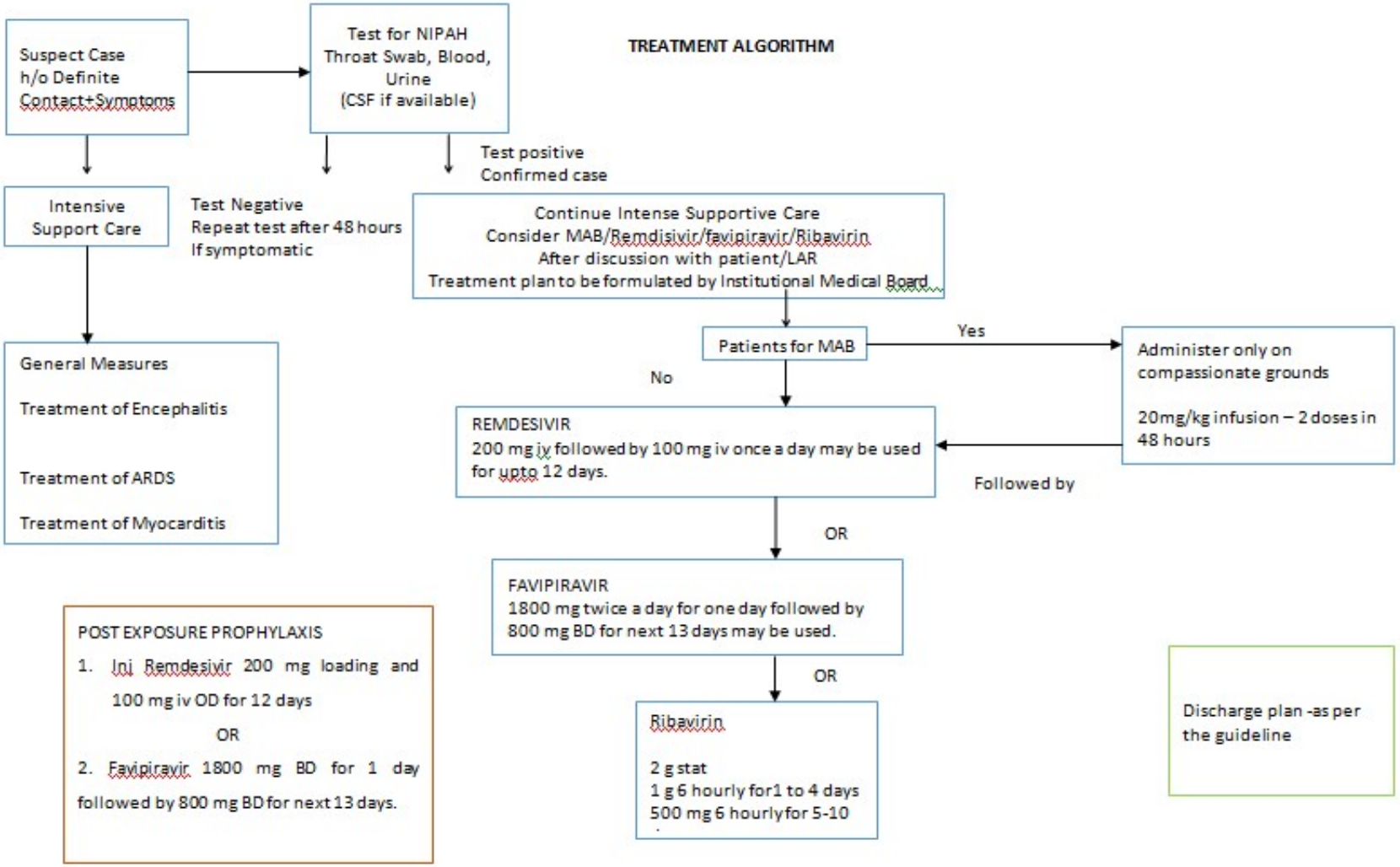
Review

A treatment for and vaccine against the deadly Hendra and Nipah viruses

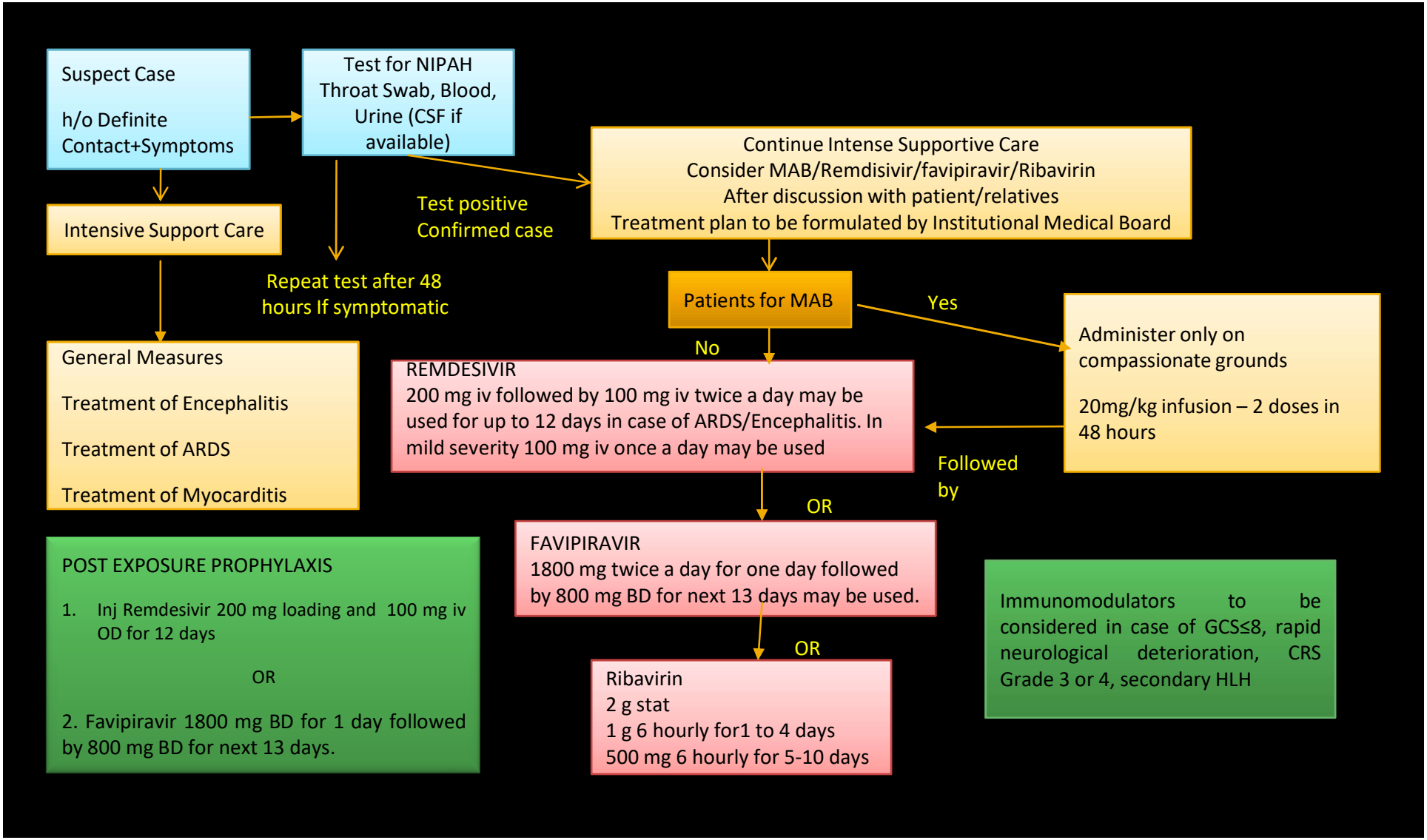
Christopher C. Broder [a,*], Kai Xu [b], Dimitar B. Nikolov [b], Zhongyu Zhu [c], Dimiter S. Dimitrov [c], Deborah Middleton [d], Jackie Pallister [d], Thomas W. Geisbert [e,f], Katharine N. Bossart [g,h], Lin-Fa Wang [d]

transboundary biological threats. Recent experimental findings in animals have demonstrated that a human monoclonal antibody targeting the viral G glycoprotein is an effective post-exposure treatment against Hendra and Nipah virus infection. In addition, a subunit vaccine based on the G glycoprotein of Hendra virus affords protection against Hendra and Nipah virus challenge. The vaccine has been developed for use in horses in Australia and is the first vaccine against a Biosafety Level-4 (BSL-4) agent to be licensed and commercially deployed. Together, these advances offer viable approaches to address Hendra and Nipah virus infection of livestock and people.

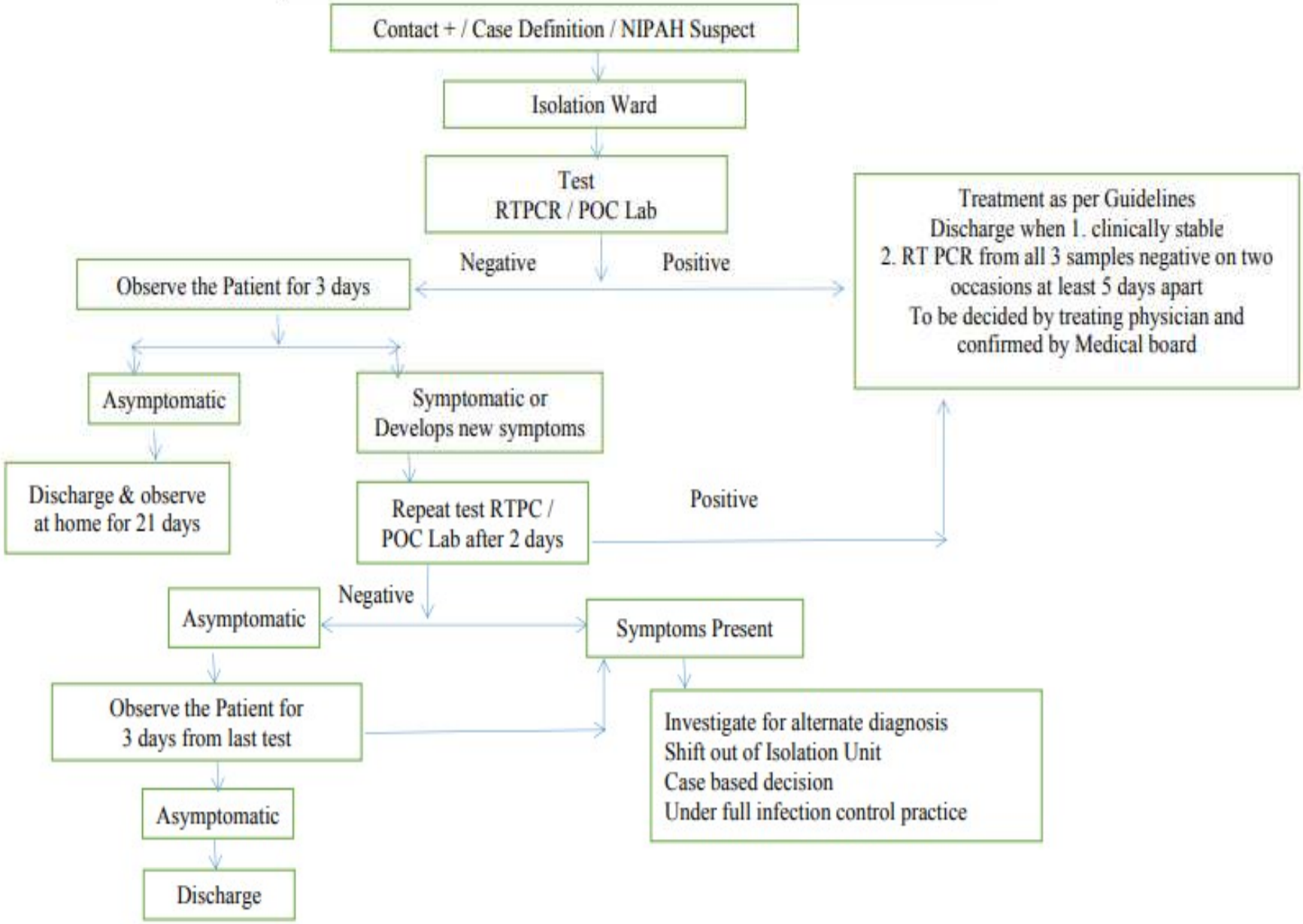
Treatment-Algorithm 2021



Treatment Algorithm-2023



ANNEXURE 4 - GUIDELINES FOR DISCHARGE OF PATIENTS



NB: Any amendment to this Guidelines be done only with the concurrence of Medical Board

3.4 Criteria for discharge and follow up

Criteria for discharge of a patient from isolation facility presented with suspected Nipah and tested negative

1. Tested negative and totally symptom free can be discharged with observation at home for total of 21 days.
2. Tested negative and continue to have fever and other symptoms need a repeat testing after two days to exclude NiV infection and there exist a strong history of contact with NiV infected patient/sample must have repeat testing in every two days till patient becomes symptom free.
3. No need of repeat testing if tested negative on two occasions found negative and an alternate diagnosis is made.

Criteria for discharge of confirmed case

- Clinically stable
- Nipah RT-PCR from all three samples (Throat swab, Urine and blood)reported negative on two occasions at least 5 days apart.
- To be decided by the treating clinician and confirmed by the Medical board

Sample collection

- **Sample collection:**
  - as early as possible (preferably within 4 days)
  - with all biosafety precautions
  - and accompanied with detailed history of patients on the performa which can be obtained from the testing laboratory

- During sample collection
  - wear complete disposable Personal Protective Equipments (N 95 mask, double surgical gloves, gowns, goggles etc).
  - Wash hands with soap and water atleast for 30 seconds and then clean hand using 1-2 ml alcohol based hand sanitizer before and after collection of samples

- The samples may be as follows
  - Throat swab in viral transport medium
  - Urine 10 ml in universal sterile container
  - Blood in plain vial (atleast 5ml)
  - CSF (atleast 1 ml) in sterile container

Sample collection

- ***Sample collection should be done only AFTER ADMISSION in an appropriately secure isolation facility, and ensuring that the staff member doing the collection is using adequate PPE***
- During sample collection wear complete disposable Personal Protective Equipments (N 95 mask, double surgical gloves, gowns, goggles foot cover, etc). Wash hands with soap and water at least for 30 seconds and then clean hand using 1-2 ml alcohol based hand sanitizer before and after collection of samples.

IPC ADVISORY

- Wash hands thoroughly with soap and water for 20 seconds after contact with a sick patient
- Use appropriate mask and gloves during history- taking, physical examination, sample collection and other care-giving to suspected Nipah cases
- Follow Standard precautions for infection control at hospital settings:

IPC ADVISORY

- Hand Hygiene
- Use of PPE
- Use disposable items (NG tube, ET tube, oxygen mask) while handling the patient
- Safe waste disposal for potentially infected material including used PPE, linen, clothing of patient

IPC ADVISORY

- Admit all suspect cases to the designated isolation ward/ facility in the hospital. Once the case is suspected of NIPAH, attendants should not be permitted in the ward.
- Segregate all suspect cases of Nipah from all patients in the isolation ward/ facility
- Avoid unnecessary contact with suspected Nipah cases or use barrier nursing
- Any spillage of body fluids in the OP/Ward should be managed as per Infection control guidelines.
- Immediately report admission of a suspected Nipah case to State Surveillance Officer and CSU (IDSP)

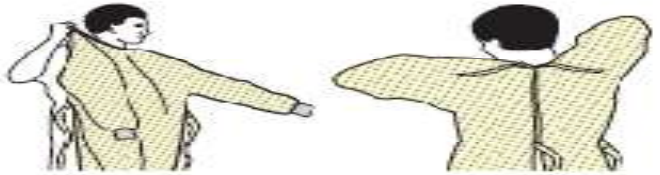
DONNING STEPS

SEQUENCE FOR PUTTING ON PERSONAL PROTECTIVE EQUIPMENT (PPE)

The type of PPE used will vary based on the level of precautions required, such as standard and contact, droplet or airborne infection isolation precautions. The procedure for putting on and removing PPE should be tailored to the specific type of PPE.

1. GOWN

- Fully cover torso from neck to knees, arms to end of wrists, and wrap around the back
- Fasten in back of neck and waist



2. MASK OR RESPIRATOR

- Secure ties or elastic bands at middle of head and neck
- Fit flexible band to nose bridge
- Fit snug to face and below chin
- Fit-check respirator

3. GOGGLES OR FACE SHIELD

- Place over face and eyes and adjust to fit

4. GLOVES

- Extend to cover wrist of isolation gown

USE SAFE WORK PRACTICES TO PROTECT YOURSELF AND LIMIT THE SPREAD OF CONTAMINATION

- Keep hands away from face
- Limit surfaces touched
- Change gloves when torn or heavily contaminated
- Perform hand hygiene

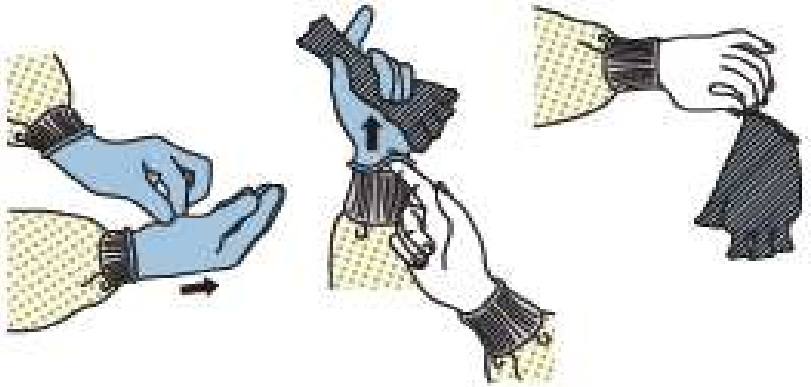
DOFFING PROCEDURE

HOW TO SAFELY REMOVE PERSONAL PROTECTIVE EQUIPMENT (PPE) EXAMPLE 1

There are a variety of ways to safely remove PPE without contaminating your clothing, skin, or mucous membranes with potentially infectious materials. Here is one example. **Remove all PPE before exiting the patient room** except a respirator, if worn. Remove the respirator **after** leaving the patient room and closing the door. Remove PPE in the following sequence:

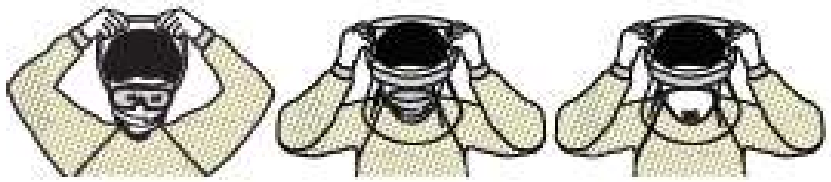
1. GLOVES

- Outside of gloves are contaminated!
- If your hands get contaminated during glove removal, immediately wash your hands or use an alcohol-based hand sanitizer
- Using a gloved hand, grasp the palm area of the other gloved hand and peel off first glove
- Hold removed glove in gloved hand
- Slide fingers of ungloved hand under remaining glove at wrist and peel off second glove over first glove
- Discard gloves in a waste container



2. GOGGLES OR FACE SHIELD

- Outside of goggles or face shield are contaminated!
- If your hands get contaminated during goggle or face shield removal, immediately wash your hands or use an alcohol-based hand sanitizer
- Remove goggles or face shield from the back by lifting head band or ear pieces
- If the item is reusable, place in designated receptacle for reprocessing. Otherwise, discard in a waste container



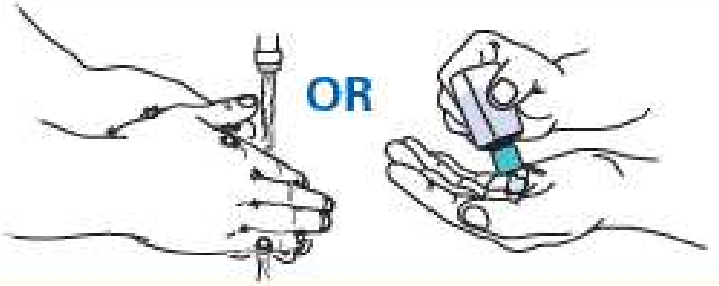
3. GOWN

- Gown front and sleeves are contaminated!
- If your hands get contaminated during gown removal, immediately wash your hands or use an alcohol-based hand sanitizer
- Unfasten gown ties, taking care that sleeves don't contact your body when reaching for ties
- Pull gown away from neck and shoulders, touching inside of gown only
- Turn gown inside out
- Fold or roll into a bundle and discard in a waste container

4. MASK OR RESPIRATOR

- Front of mask/respirator is contaminated — DO NOT TOUCH!
- If your hands get contaminated during mask/respirator removal, immediately wash your hands or use an alcohol-based hand sanitizer
- Grasp bottom ties or elastics of the mask/respirator, then the ones at the top, and remove without touching the front
- Discard in a waste container

5. WASH HANDS OR USE AN ALCOHOL-BASED HAND SANITIZER IMMEDIATELY AFTER REMOVING ALL PPE



PERFORM HAND HYGIENE BETWEEN STEPS IF HANDS BECOME CONTAMINATED AND IMMEDIATELY AFTER REMOVING ALL PPE

CDC

Doffing (Removal) = Critical Process

Most Provider exposures occur during PPE Removal (doffing)!

"Buddy System"

- **A trained observer shall monitor the doffing procedure**
  - Can be used during donning, as well
- "Buddy" (in PPE) watches to prevent compromises or other procedural breaches
- Any compromise/breach must be reported to your ICN immediately