Soochow University

The therapeutic value of favipiravir on influenza and other virus

法匹拉韦治疗流感病毒和其他病毒中的价值

The First Affiliated Hospital of Soochow University

苏州大学附属第一医院

GUO Qiang

郭 强

New influenza antivirals（favipiravir） in the treatment of severe influenza patients?

Confused

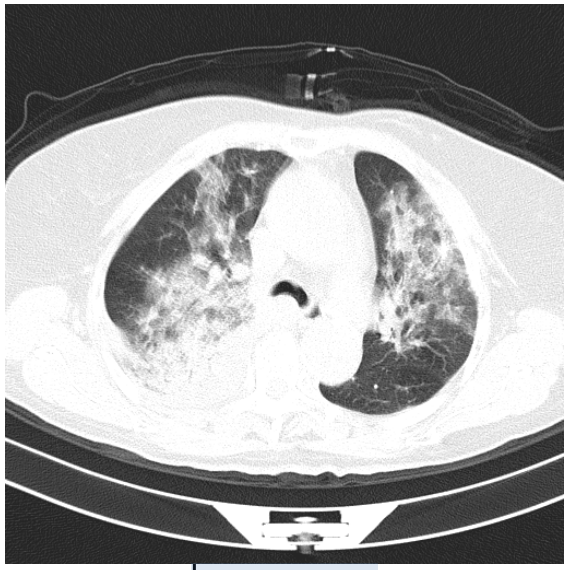
→ Question

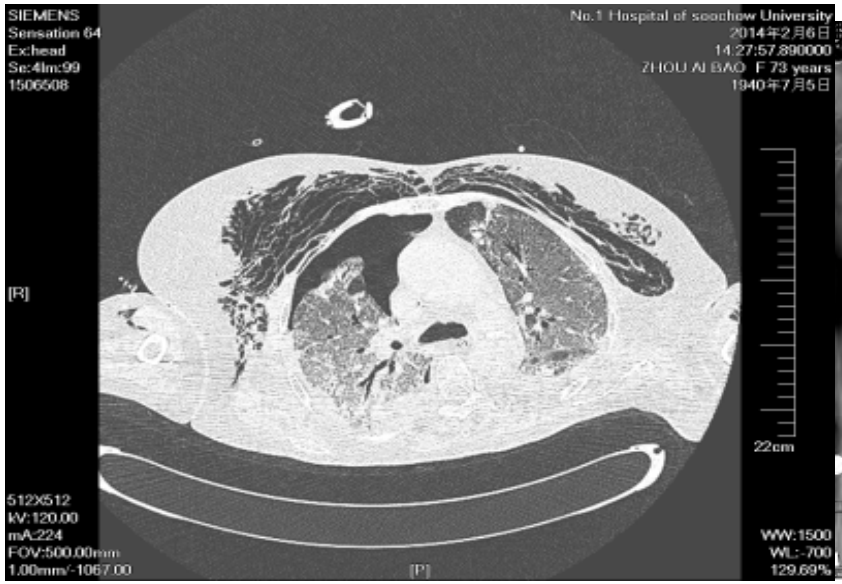
→ Accept

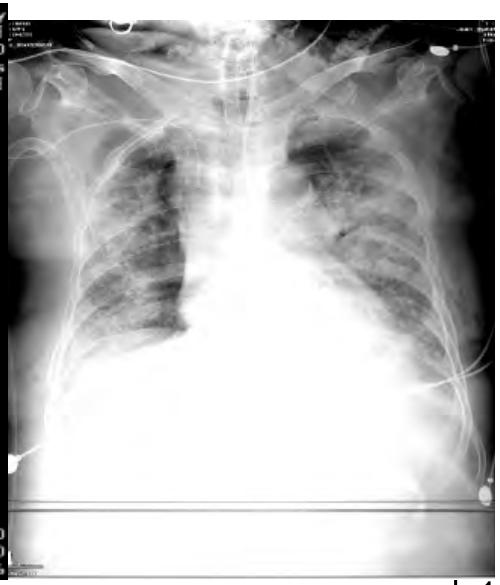
Confused Cases

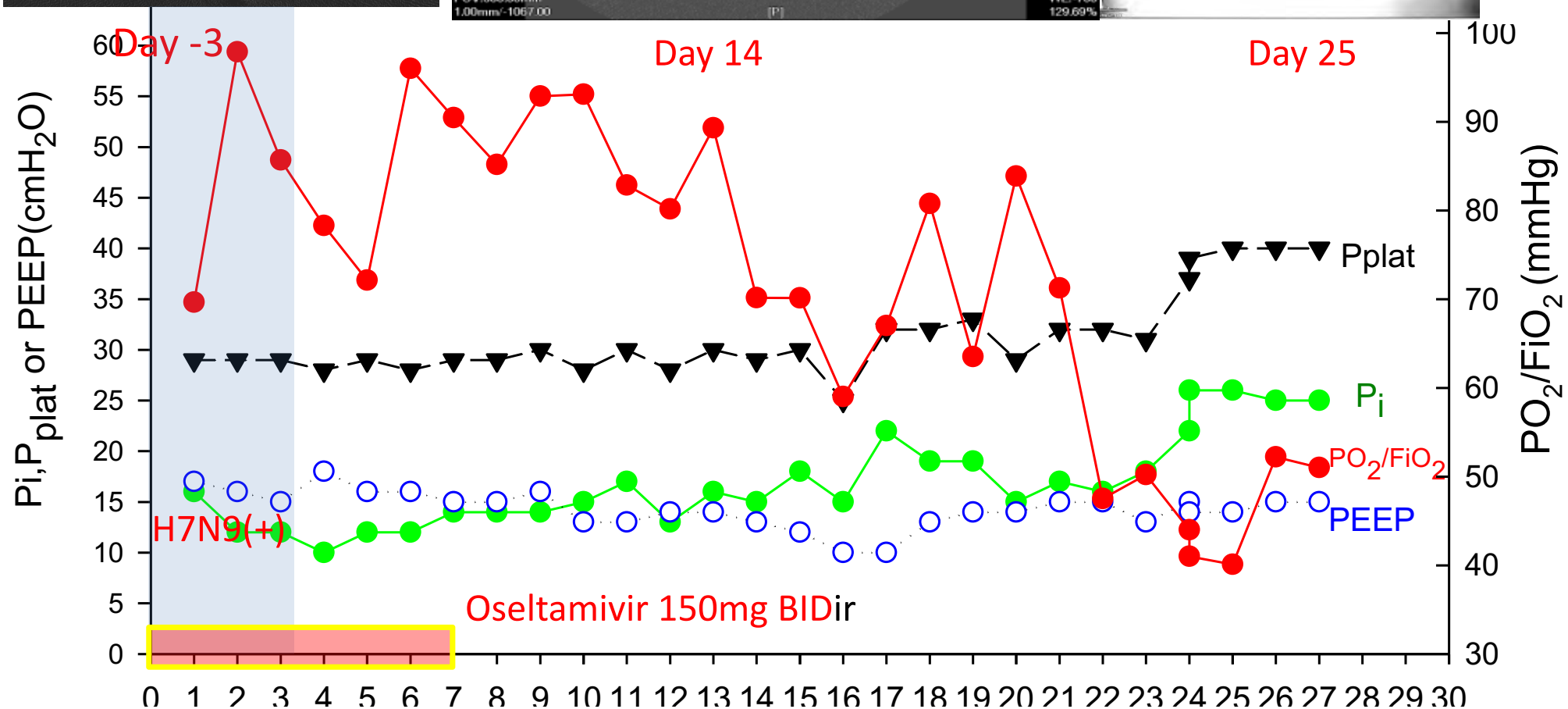
Case 1

Male，73 years old，H7N9（+）
ARDS
FiO_2 100% PO_2 52mmHg



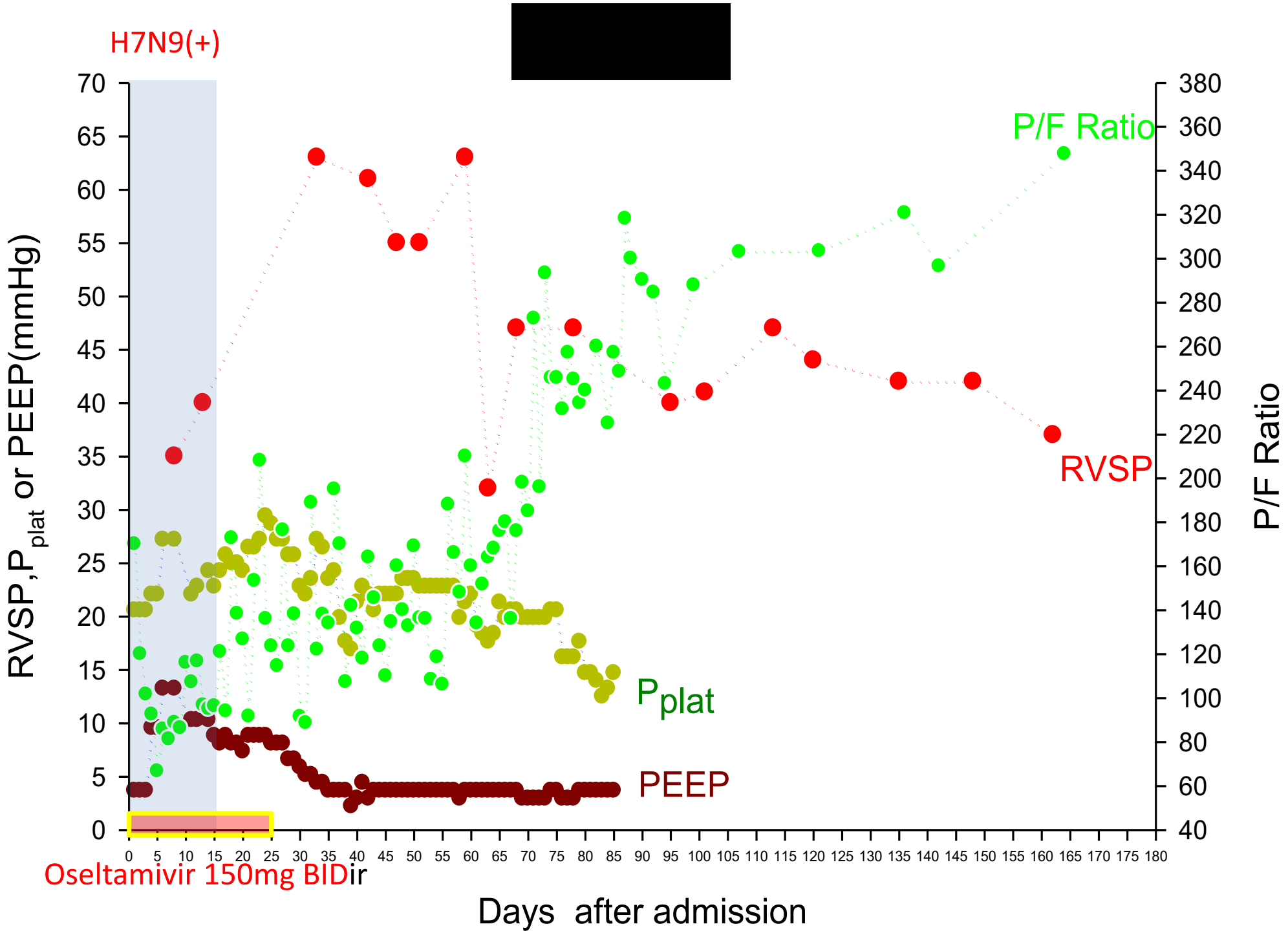

SIEMENS
Sensation 64
No.1 Hospital of soochow University
ZHOU AI BAO F 73 years
[R]
22cm
512X512
kV:120.00
mA:224
WW:1500
WL:-700
129.69%
[P]

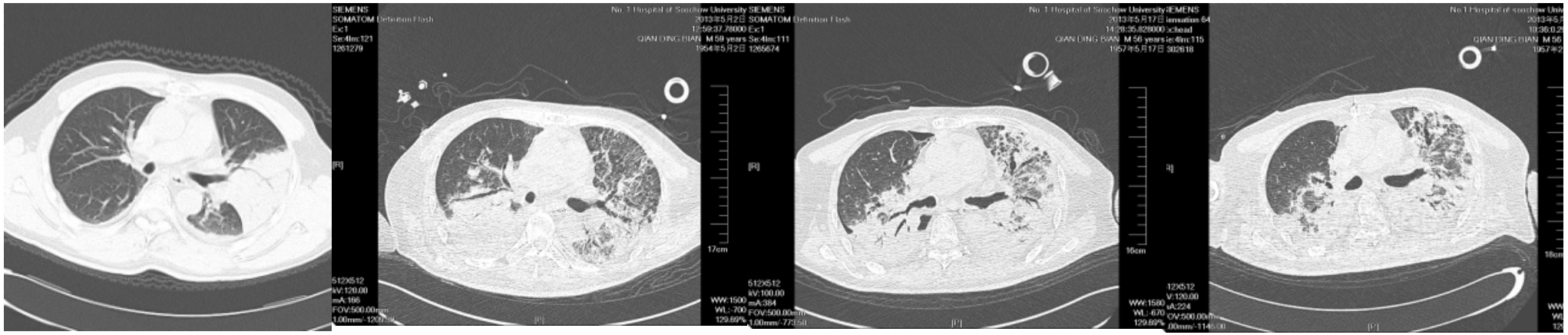



Day -3
Day 14
Day 25
Pplat
Pi
PO2/FiO2
PEEP
H7N9(+)
Oseltamivir 150mg BIDir
Pi,Pplat or PEEP(cmH2O)
PO2/FiO2 (mmHg)
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
0 5 10 15 20 25 30 35 40 45 50 55 60
30 40 50 60 70 80 90 100

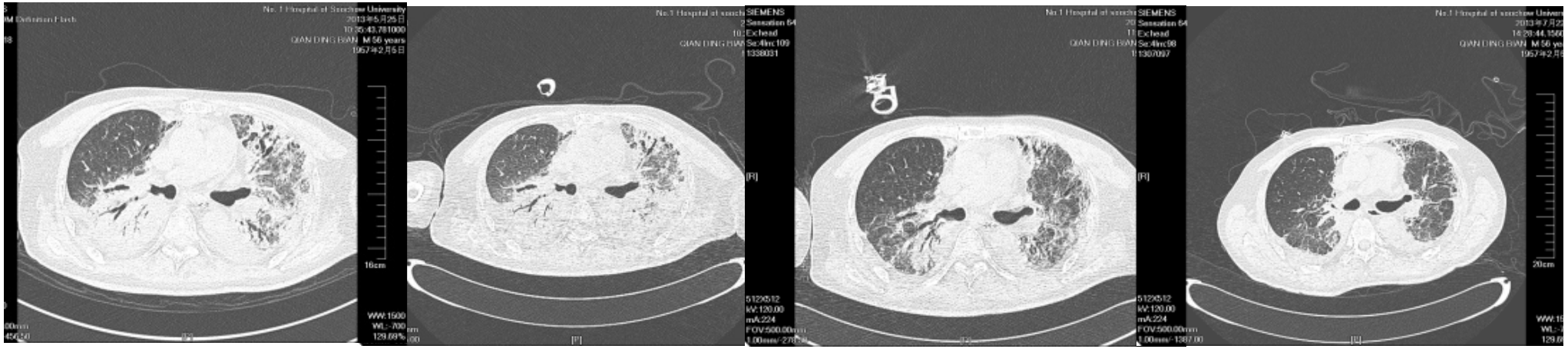
Case 2

Male，57 years old，H7N9（+）
ARDS
FiO_2 100% PO_2 55mmHg

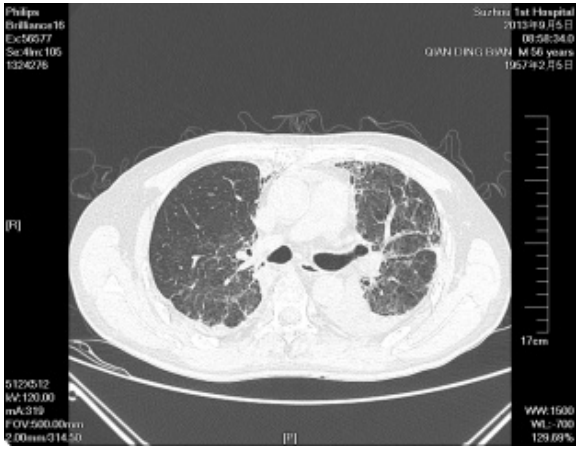

H7N9(+)
[redacted]
RVSP,P$_{plat}$ or PEEP(mmHg)
P/F Ratio
RVSP
P$_{plat}$
PEEP
Oseltamivir 150mg BIDir
Days after admission



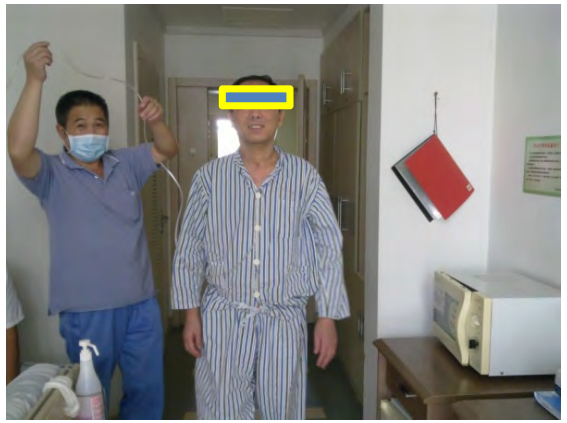
Day -3 Day 25 Day 40 Day 42



Day 48 Day 55 Day 75 Day 106



Day 151



Guo Qiang et al Critical Care2014,18:588-589

Oseltamivir

- Effective influenza antivirals?

Severe influenza treatments

Confused

Organ function support --New compounds

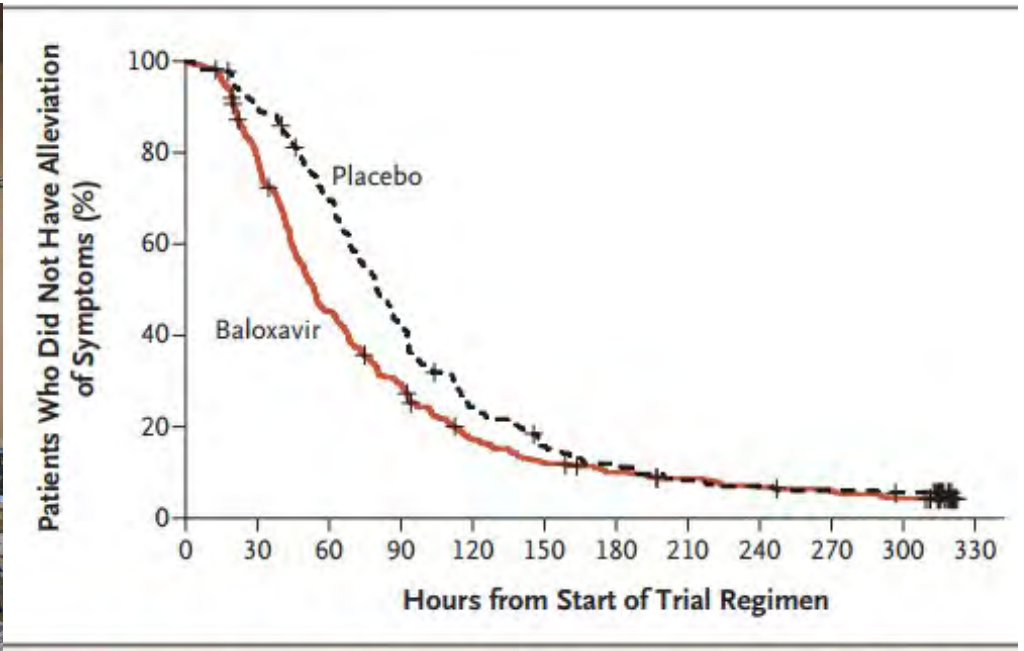
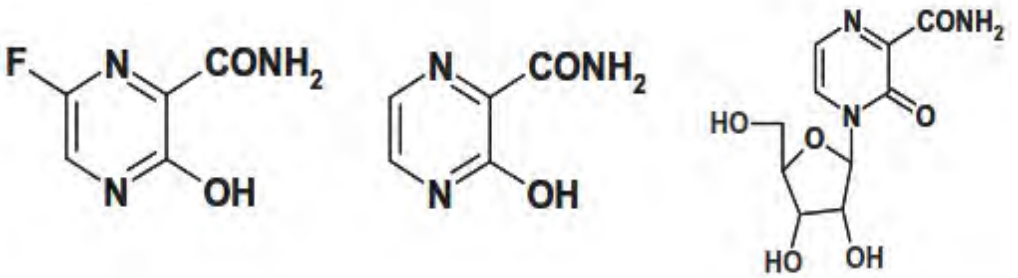


Figure 2. Kaplan–Meier Curves of the Time to Alleviation of Influenza Symptoms with Baloxavir versus Placebo in the Phase 3 Trial.

N Engl J Med 2018;379:913-23.

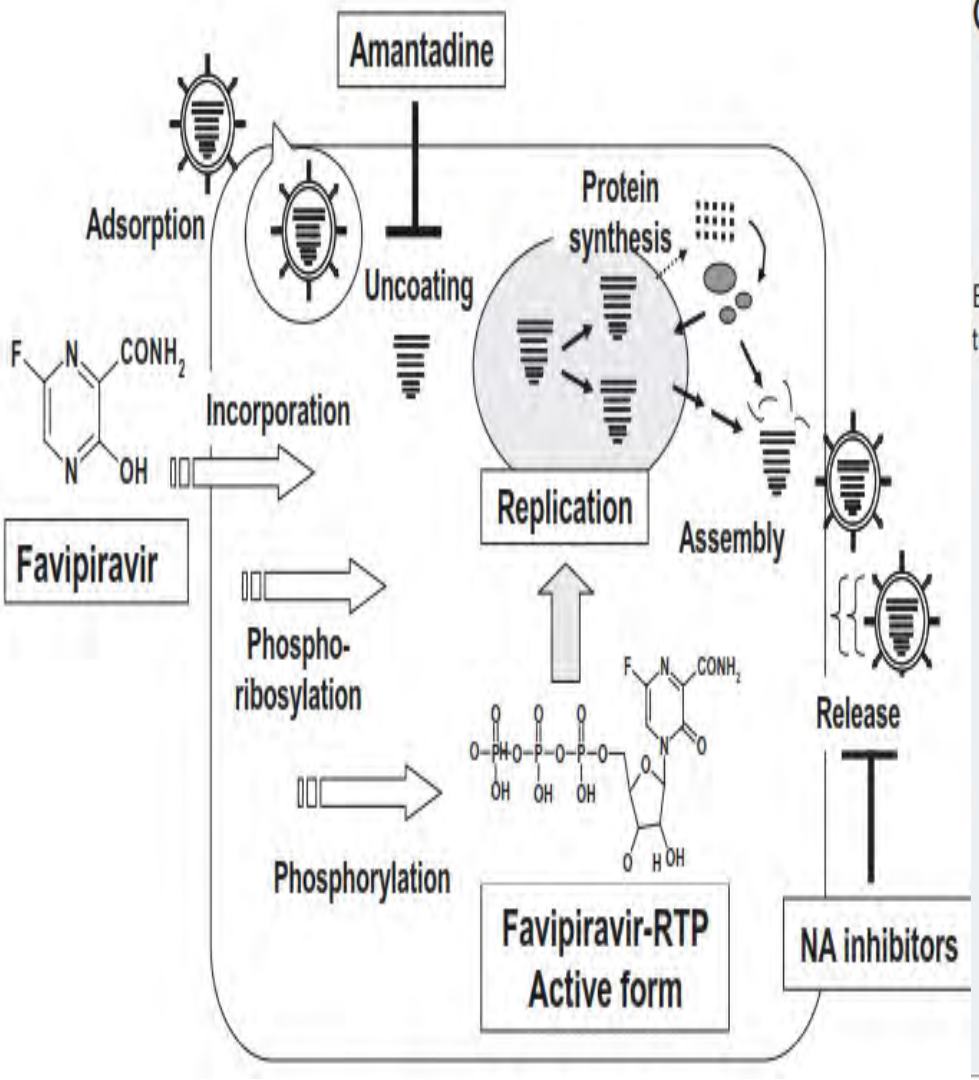


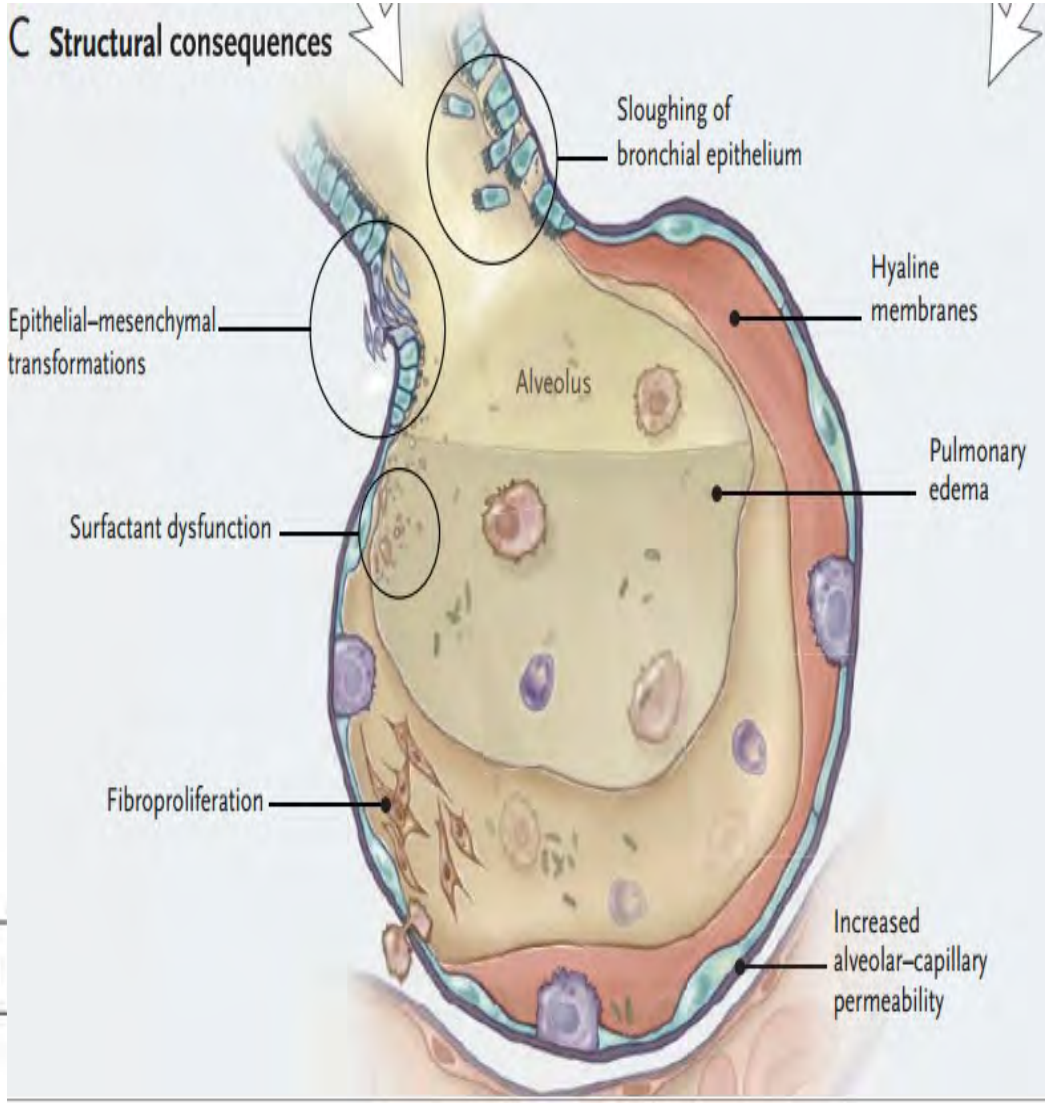
Favipiravir (T-705) T-1105 T-1106

Severe influenza treatments

Confused

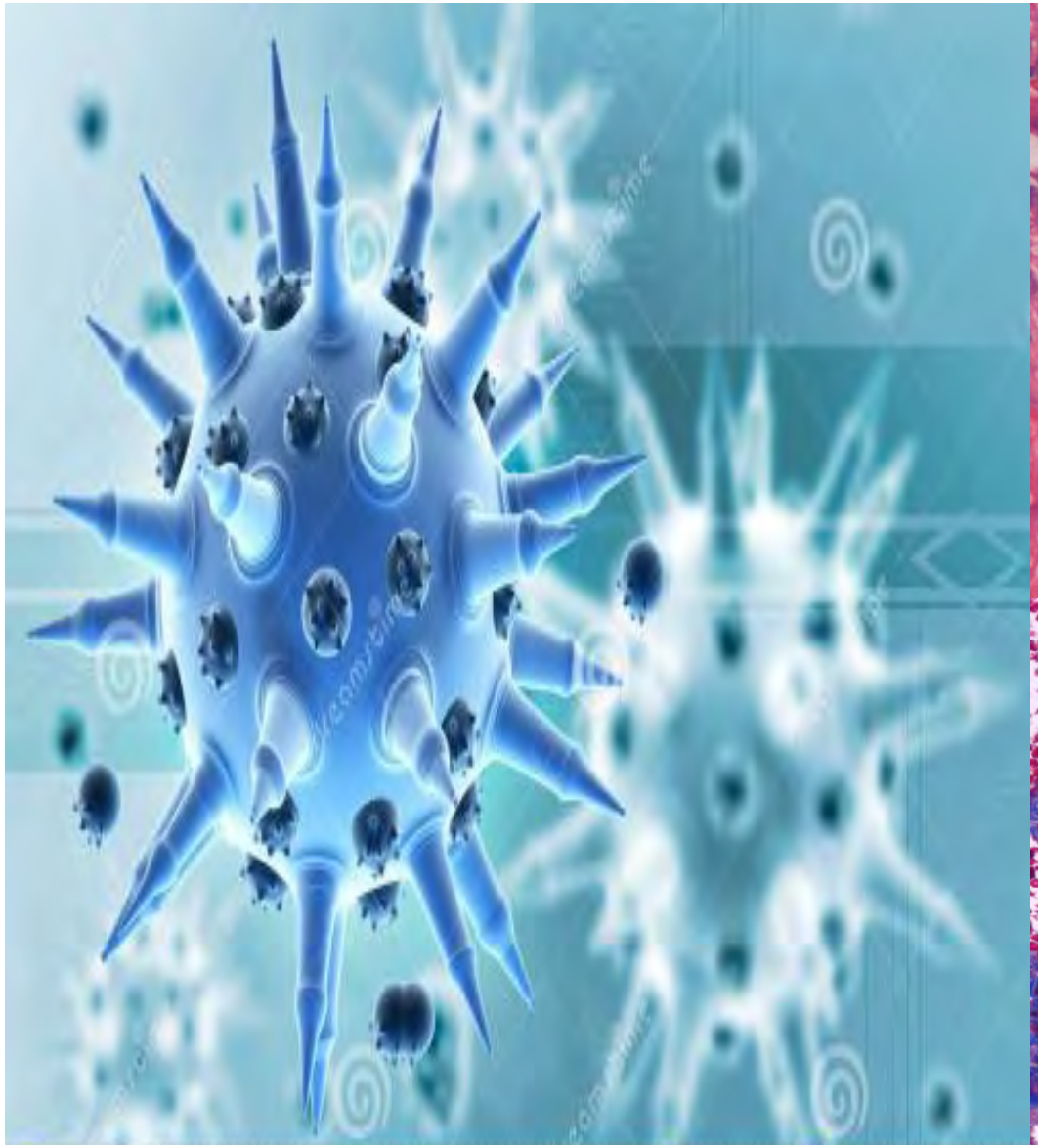
Influenza viruses mechanism-- ALI/AKI/AGI mechanism

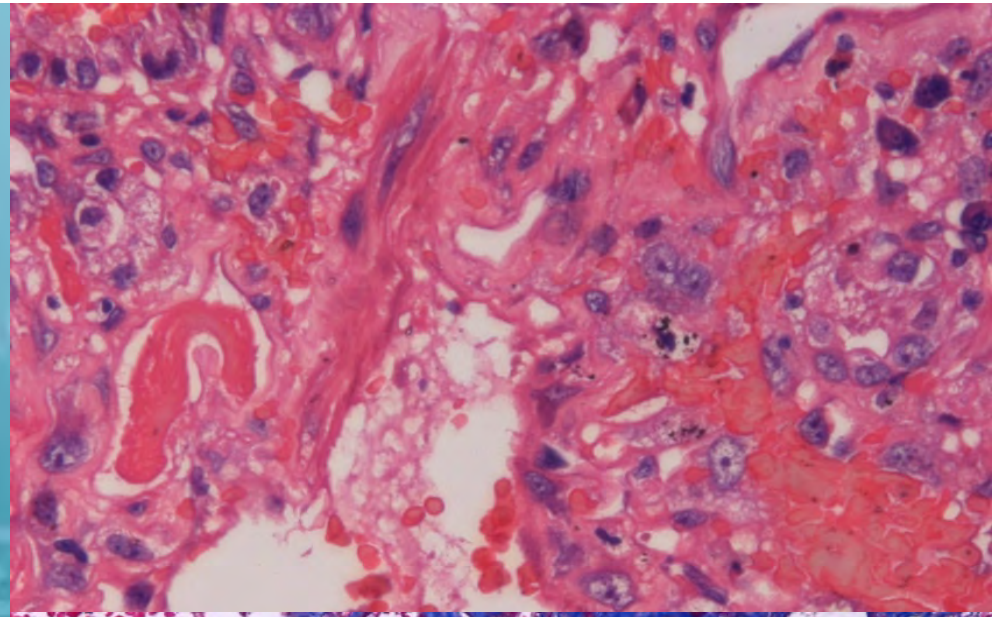


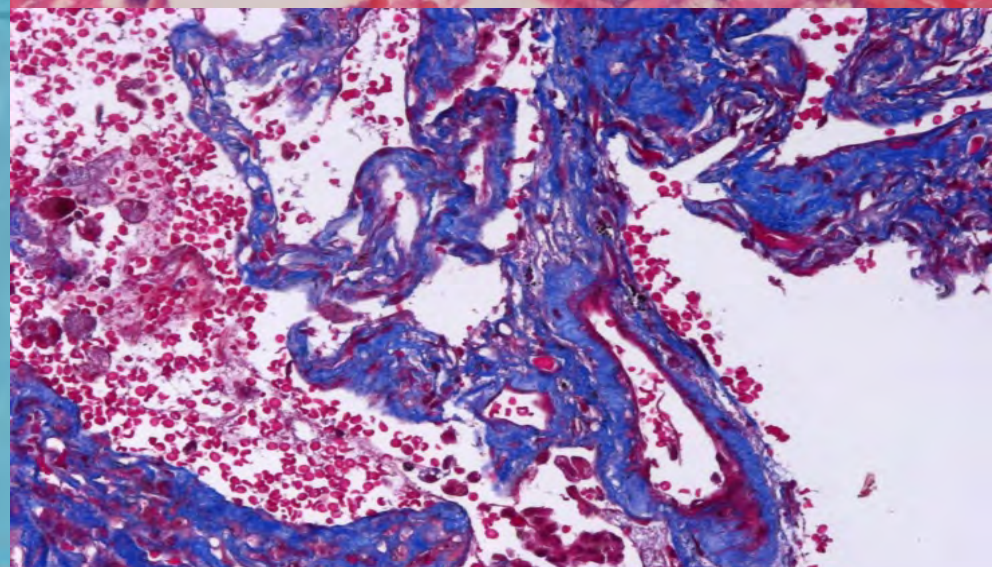


Severe influenza treatments

Confused-- Viruses replication / Histopathology

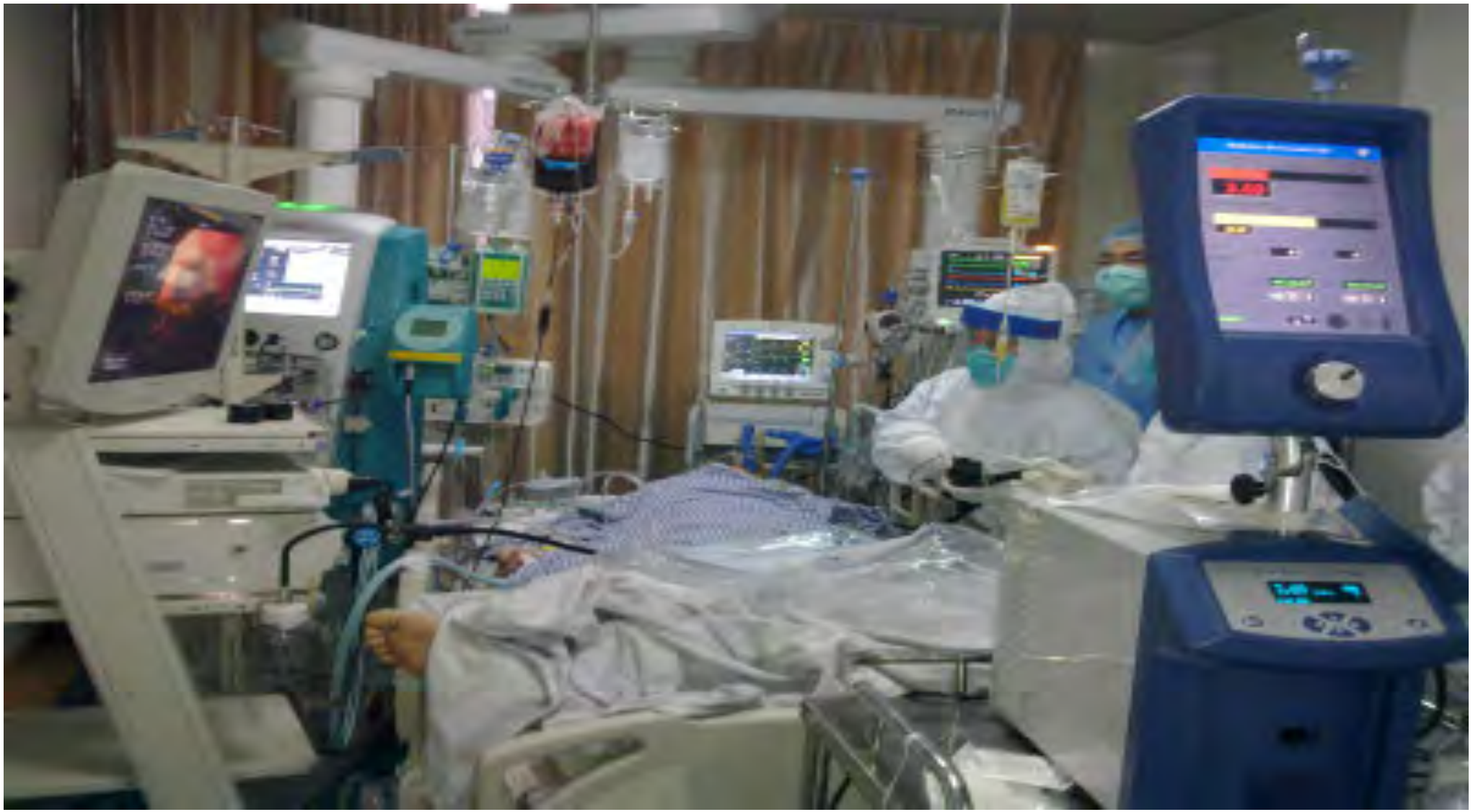






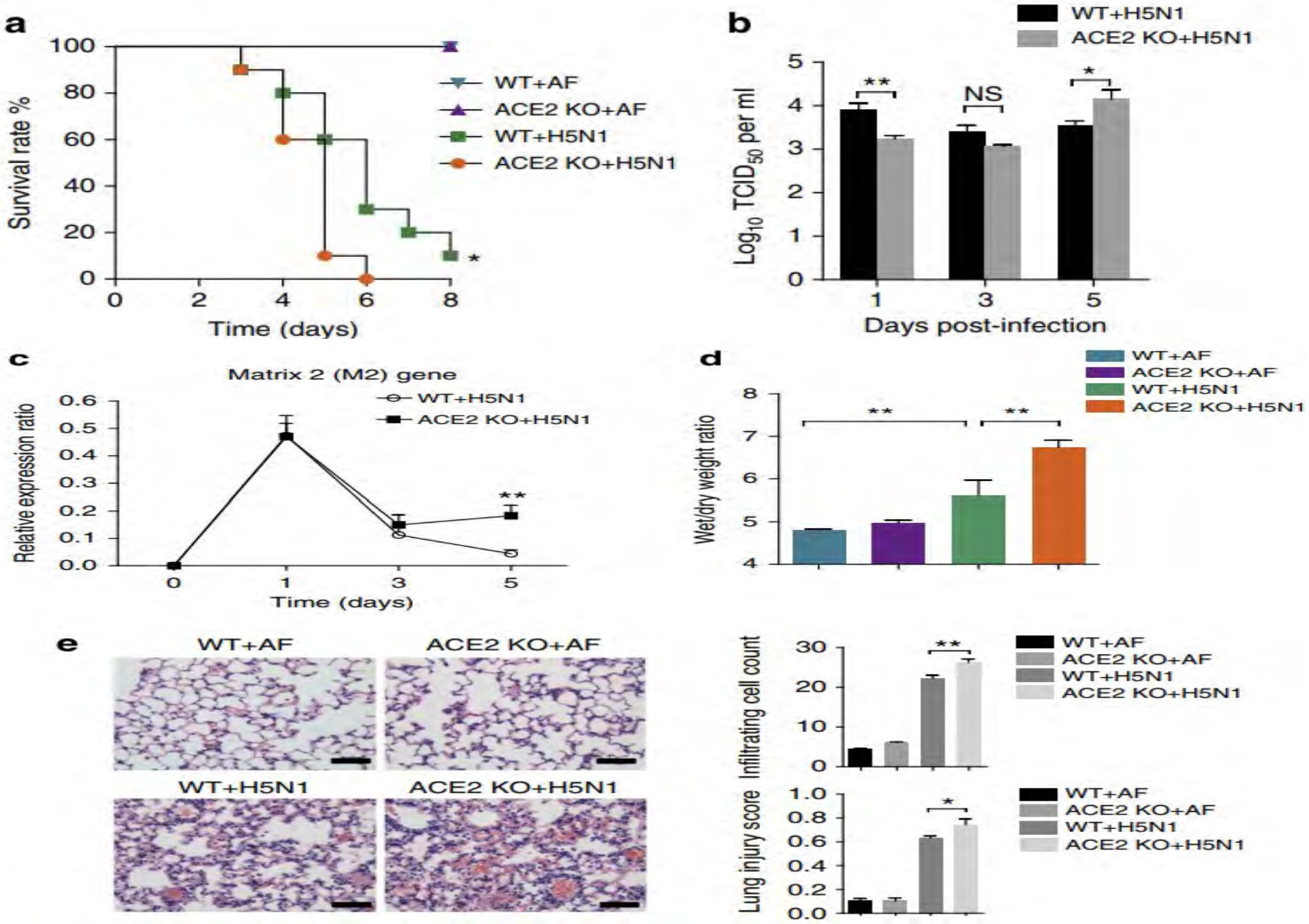
ECMO

Extracorporeal membrane oxygenation as rescue therapy for H7N9 influenza-associated acute respiratory distress syndrome



ACE2 deficiency increases the severity of H5N1-induced acute lung injury.

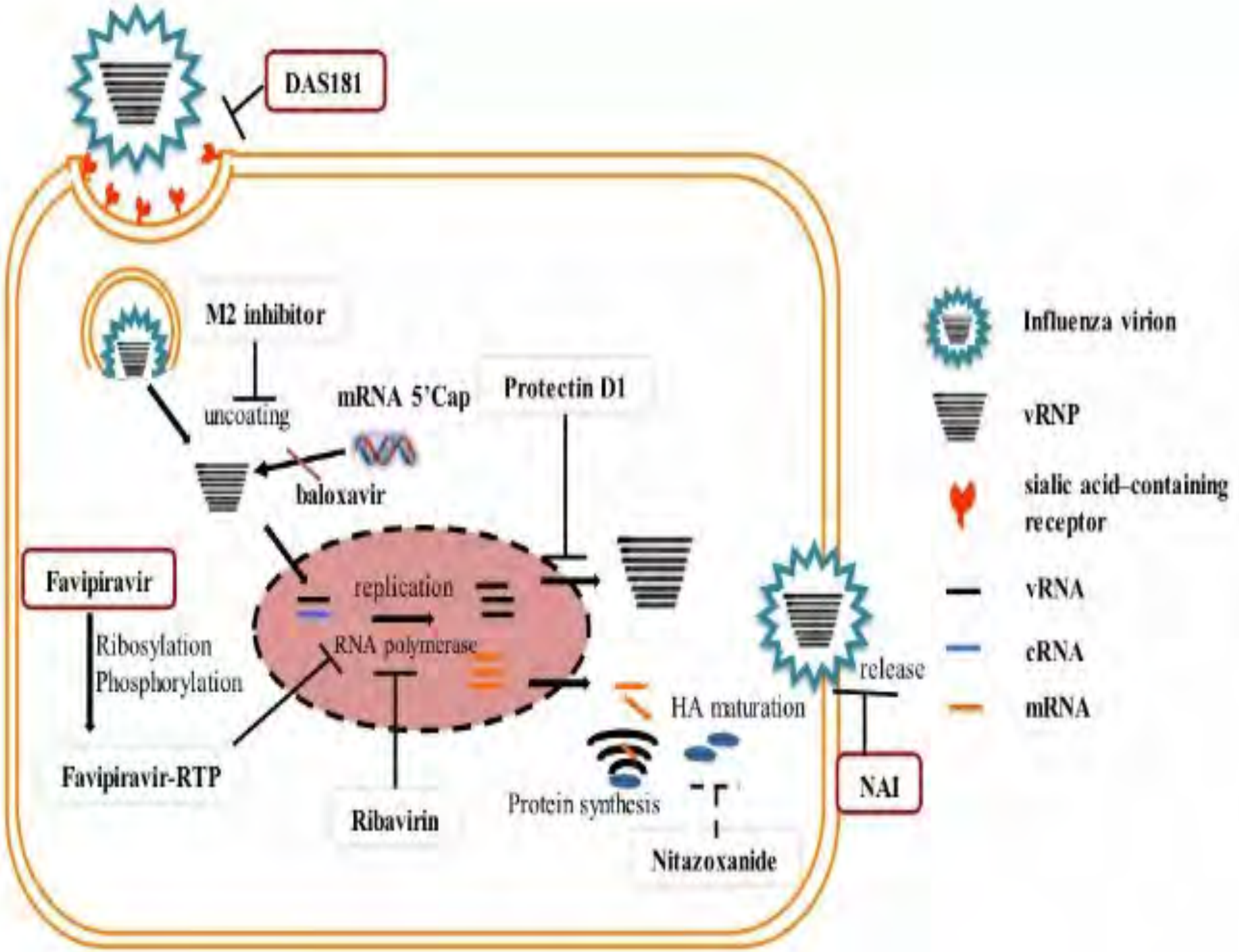
Nat Commun.
2014 May 6;5:3594.



New influenza antivirals

- Antiviral activity
- Host protection

Questions?


DAS181
M2 inhibitor
uncoating
mRNA 5'Cap
baloxavir
Protectin D1
Favipiravir
Ribosylation
Phosphorylation
Favipiravir-RTP
replication
RNA polymerase
Ribavirin
HA maturation
Protein synthesis
Nitazoxanide
release
NAI
Influenza virion
vRNP
sialic acid–containing receptor
vRNA
cRNA
mRNA

Favipiravir

- Broad antiviral activity against RNA viruses

Hemorrhagic fever viruses, such as Lassa,
Marburg, and Crimean–Congo hemorrhagic fever viruses(mice models)

PLoS Negl Trop Dis. 2014; 8:e2804.

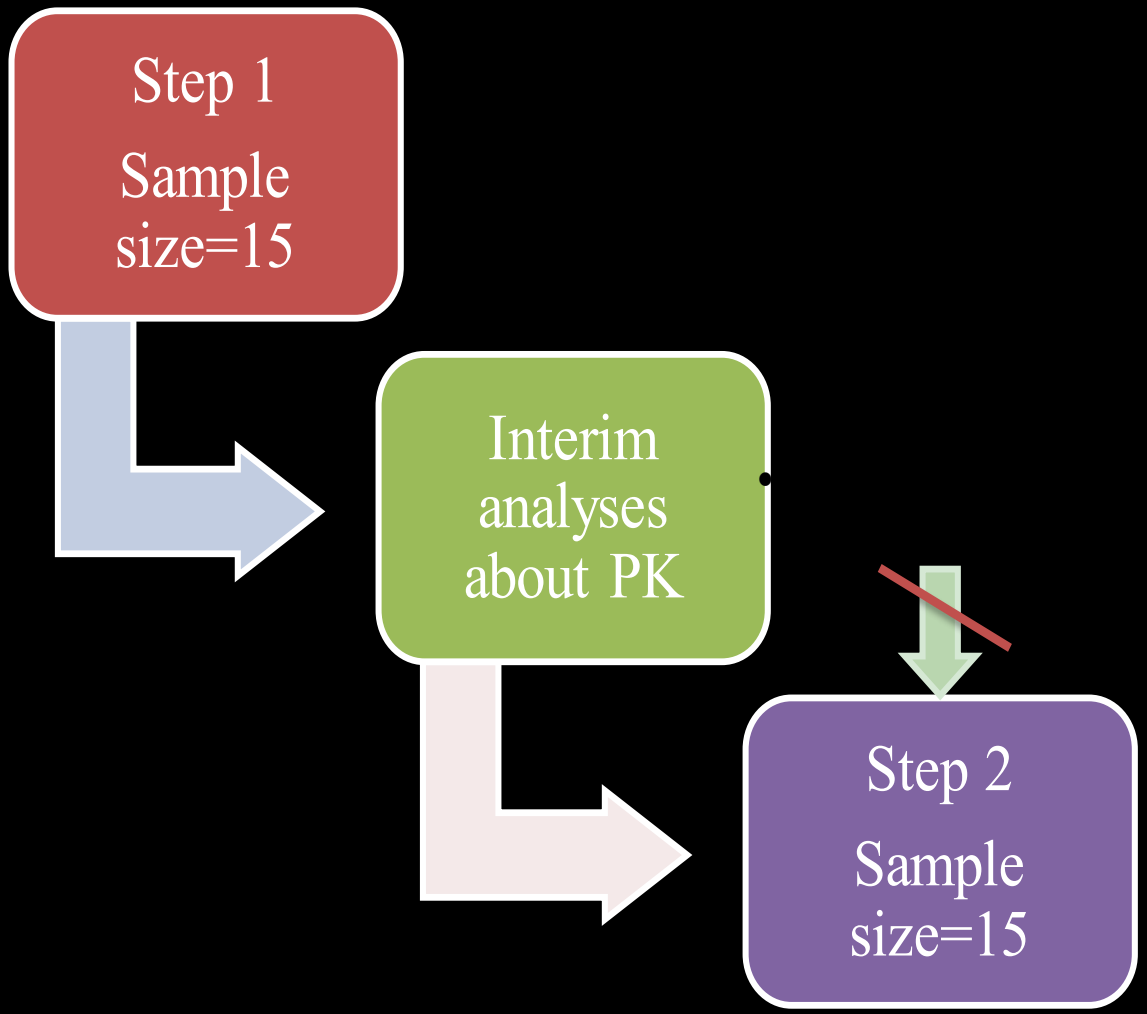
J Infect Dis.2016; 213:934–8.

A pilot study of the pharmacokinetics of favipiravir in favipiravir/oseltamivir combination therapy for severe influenza

Bin Cao

China-Japan Friendship Hospital

Design


Step 1
Sample size=15
Interim analyses about PK
Step 2
Sample size=15

Case 1 62 year 张*

ICU DAYS 29天(2018-3-19~2018-4-17)

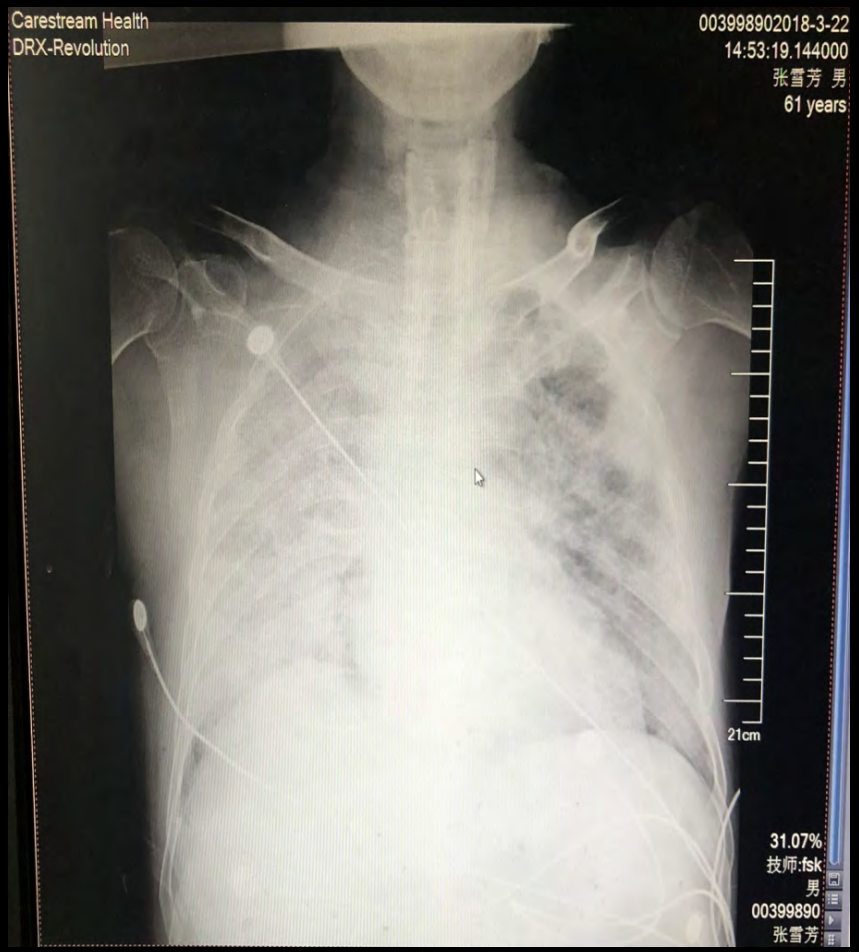
SYMPTOM RELIEVED DAY 9 (2018-3-28)

MV 5 DAYS(2018-3-22 ~2018-3-27)

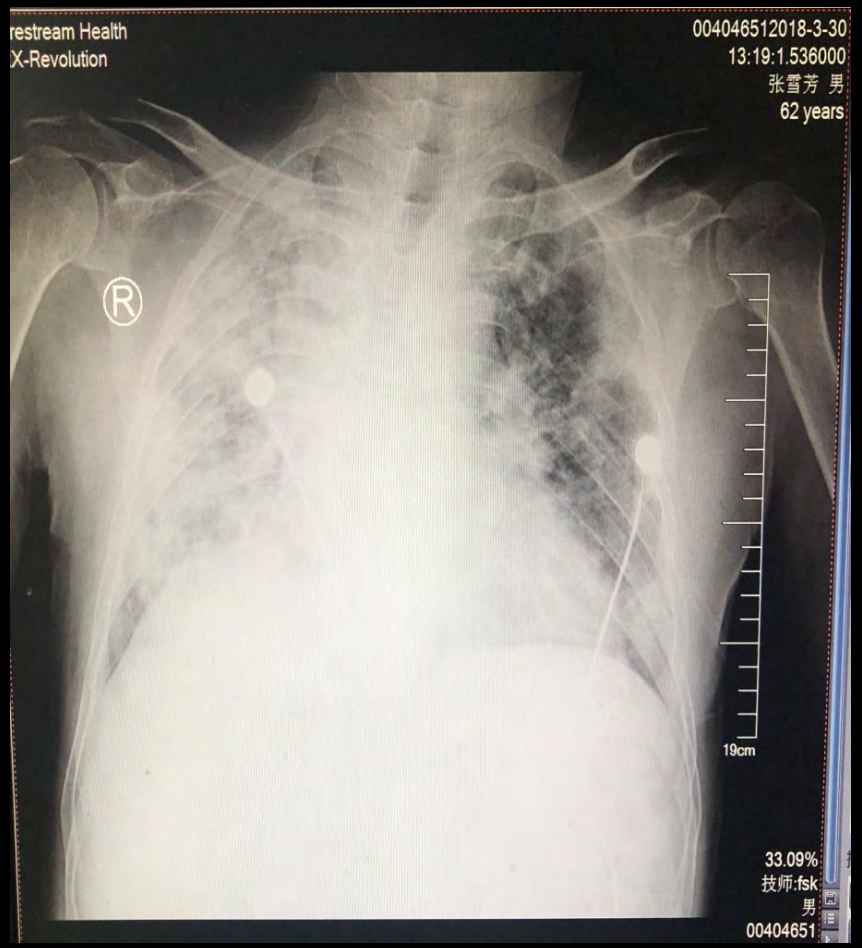
Flu A (+) DAY 2 (2018-3-21)

(-) DAY 8 (2018-3-27)

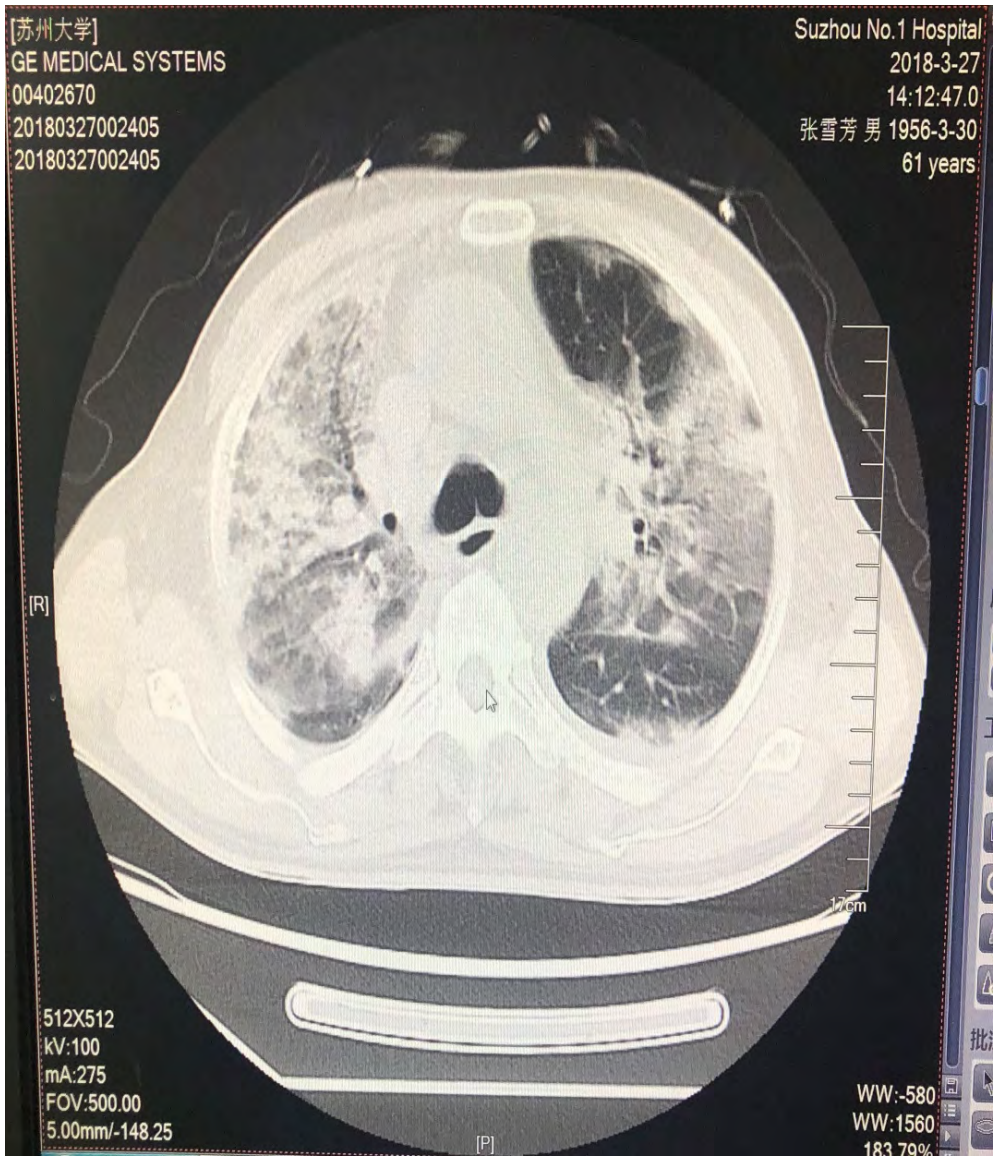
Favipiravir/oseltamivir combination therapy DAY1-10

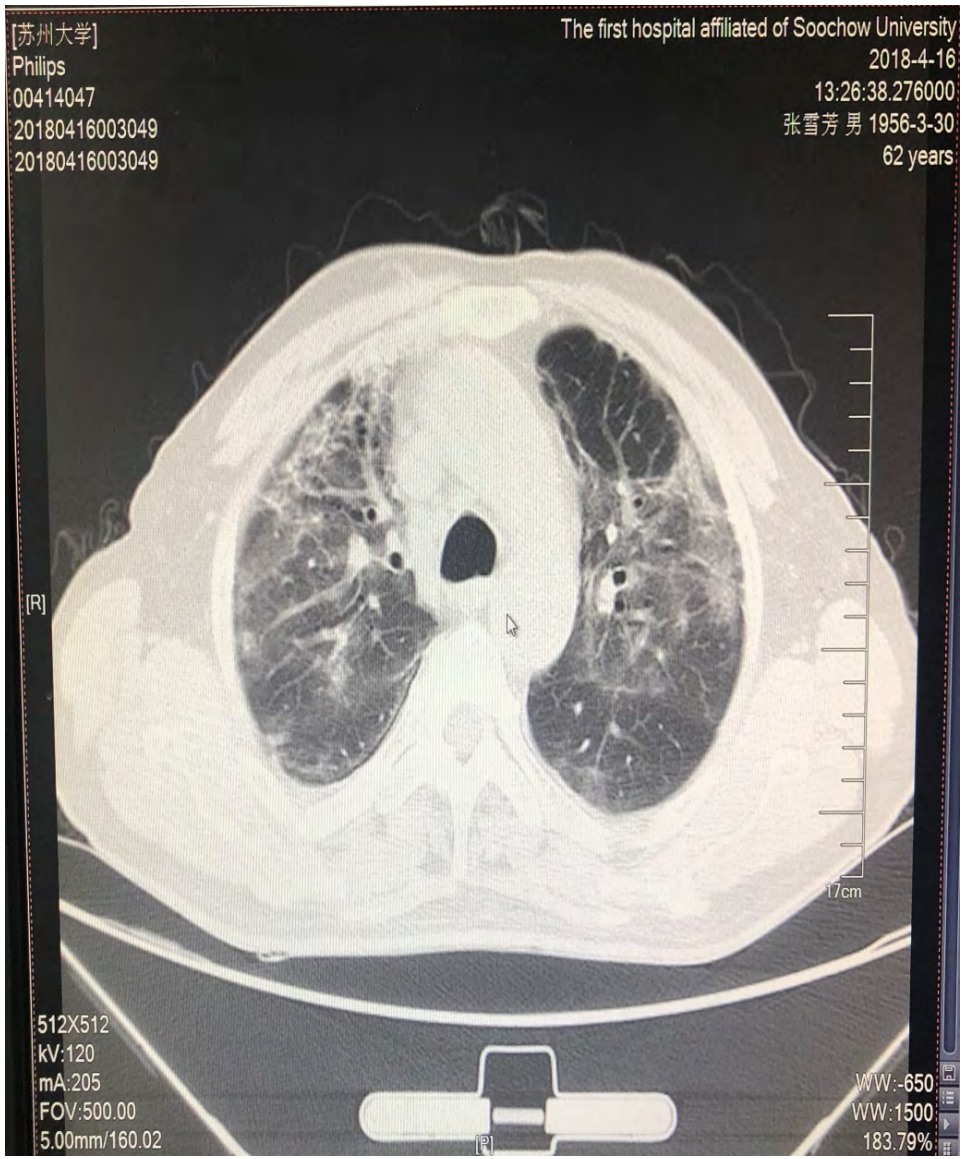


2018-3-22



2018-3-30





2018-3-27

2018-4-16

Favipiravir/oseltamivir combination therapy DAY1-10

Case 2 张*

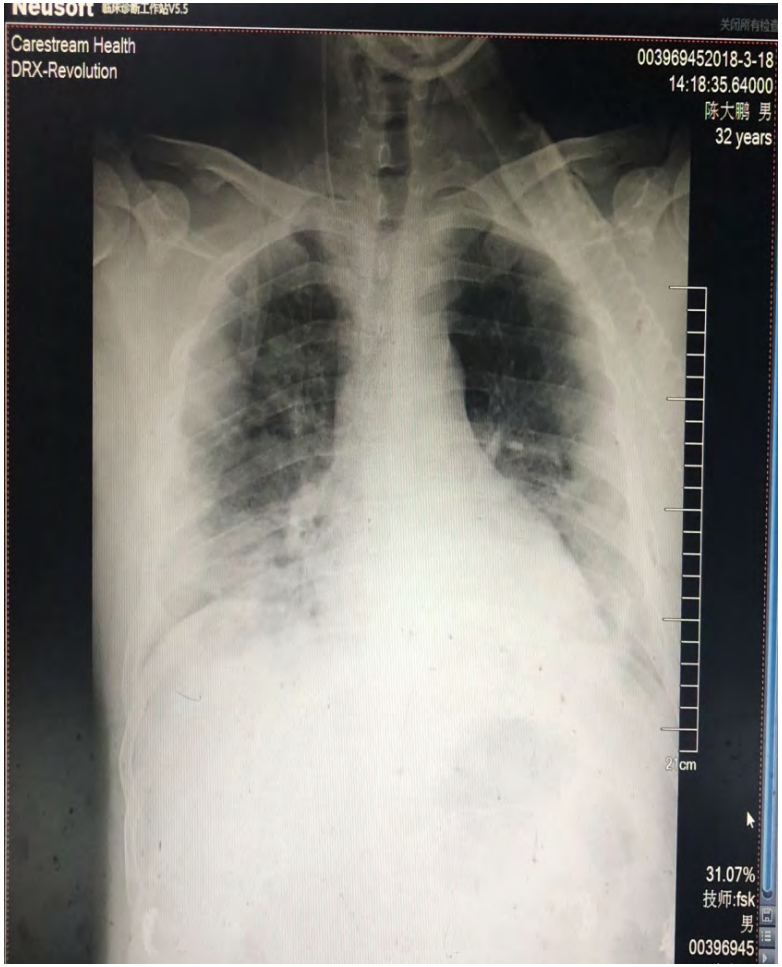
In hospital 24days(2018-3-17 ~2018-4-10)

Symptoms relieved Day 14 (2018-3-31)

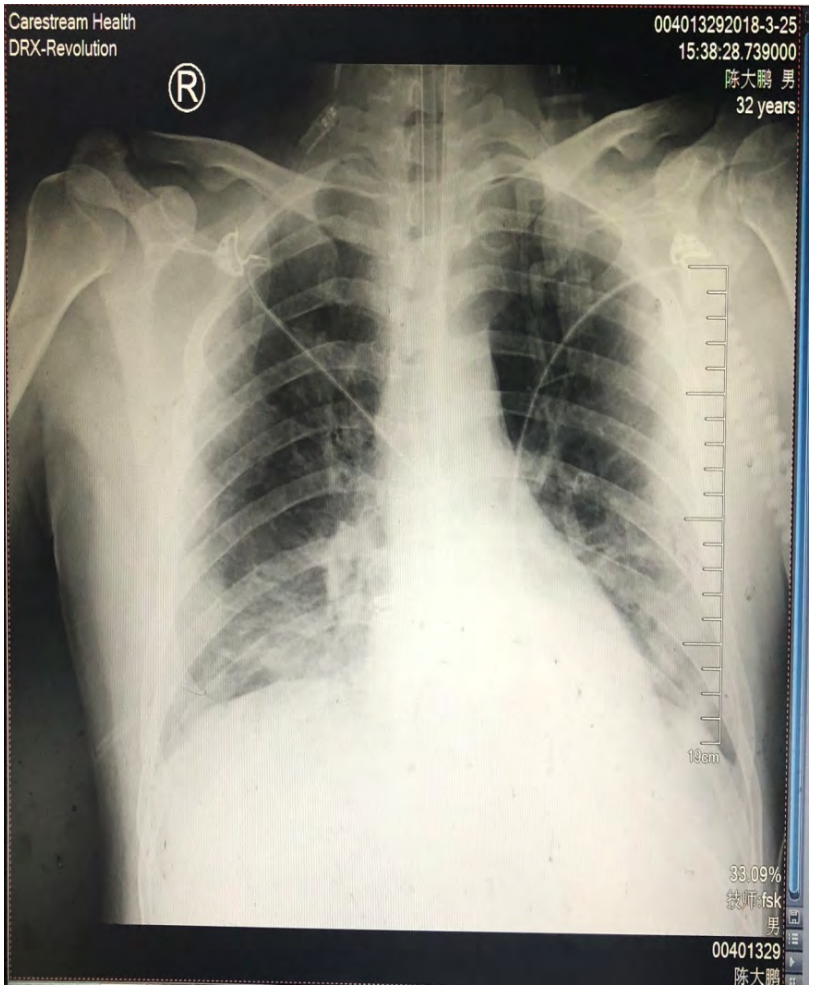
NPPV-MV 11days(2018-3-17 ~2018-3-28)

Flu A (+)Day 6 (2018-3-23)

(-) Day 13 (2018-3-30)



2018-3-18



2018-3-25

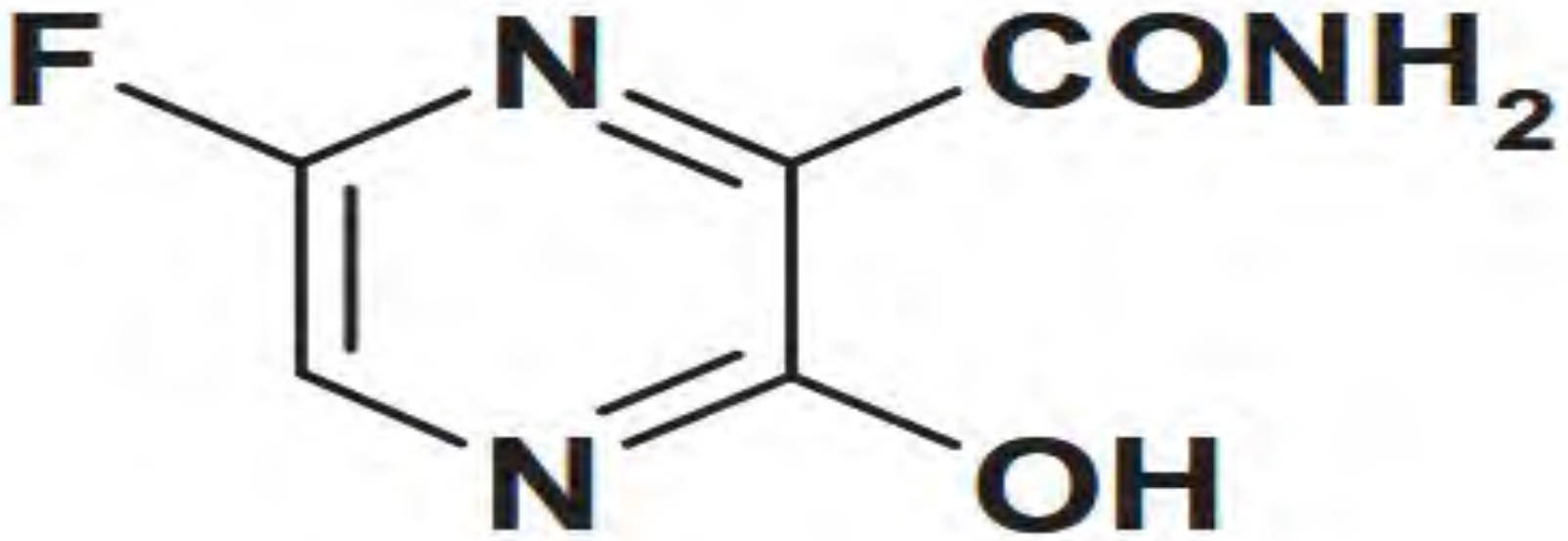
Favipiravir/oseltamivir combination therapy DAY1-10

Favipiravir (T-705),
a novel viral RNA polymerase inhibitor
severe influenza

Antiviral Research 100 (2013) 446–454

Favipiravir - a novel viral RNA polymerase inhibitor

(T-705; 6-fluoro-3-hydroxy-2 pyrazinecarboxamide)



Favipiravir (T-705)

Favipiravir

- It has been found to inhibit all serotypes and strains of influenza A, B and C viruses against which it has been tested, including those resistant to currently approved neuraminidase inhibitors.

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Favipiravir

1. Arenaviruses沙粒病毒
2. Bunyaviruses崩芽病毒
3. Flaviviruses虫媒病毒

（ in vitro and in rodent models ）

Potent in vitro activity against

1. Alphavirus甲病毒属
2. Paramyxovirus副粘病毒
3. Norovirus 诺如病毒

Virus susceptibility to favipiravir testing by plaque reduction assays in MDCK cells.

Viral Type	Favipiravir EC_{50}:μg/ml (μM)	No. of strains	No. of drug-resistant strains[a]		
			A	O	Z
A(H1N1)	0.03–0.79 (0.19–5.0)	15	3	8	2
A(H3N2)	0.07–0.94 (0.45–6.0)	9	7	4	1
B	0.09–0.83 (0.57–5.3)	8	8	4	2
A(H2N2)	0.06 (0.38)	1	0	0	0
A(H4N2)	0.14–0.15 (0.89–0.96)	2	0	0	1
A(H7N2)	0.24–1.60 (1.5–10.2)	2	1	0	0
A(H5N1)[b]	0.20–0.82 (1.3–5.2)	6	3	3	2
A(H1N1)[c]	0.13–0.71 (0.83–4.5)	2	0	0	0
A(H1N2)[c]	0.35 (2.2)	1	0	0	0
A(H1N1)2009	0.13–3.53 (0.83–22.5)	7	7	2	0

EC_{50}, 50% effective concentration.

Favipiravir is active against a broad range of influenza viruses

Therapeutic effects of favipiravir in mouse influenza infection models.

Viral Type	Favipiravir EC_{50}:μg/ml (μM)	No. of strains	No. of drug-resistant strains[a]		
			A	O	Z
A(H1N1)	0.03–0.79 (0.19–5.0)	15	3	8	2
A(H3N2)	0.07–0.94 (0.45–6.0)	9	7	4	1
B	0.09–0.83 (0.57–5.3)	8	8	4	2
A(H2N2)	0.06 (0.38)	1	0	0	0
A(H4N2)	0.14–0.15 (0.89–0.96)	2	0	0	1
A(H7N2)	0.24–1.60 (1.5–10.2)	2	1	0	0
A(H5N1)[b]	0.20–0.82 (1.3–5.2)	6	3	3	2
A(H1N1)[c]	0.13–0.71 (0.83–4.5)	2	0	0	0
A(H1N2)[c]	0.35 (2.2)	1	0	0	0
A(H1N1)2009	0.13–3.53 (0.83–22.5)	7	7	2	0

EC_{50}, 50% effective concentration.

[a] Number of strains resistant to adamantanes (A), oseltamivir (O), or zanamivir (Z). Changes to M2 and NA were detected by surveillance criteria (Sheu et al., 2008).

[b] Isolated from both humans and birds.

[c] Swine origin which were isolated from human.

Drug resistant viruses/Host protection

- Favipiravir has shown a wide range of antiviral activity against all strains including –drug resistant viruses.

- The 50% cytotoxic concentration (CC50) of favipiravir in host MDCK cells was more than 2000 ug/ml, demonstrating the highly selective inhibition of influenza virus replication.

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Dose--- Oseltamivir/ Favipiravir

- For comparison, the dose of oseltamivir was set at 10 mg/kg/day for seasonal A(H3N2) infection in mice and at 20 mg/kg/day for A(H5N1) virus infections.

- Favipiravir was orally administered 2 or 4 times a day for 5 days in mice infected with lethal doses of influenza virus A/ (H3N2), A/ (H3N2) or A/ (H5N1), improved survival compared to placebo was shown at a dose of 30 mg/kg/day or more.

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- Favipiravir also provided significant protection against the A/Duck/MN/1525/81(H5N1) virus at a dose of 33 mg/kg/day or more, regardless of the number of daily doses. When given 4 times a day, all mice survived.

- In contrast, oseltamivir therapy failed to impact survival at a dose of 20 mg/kg twice daily for 5 days.

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- Mice infected with the A/California/04/09(H1N1) virus or A/Anhoi/1/2013(H7N9) virus were also studied for the effect of favipiravir on pulmonary viral load on the third and sixth days after infection.

- Treatment with 60 and 300 mg/kg/day reduced viral replication in a dose-dependent manner.

- The inhibitory activity was the same or greater than that of oseltamivir and zanamivir against the A(H1N1)pdm09 virus and A(H7N9) virus.

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- Favipiravir was also found to have a significant therapeutic effect compared to oseltamivir in mice challenged with a 100-fold larger dose of virus, and when treatment was delayed until 96 h post infection.

Sidwell et al., 2007;Takahashi et al., 2003

Combinations with other drugs

In vitro

- 20 mg/kg/day dose of favipiravir combined with 0.1 and 0.3 mg/kg/day of oseltamivir against the A/NWS/33(H1N1) virus.
- In mice infected with A/Duck/MN/1525/81(H5N1), combining doses of both drugs, which were ineffective as monotherapies, significantly improved survival and body weights.

A synergistic effect in combination with oseltamivir

Effects of combinations of favipiravir and oseltamivir on an influenza A/Victoria/3/75 (H3N2) virus infection in mice with treatments started 24 h after infection

Treatment (mg/kg/day)	Survivors/Total	Day of death[b] (mean ± SD)
Control (Placebo)	0/20	8.2 ± 1.1
Favipiravir (100)	7/9*	5.5 ± 0.7
Favipiravir (50)	7/10*	8.3 ± 1.2
Favipiravir (25)	1/10	7.9 ± 1.5
Oseltamivir (50)	6/10*	8.8 ± 1.5
Oseltamivir (25)	1/9	7.5 ± 1.3
Favipiravir (100) + Oseltamivir (50)	10/10*	>21
Favipiravir (100) + Oseltamivir (25)	10/10*	>21
Favipiravir (50) + Oseltamivir (50)	9/10*	8
Favipiravir (50) + Oseltamivir (25)	9/10*	8
Favipiravir (25) + Oseltamivir (50)	10/10*	>21
Favipiravir (25) + Oseltamivir (25)	9/10*,+	8

[a] Oral treatments were given twice a day for 7 days starting 24 h after infection.

[b] Results for day of death are shown for mice that died prior to day 21.

* $P < 0.001$ compared to control group (Fisher's exact test).

+ $P < 0.01$ compared to either compound used alone (Fisher's exact test).

Antiviral Research 100 (2013) 446–454

Clinical evaluation

- A Phase III clinical evaluation,Japan
- Two Phase II studies have been completed in the United States.

Japan :NCT02026349，NCT02008344

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Activity against other pathogenic RNA viruses

Arenaviruses沙粒病毒

- Aside from ribavirin, which has toxicity concerns, there are no small-molecule drugs approved for therapeutic use.

In vitro inhibitory effects of favipiravir and ribavirin against arenavirsues. (Based on Gowen et al., 2007 and Mendenhall et al., 2011a).

Virus[a]	Strain	Favipiravir[b]			Ribavirin[b]		
		CC_{50} ± SD	$EC_{50\ or\ 90}$ ± SD	SI	CC_{50} ± SD	$EC_{50\ or\ 90}$ ± SD	SI
JUNV	Candid 1	188 ± 53 (1197 ± 337)	0.79 ± 0.47 (5 ± 3)	239	51 ± 15 (209 ± 61)	2.7 ± 2.2 (11 ± 9)	19
PICV	An 4763	175 ± 63 (1114 ± 401)	0.94 ± 0.47 (6 ± 3)	186	38 ± 21 (156 ± 86)	3.2 ± 2.2 (13 ± 9)	12
TCRV	TRVL 11573	214 ± 31 (1362 ± 197)	0.94 ± 0.63 (6 ± 4)	227	68 ± 8.1 (278 ± 33)	2.4 ± 0.73 (10 ± 3)	28
GTOV	S-26764	>157 (>1000)	6.8 ± 3.1 (43 ± 20)	>23	>244 (> 1000)	74 ± 52 (303 ± 228)	>3.3
JUNV	Romero	>157 (>1000)	3.3 ± 3.0 (21 ± 19)	>48	>244 (> 1000)	12 ± 20 (71 ± 81)	>20
MACV	Carvallo	>157 (>1000)	8.4 ± 1.7 (53 ± 11)	>19	>244 (> 1000)	17 ± 5.1 (122 ± 13)	>14

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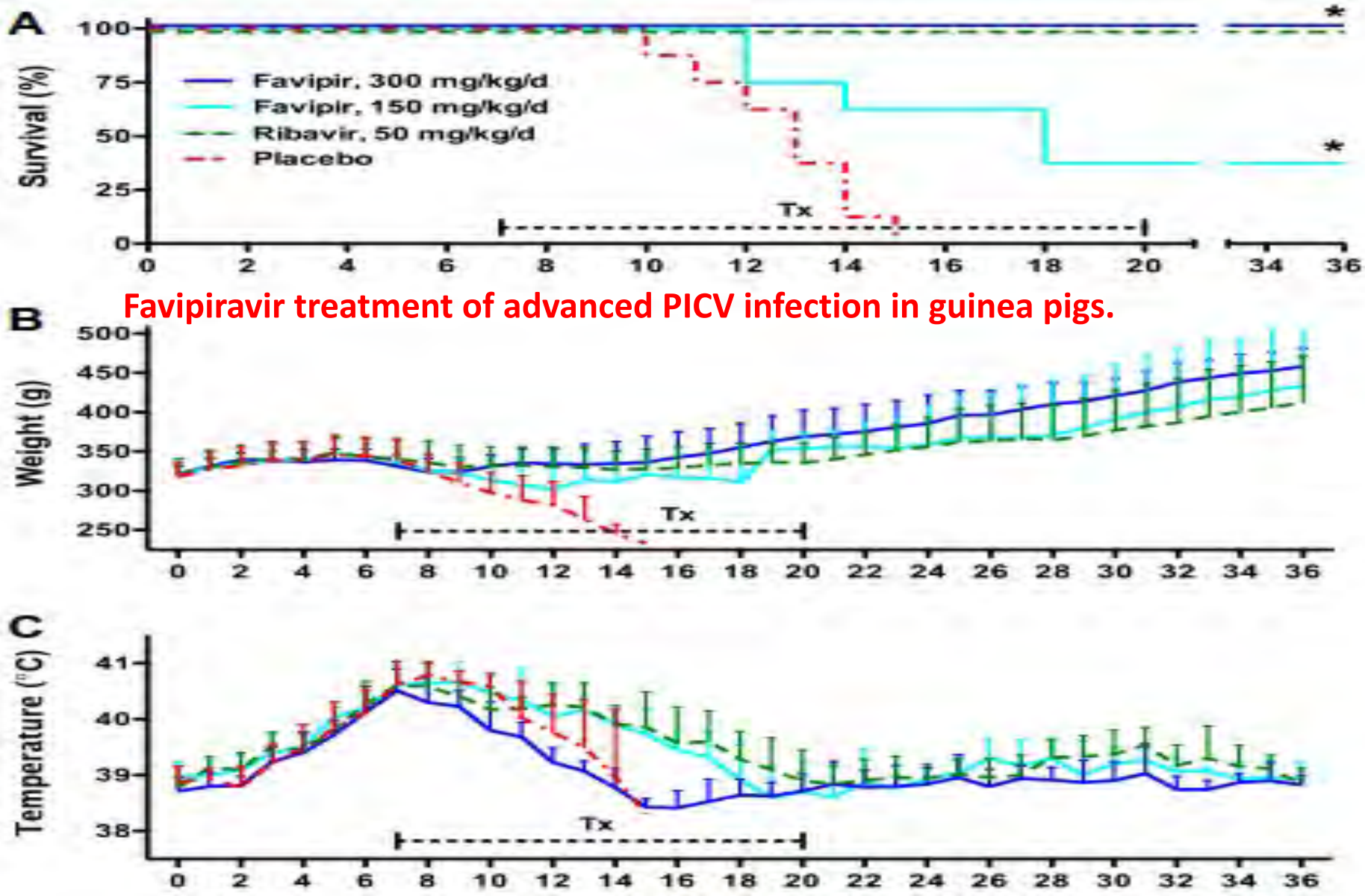
- Favipiravir also protected hamsters challenged with PICV.
- A dose of 300 mg/kg/day showed effects on survival (A), preservation of body weight (B),and reduction of fever (C).



Bunyaviruses崩芽病毒

- La Crosse virus (LACV), Rift Valley fever virus (RVFV), Crimean-Congo HF virus and hantavirus.

- Severe symptoms: hemorrhagic fever, severe fever with thrombocytopenia, and reanl or pulmonary syndrome.

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In vitro inhibitory effects of favipiravir and ribavirin against bunyavirsues.

Virus[a]	Strain	Favipiravir[b]			Ribavirin[b]		
		CC_{50} ± SD	EC_{50} ± SD	SI	CC_{50} ± SD	EC_{50} ± SD	SI
LACV	–	>1000 ± 0 (>6365 ± 0)	5.0 ± 2.0 (32 ± 13)	>199	877 ± 211 (3595 ± 864)	17 ± 12 (70 ± 49)	51
PTV	Adames	>1000 ± 0 (>6365 ± 0)	30 ± 5.0 (191 ± 32)	>33	898 ± 88 (3681 ± 360)	42 ± 22 (172 ± 90)	21
RVFV	MP-12	>980 ± 29 (>6257 ± 185)	5.0 ± 0.9 (32 ± 6)	>196	>906 ± 161 (>3714 ± 659)	13 ± 4 (53 ± 16)	>70
SFNV	Naples	>1000 ± 0 (>6365 ± 0)	18 ± 26 (115 ± 166)	>55	>729 ± 220 (>2989 ± 901)	22 ± 12 (90 ± 49)	>33
DOBV	Sotkamo	756 ± 104 (4816 ± 662)	10 ± 1.1 (93 ± 18)	52	296 ± 153 (1215 ± 628)	18 ± 0.6 (72 ± 2.4)	17
MPRLV	HV9021050	753 ± 186 (4795 ± 1186)	15 ± 2.8 (65 ± 17)	74	256 ± 33 (1051 ± 135)	11 ± 0.7 (47 ± 2.9)	22
PHV	MP40	600 ± 10 (3819 ± 64)	10 ± 4.1 (66 ± 26)	58	248 ± 211 (1018 ± 866)	5.6 ± 0.5 (23 ± 1.9)	44

Flaviviruses虫媒病毒

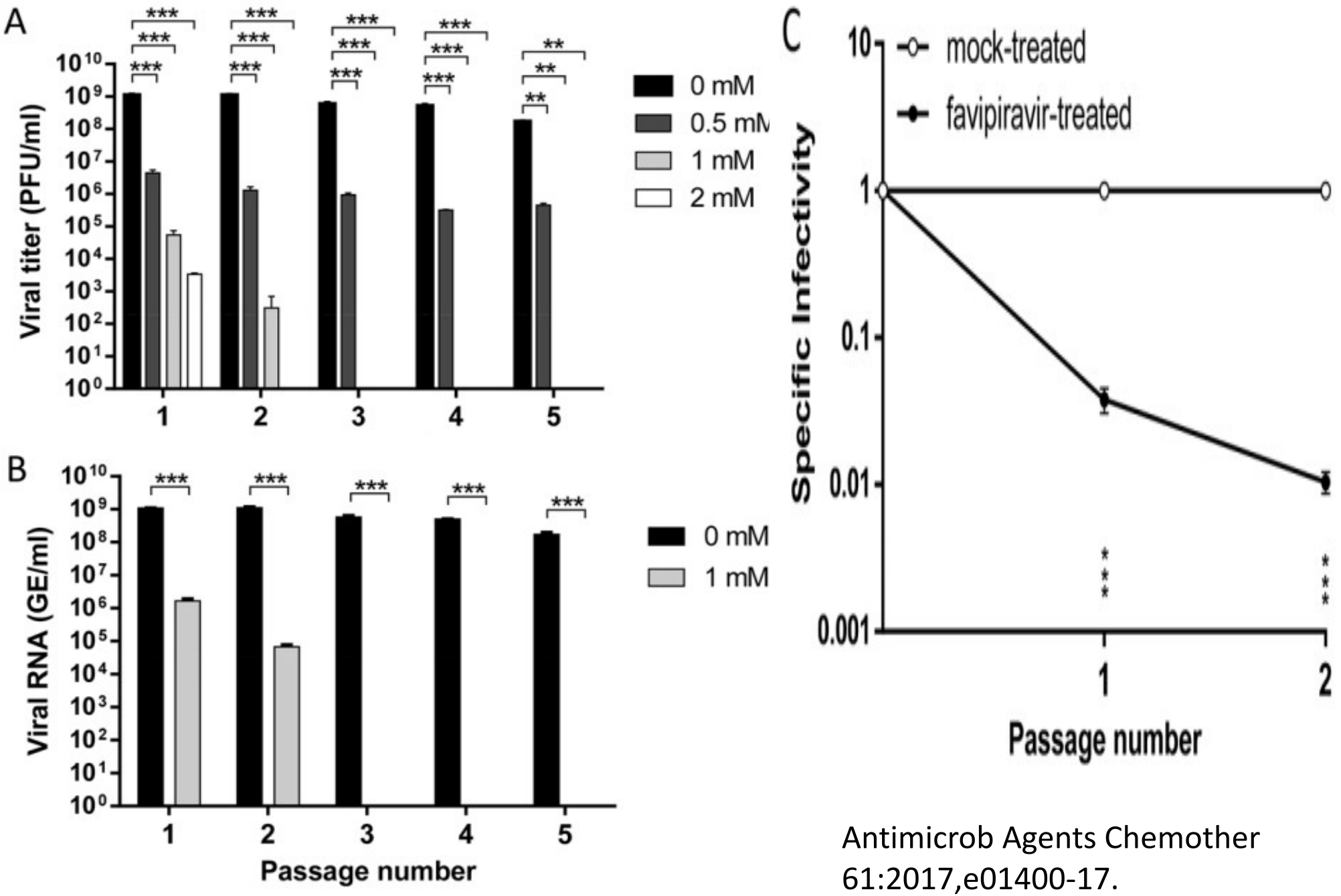
- Favipiravir inhibits several pathogenic flaviviruses including yellow fever virus (YFV) and West Nile virus (WNV).

- The drug was effective when added 4, 8, or 12 h after virus challenge. In YFV-infected hamsters,

  favipiravir administered orally at 200 or 400 mg/kg/d for 8 days, beginning 4 h prior to virus exposure, significantly protected the animals against death.

Antiviral Research 100 (2013) 446–454

Antiviral activity of favipiravir against WNV in Vero cells.



Antimicrob Agents Chemother 61:2017,e01400-17.

Alphaviruses甲病毒

- Favipiravir has also demonstrated activity in Vero cells infected with Western equine encephalitis virus (WEEV), with an EC90 of 49 lg/ml (312 uM) .
- However, a modest improvement in clinical signs such as the amelioration of weight loss and a significant protection against death suggest that favipiravir may be an effective treatment for other severe alphavirus infections.

.

Julander et al., 2009

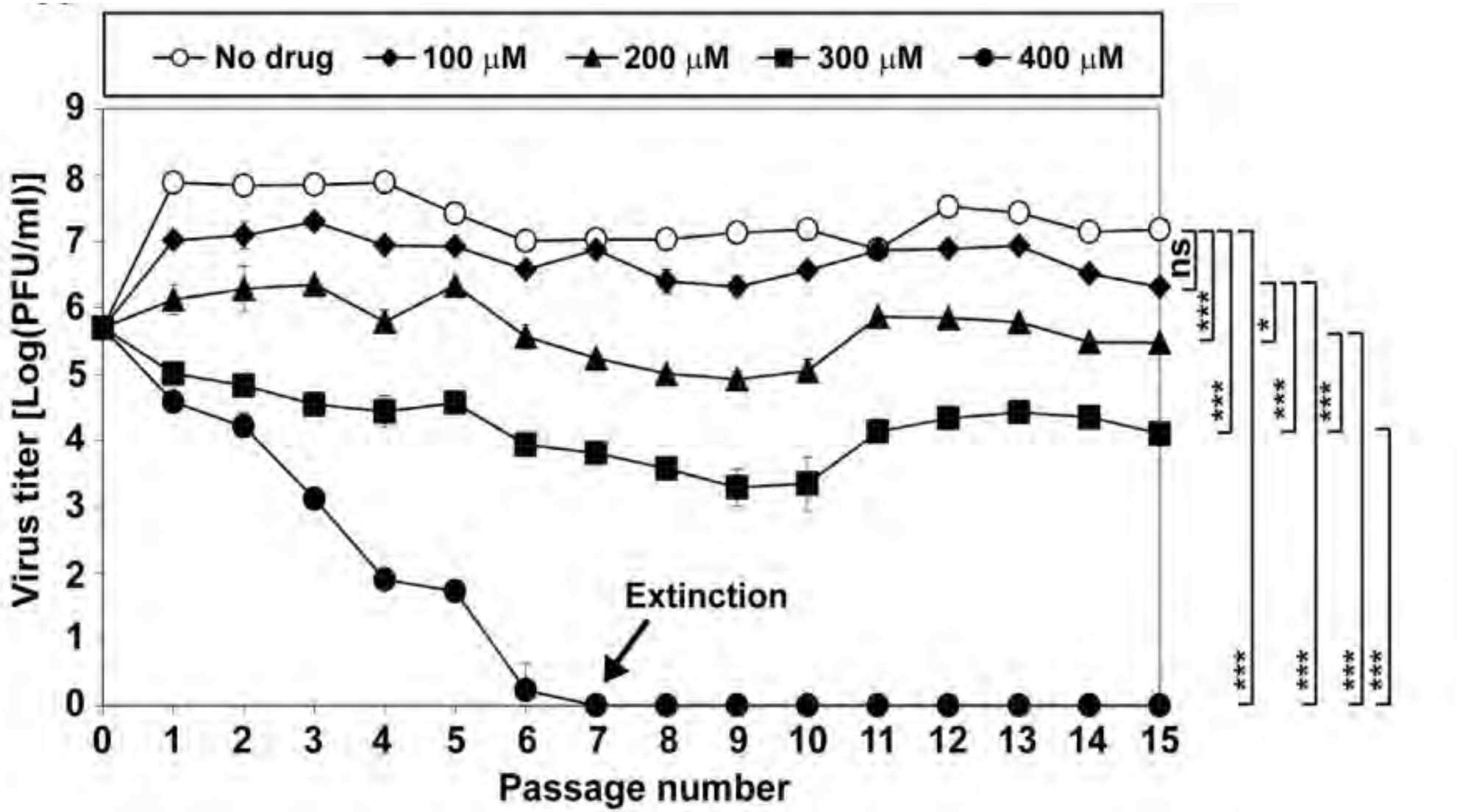
Picornaviruses微小核糖核酸病毒

- Favipiravir inhibited the replication of foot-and-mouth disease virus (FMDV) in vitro with an EC50 equal to 14 lg/ml (89 uM).

- Favipiravir also selectively inhibited poliovirus in Vero cells, with an EC50 of 4.8 lg/ml(31 lM) and a selectivity index of 29, and inhibited rhinovirus replication in HeLa cells, with an EC50 of 29 lg/ml (186 uM and an SI > 43)

Furuta et al., 2009

Extinction of FMDV by favipiravir.



Foot-and-mouth disease virus

Virus Research 233 (2017) 105–112

Noroviruses诺如病毒

- Favipiravir was recently shown to be active against murine norovirus, modestly inhibiting the development of CPE in cell culture with EC50s of 39 ± 4 lg/ml (248 ± 25 uM)

Rocha-Pereira et al.,2012

Hepatitis C Virus

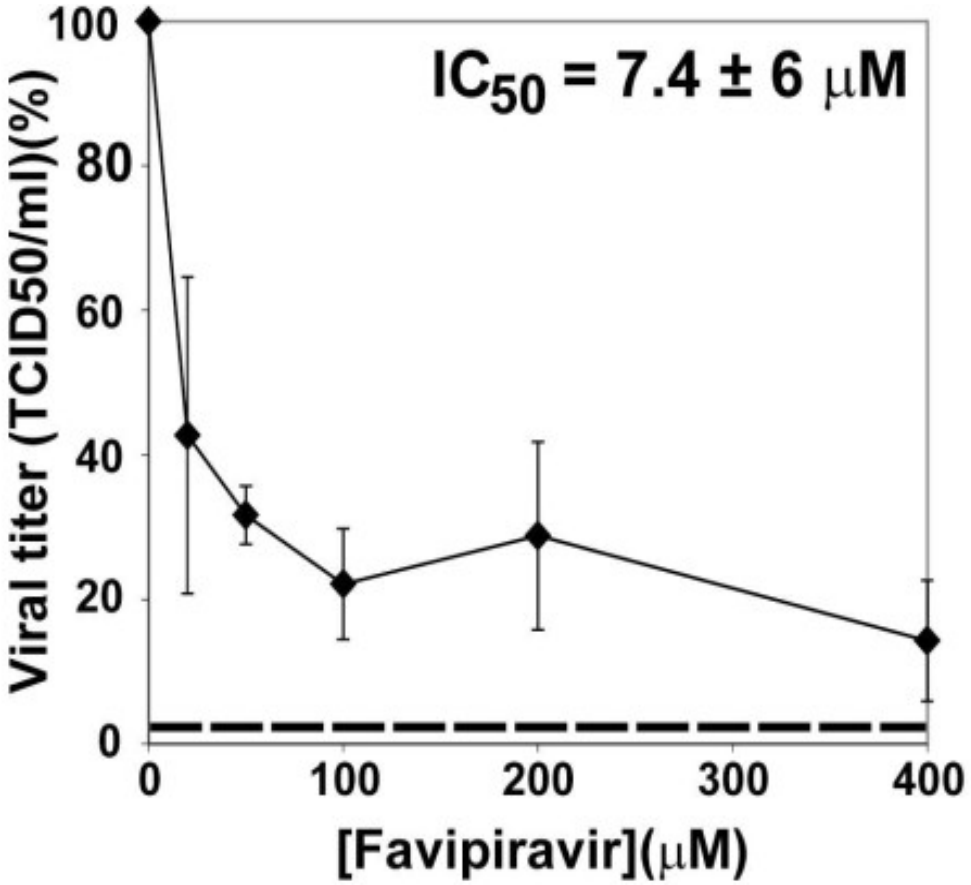
- Lethal mutagenesis is an antiviral approach.
- Favipiravir (T-705) is a potent mutagenic agent for hepatitis C virus (HCV) .
- T-705 leads to an excess of G → A and C → U transitions in the mutant spectrum
- Passaging the virus five times in the presence of 400 μM T-705 resulted in virus extinction.

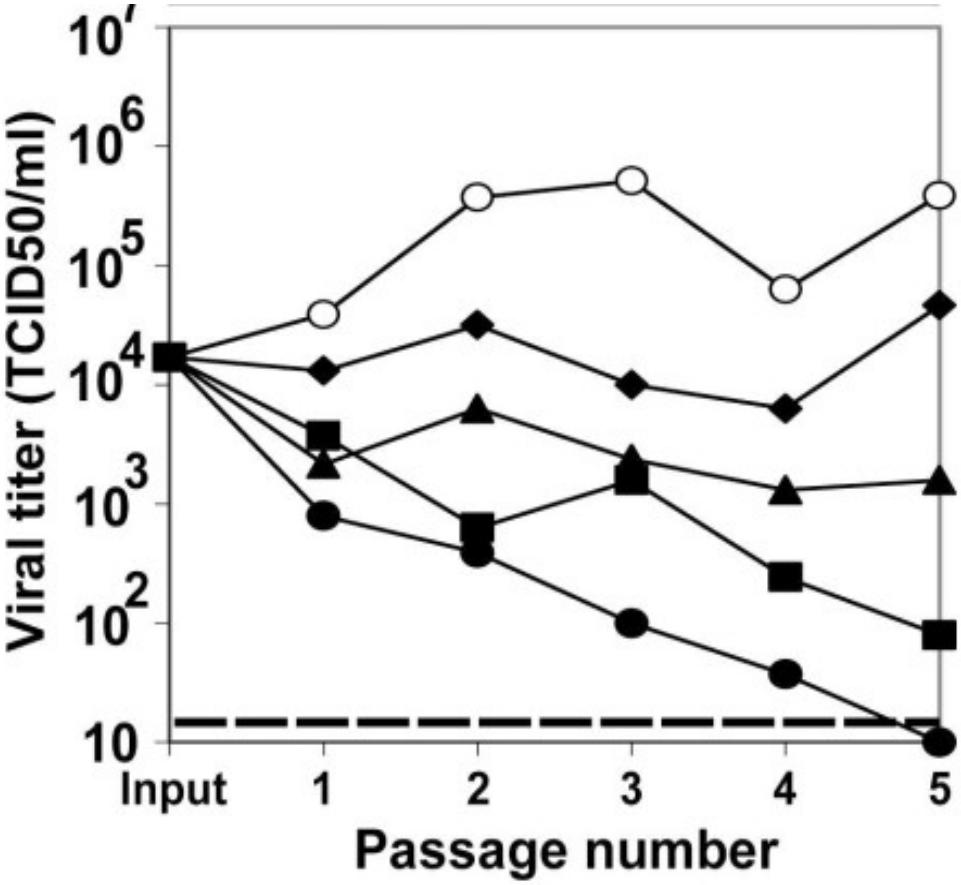
PLOS ONE. DOI:10.1371/journal.pone.0164691 October 18, 2016

Favipiravir (T-705)-new anti-HCV agent

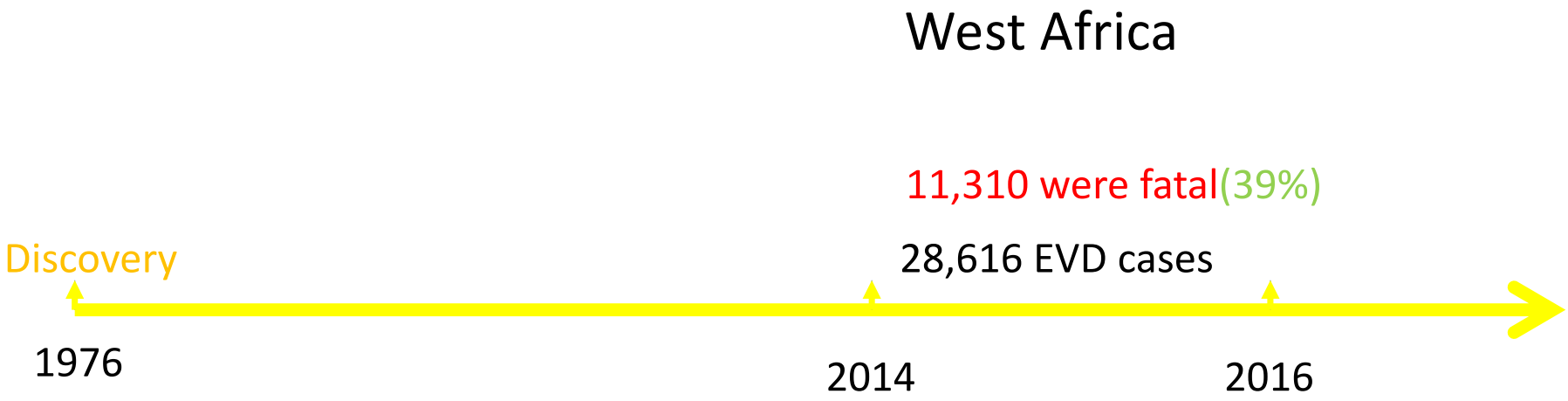
- Undergone advanced clinical trials

Inhibition of HCV progeny production by T-705





Ebola virus disease (EVD)



Effective treatments for EVD?

2014.9 Reaction!: favipiravir against Ebola virus (EBOV)

In September 2014, WHO, potential anti-Ebola drugs, and identified four classes of products

1. Immunomodulators
2. Immunoglobulins
3. Small inhibitory RNA
4. Antivirals

World Health Organization. Categorization and prioritization of drugs for consideration for testing or use in patients infected with Ebola. 2015 Jan 19

Experimental Treatment with Favipiravir for Ebola Virus Disease (the JIKI Trial): A Historically Controlled, Single-Arm Proof-of Concept Trial in Guinea

JIKI Trial

- Multicenter non-randomized trial

1. High number of patients
2. Ethically unacceptable

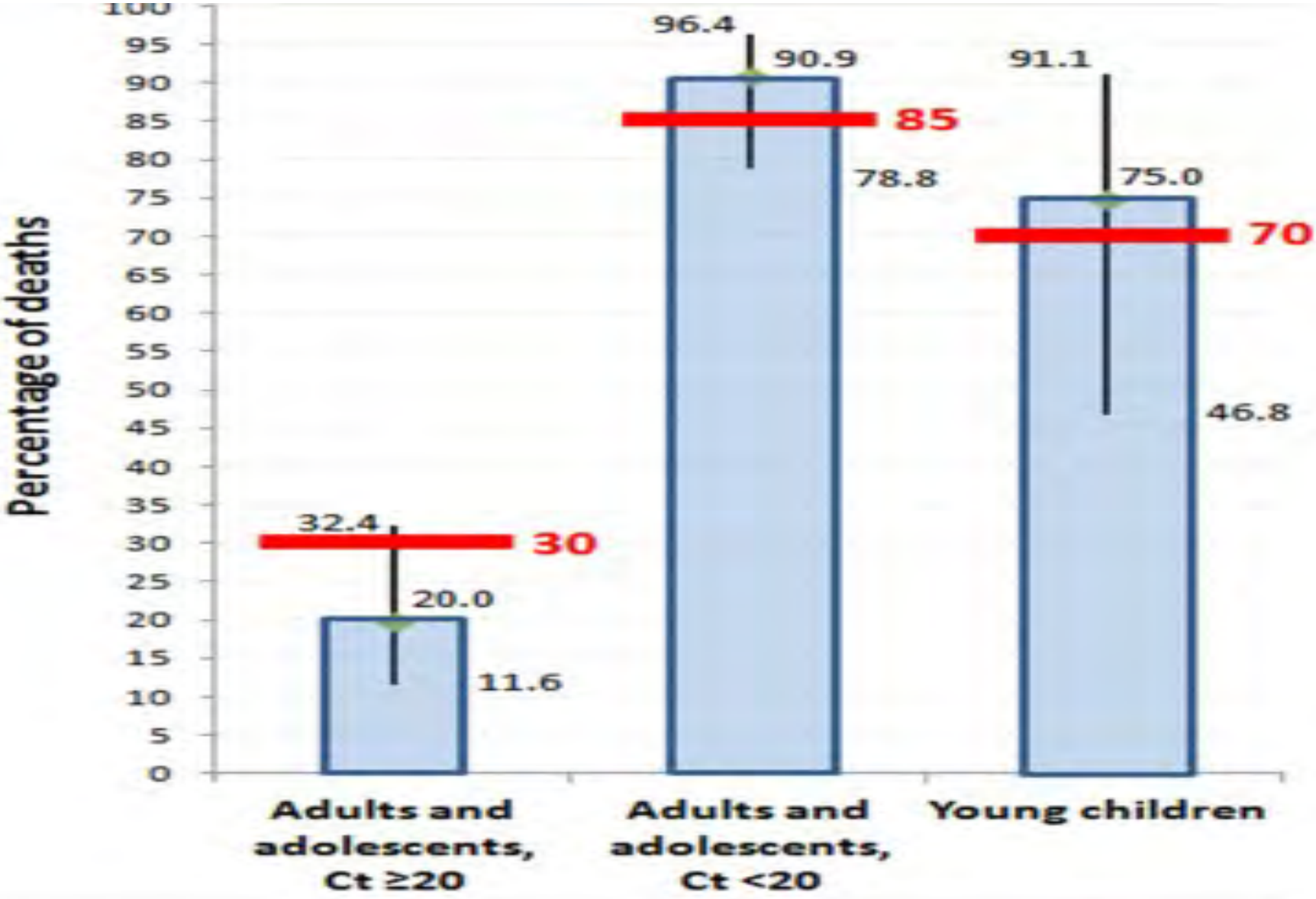
PLoS Med,2016,13(3): e1001967.

JIKI trial settings， September 2014

EBOV: JIKI trial dose

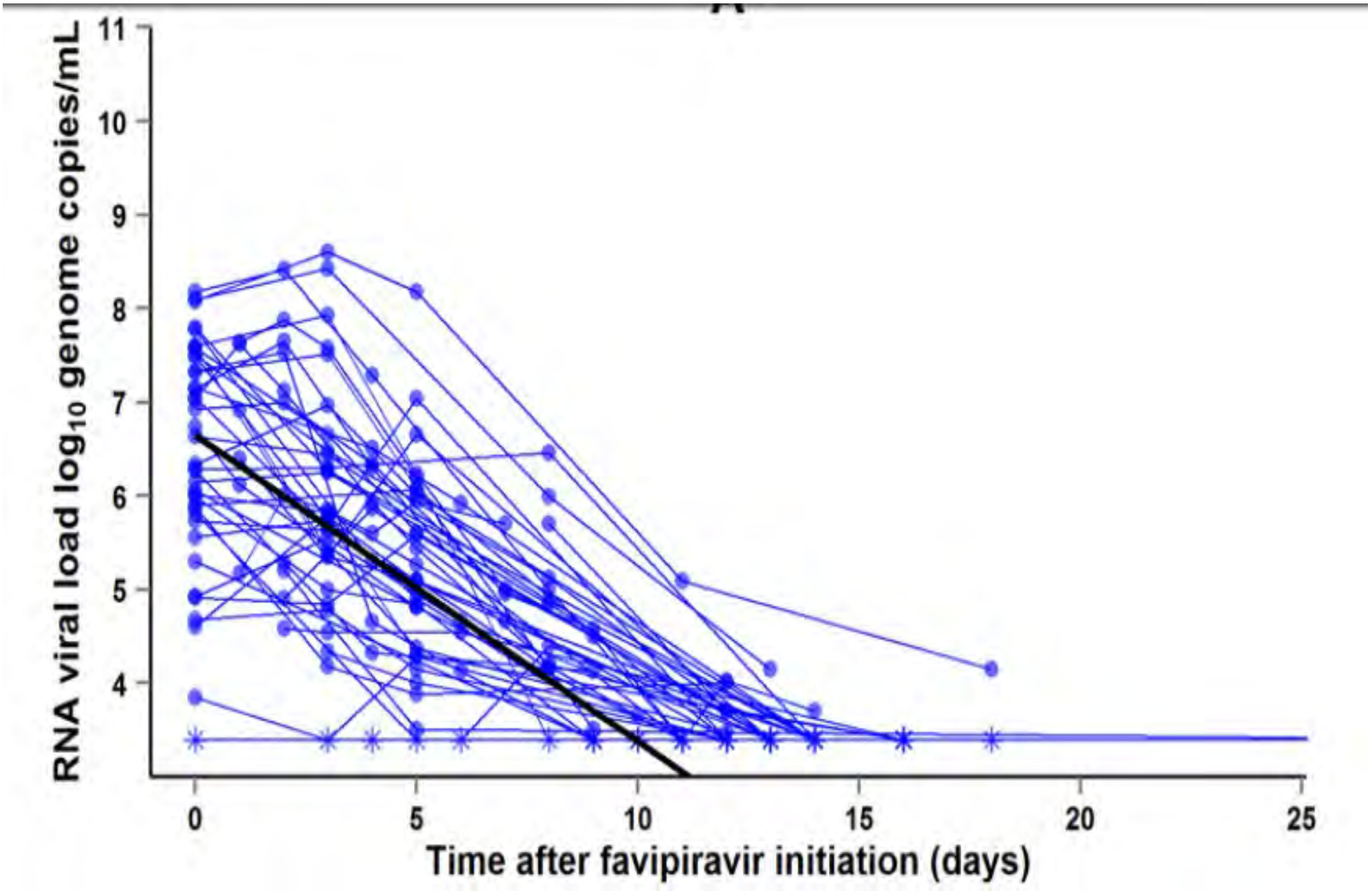
- 6,000 mg on day 0, followed by 2,400 mg/d from day 1 to day 9.
- 10 days.
- For children, the dose was adapted according to body weight.

JIKI trial mortality, according to age and baseline RT-PCR Ct value.



N of patients	55	44	12
N of deaths	11	40	9

JIKI trial: evolution of RNA viral load in adolescents and adults.



Is High-Dose Favipiravir Well Tolerated?

- The findings in Group A Ct>20 provide a convincing suggestion of the good tolerability of favipiravir.

- In this group, the patients who died all had a high viral load together with clinical and biochemical abnormalities that were clearly consistent with uncontrolled EVD.

- All the other patients in this group, even those with very abnormal biochemical markers at baseline or who developed highly abnormal values during follow-up, survived.

Is it Important to Treat Early?

- No difference between patients who showed up within 3 d of first symptoms and those who did not in terms of viral load or mortality, both in the trial and in the historical database.

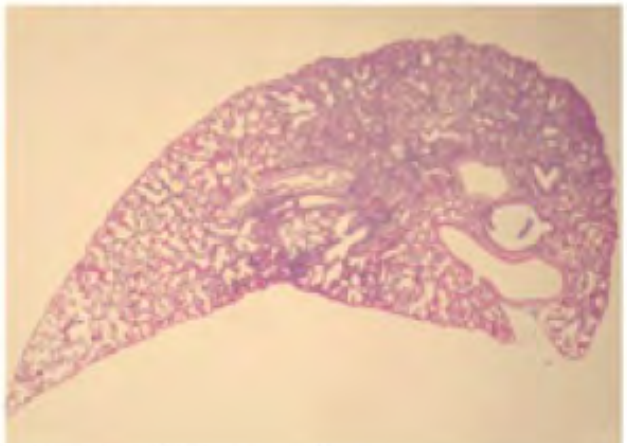
T-705 is effective against H5N1 virus

- A mouse-adapted H5N1 virus
- A/duck/Minnesota/1525/81(which is a benign duck virus)
- Authentic “highly pathogenic” H5N1 viruses(oseltamivir against highly pathogenic H5N1 viruses in animal models was limited,initiated within 1 h of infection)

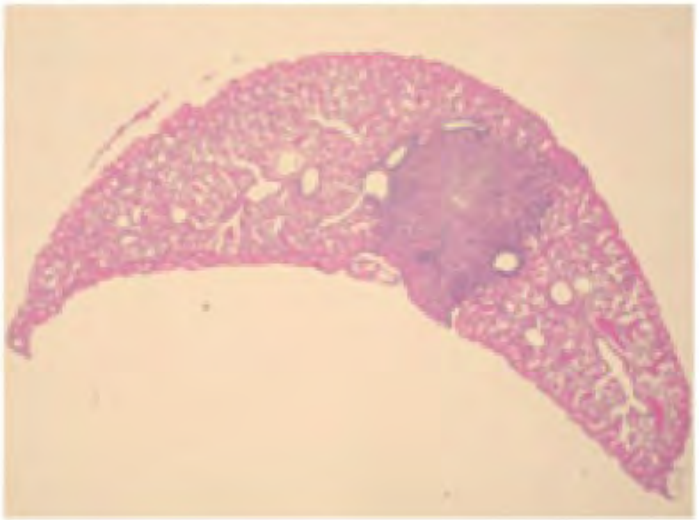
Virology, 2008,374:198–209.

Pathological findings for the lungs of H5N1 viruses infected mice

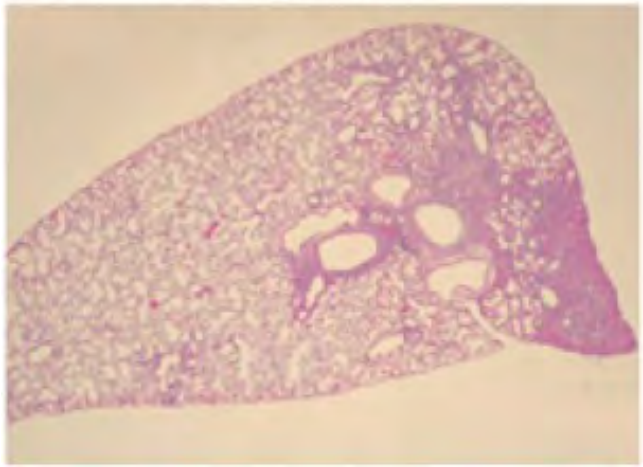
Control



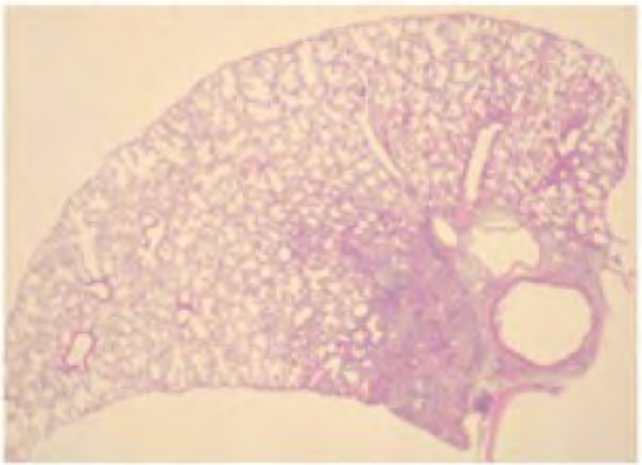
GS4104 50 mg/kg



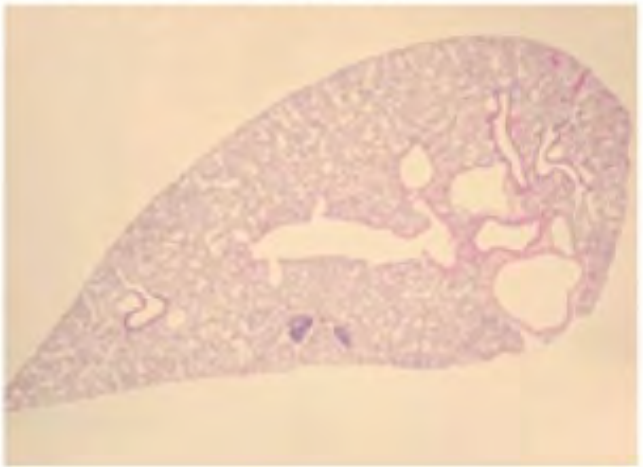
T-705 30 mg/kg



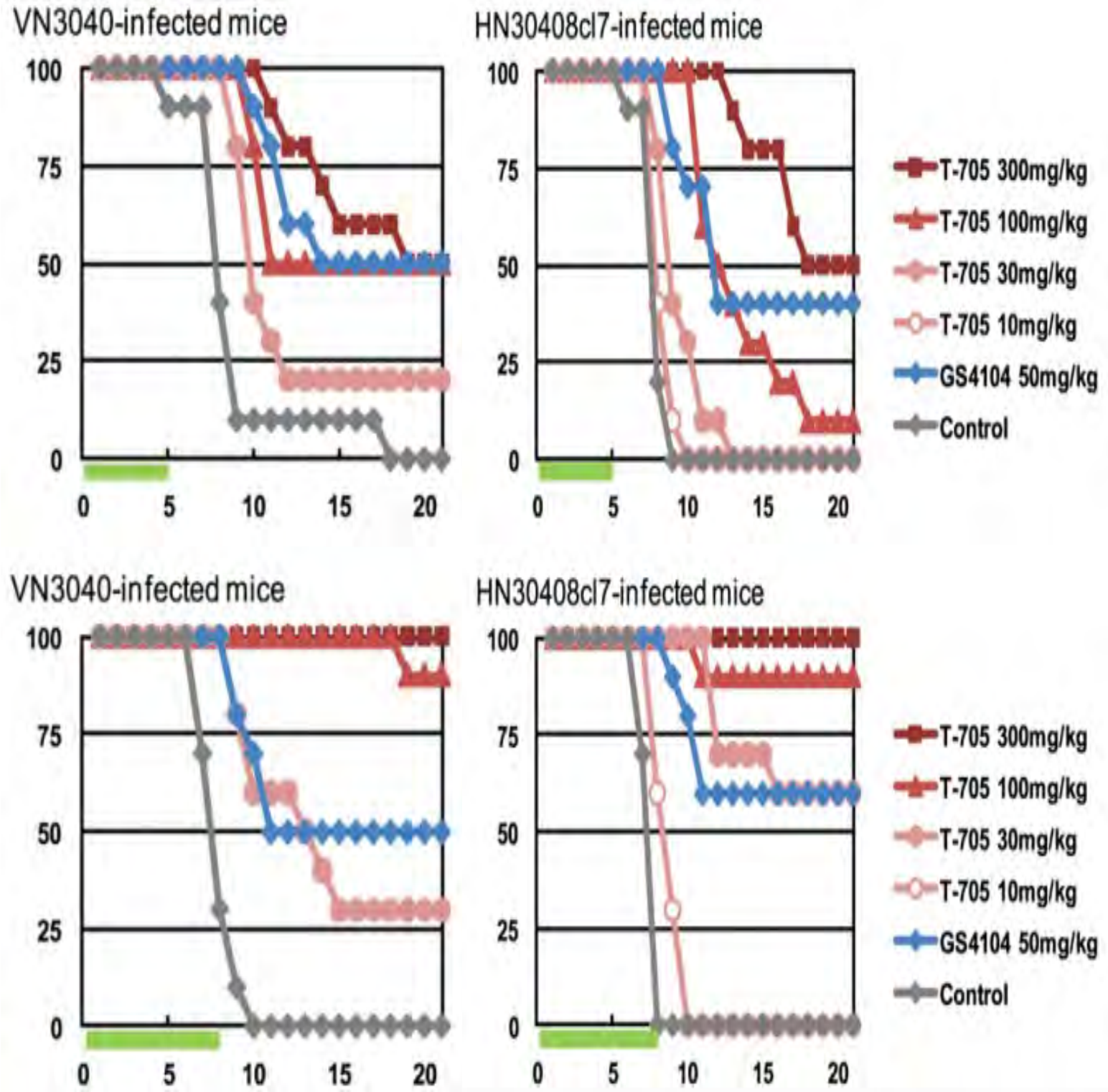
T-705 100 mg/kg



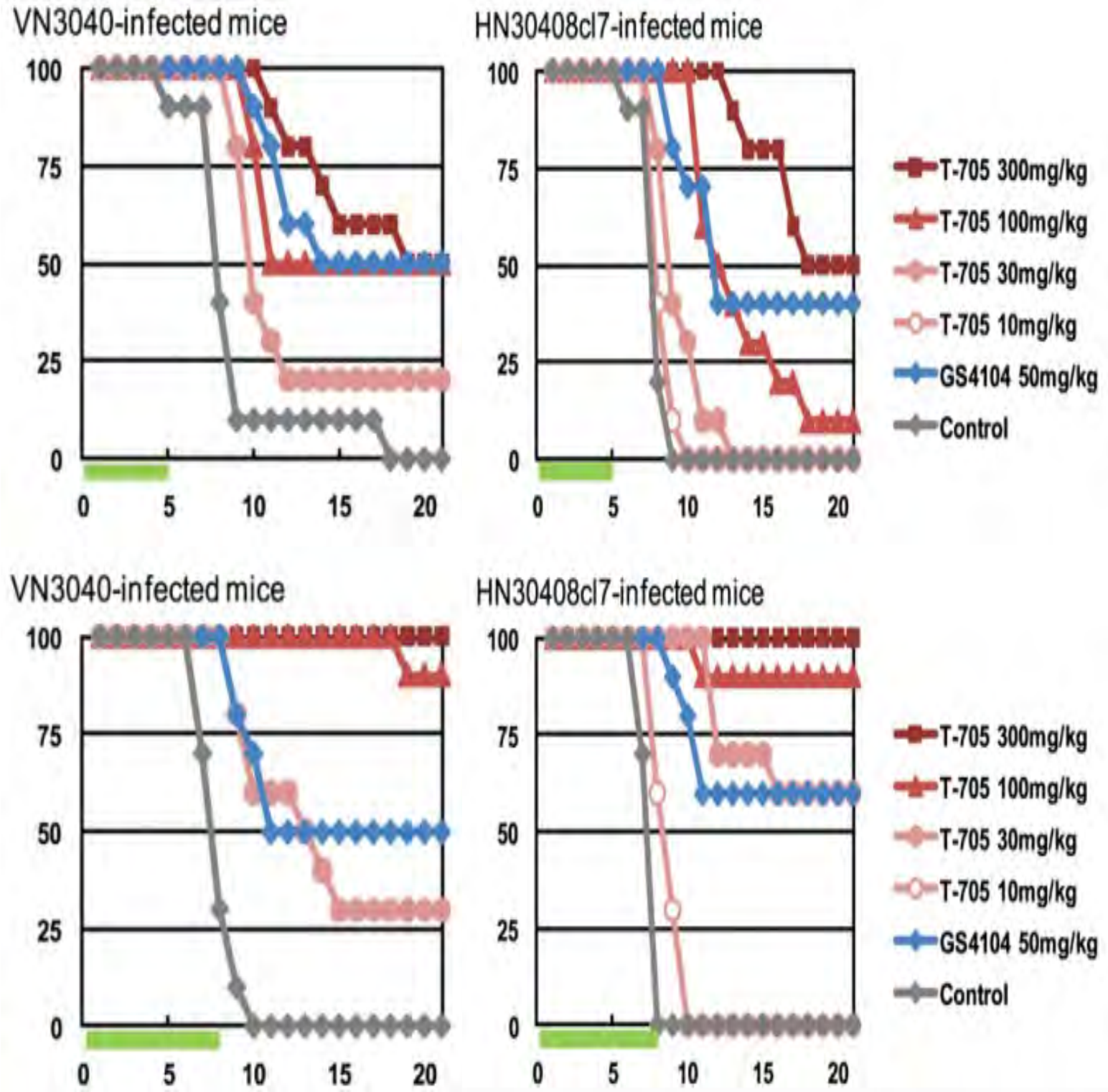
T-705 300 mg/kg



Proc Natl Acad Sci U S A SO 2010 Jan 12 107 2 882 7



Efficacy of T-705 and GS4104 against highly pathogenic H5N1influenza viruses in mice. Ten mice per group were intranasally infected with 10 MLD50 of VN3040 (A and B) or HN30408cl7 (C and D). Infected mice were orally administrated T-705 or GS4104 at the indicated doses or methyl-cellulose (control) twice daily for 5 (A and C) or 8 days (B and D), beginning 1 h postinfection. Green bars indicate the period of drug administration. Survival was monitored daily for 21 days.



Efficacy of T-705 and GS4104 against oseltamivir-resistant highly pathogenic H5N1 influenza viruses in mice. Ten mice per group were intranasally infected with 10 MLD50 of VN1203 (A), VN1203-H274Y (B), and VN1203-N294S (C). Infected mice were orally administrated T-705 or GS4104 at the indicated doses twice daily for 8 days, beginning 1 h postinfection. Green bars indicate the period of drug administration. Survival was moni- tored daily for 21 days.

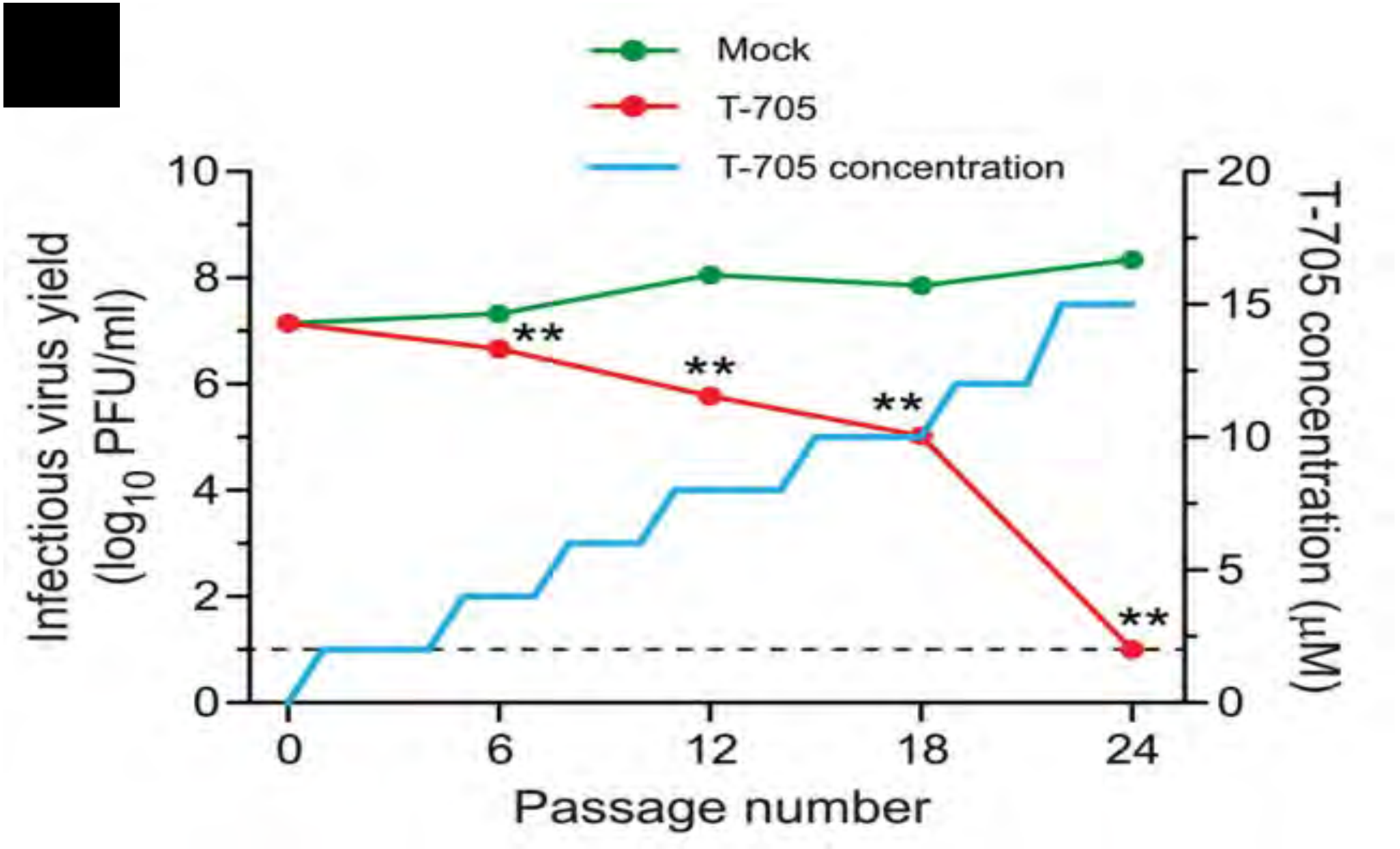
BALB/c mice lethally challenged with H5N1- and H3N2-subtype viruses

Orally administered T-705 at a dose of ≥30 mg/kg of body weight/day

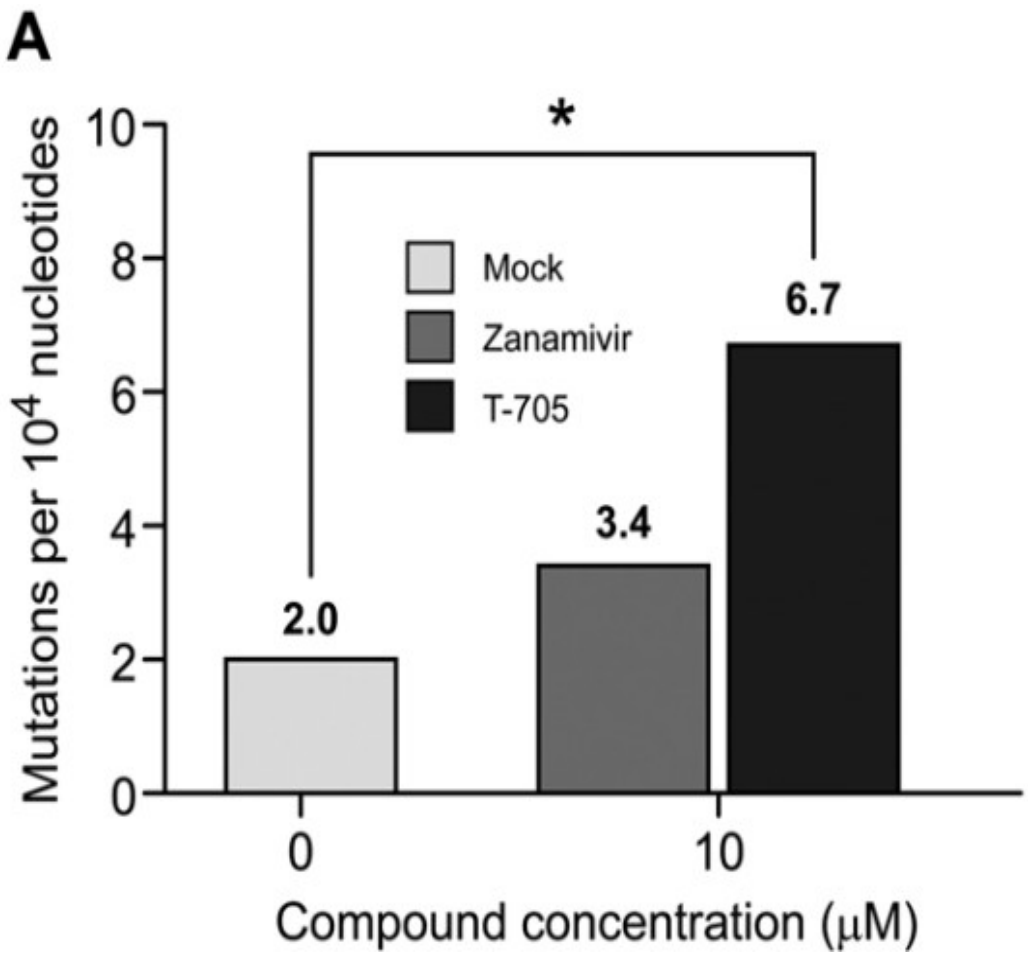
1. Prevented death
2. Inhibited lung consolidation
3. Reduced lung virus titers

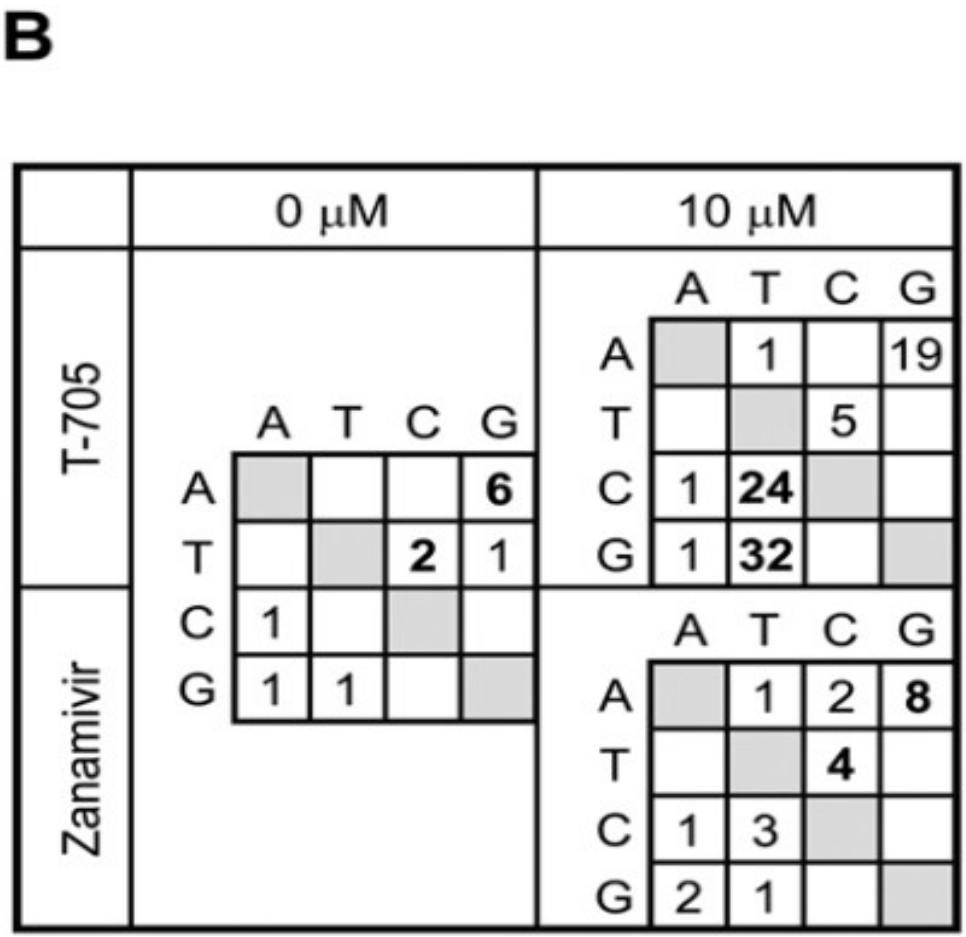
Proc. Natl. Acad. Sci. U. S. A.107:882– 887.
Agents Chemother. 54:2517–2524.

Infectivity of influenza A (H1N1) viruses(A/New Jersey/15/2007) during serial passage with T-705 in MDCK cells.

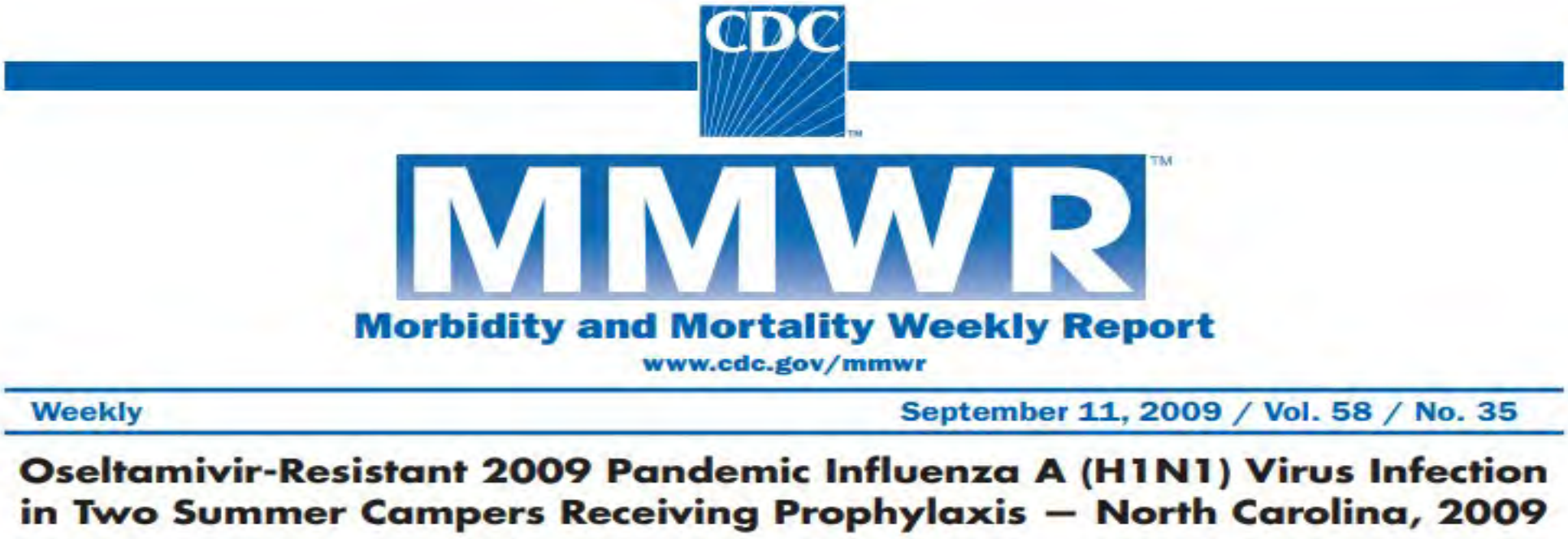


Mutation frequency and profile of nucleotide changes in influenza A/Denmark/524/2009 (H1N1) virus.





Rare cases of oseltamivir resistance have been reported in patients infected with the 2009 A(H1N1) pdm strain following exposure to oseltamivir



Mortal. Wkly. Rep.2009. 58:969–972.

Mortal. Wkly. Rep. 2009.58:893–896.

World Health Organization. Accessed 11 August 2009. Pandemic (H1N1) 2009 - update 60. World Health Organization, Geneva, Switzerland. www .who.int/csr/don/2009_08_04/en/print.html

Favipiravir- 2009 pandemic viruses- MDCK cells

1. Potency of favipiravir varied, depending upon which of the two MDCK cell lines.

   The observation that favipiravir appears to be more efficacious in MDCK-ATCC cells compared to MDCK-Mill Hill cells(virus replication and viral spread)

1. With the exception of A/Illinois/10/2009, favipiravir was found to inhibit viral infection more effectively.

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, June 2010, p. 2517–2524

Accept

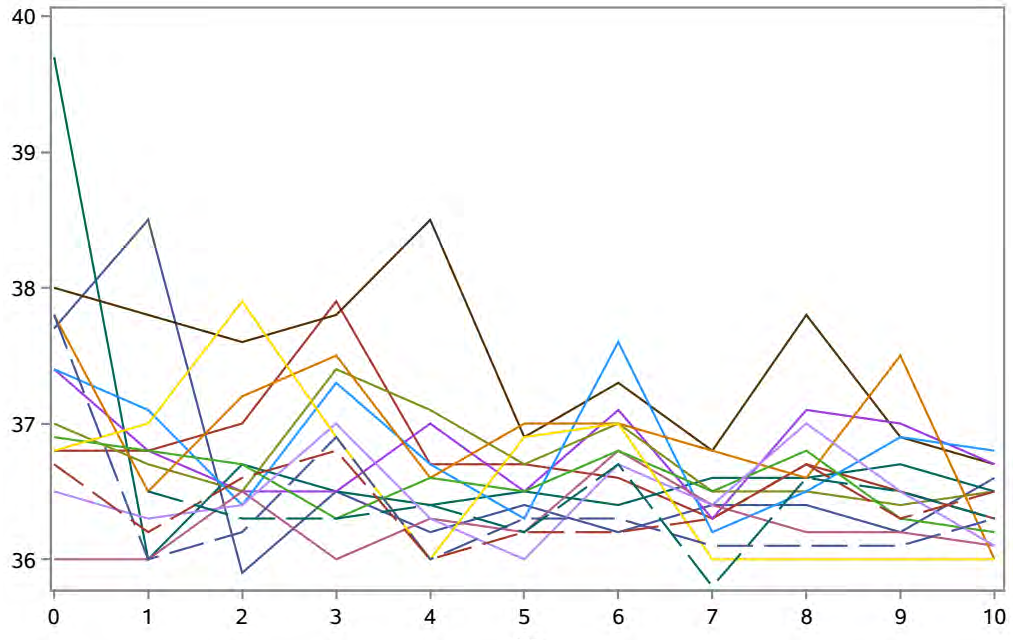
Main characters

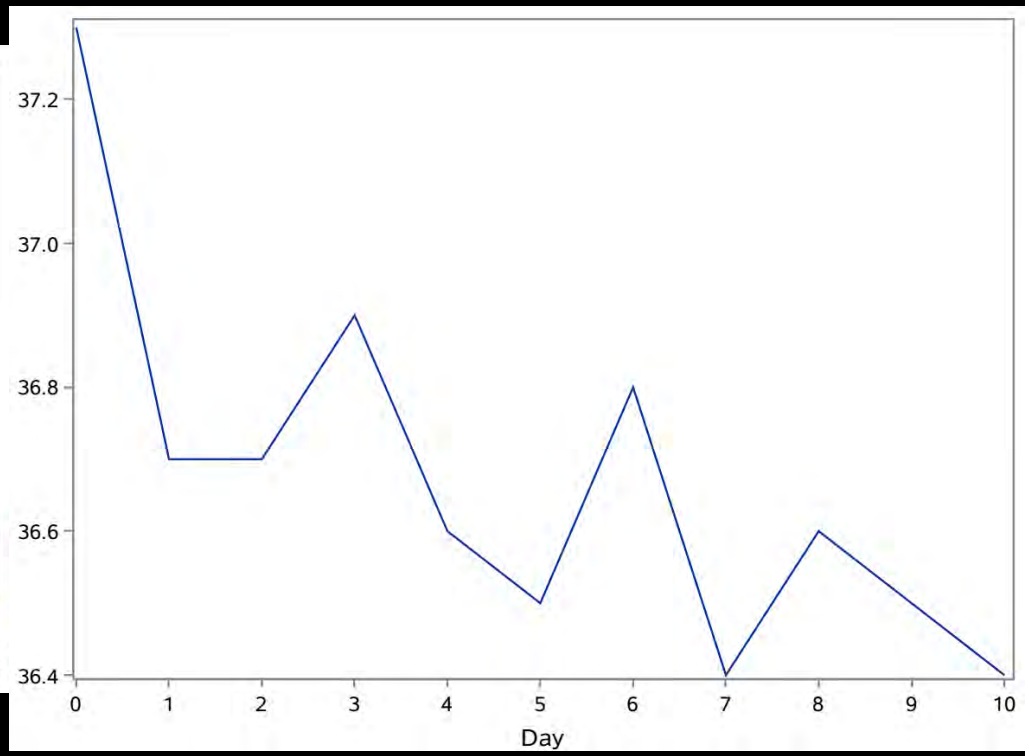
variables	N=16
Age (years)	59.4 (14.4)
Gender (male)	13 (81.3%)
BMI	23.9 (3.1)
Influenza subtype (flu A)	13 (81.3%)
PCR CT value on screening	29.1 (5.9)
PaO_2/FiO_2 on screening	157.2 (57.1)
AST on screening	67.2 (41.2)
APACHE II on screening	11.1 (4.1)
SOFA on screening	4.7 (1.9)
NEWS on screening	5.9 (2.7)
Lymphocyte count on screening	0.8 (0.4)
PCT on screening	1.1 (2.5)
Admission to ICU	14 (87.5)
Hospital mortality	1 (6.3%)

Comparison of clinical characters between low and high concentration group

	Low concentration group (n=13)	High concentration group (n=3)
Age	56	72.8
female	15.4% (2)	33.3% (1)
Ventilated YES/NO	23.1% (3)	0
Mean daily temperature	37	37
Weight	67	60
BMI	24	23
Baseline		
Lymphocyte	0.74	0.85
Haemoglobin	14	13
Sodium	138	134
Creatinine	76	80
AST	65	14
Albumin	32	34
APACHEII	11	14
SOFA	5	5
NEW	6	7
PaO_2/FiO_2	167	115
HCT	37	39
During the whole hospitalization		
Lymphocyte	1.0	1.2
Haemoglobin	13	12
Sodium	140	138
Creatinine	71	65
ALT	68	30
Albumin	33	34
APACHEII	8	11
SOFA	4	3
NEW	4	4
PaO_2/FiO_2	161	142
HCT	36	36

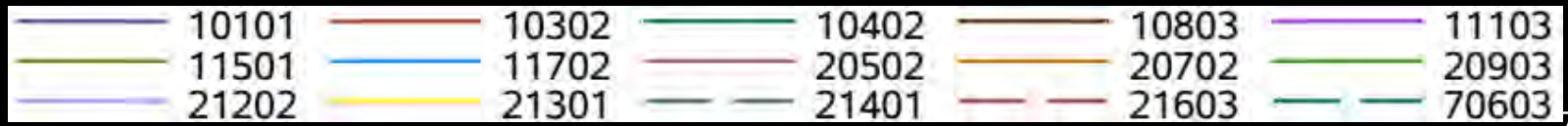
Dynamic changes of body temperature



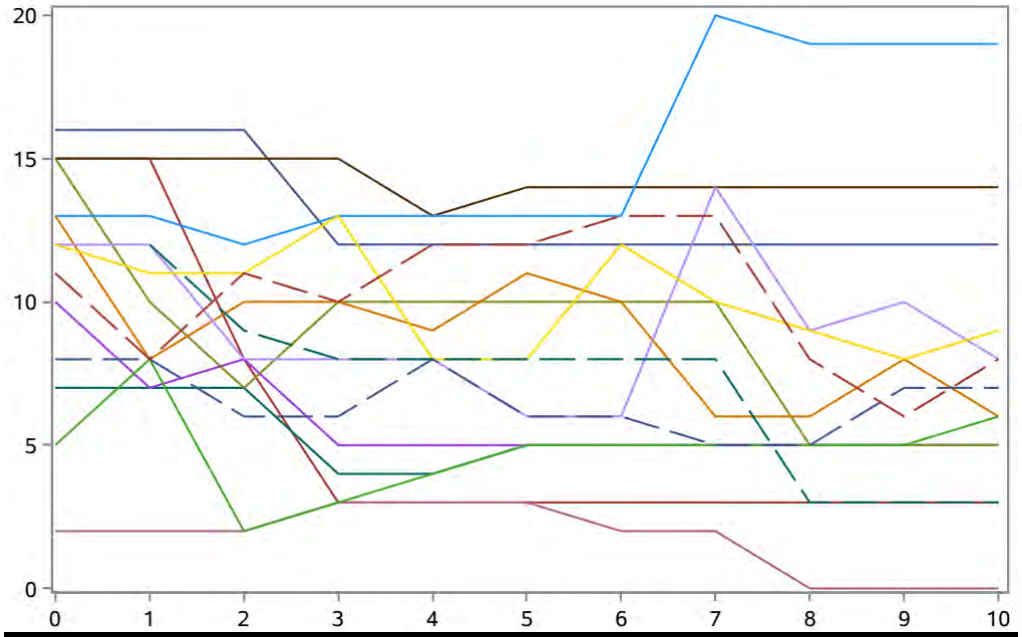


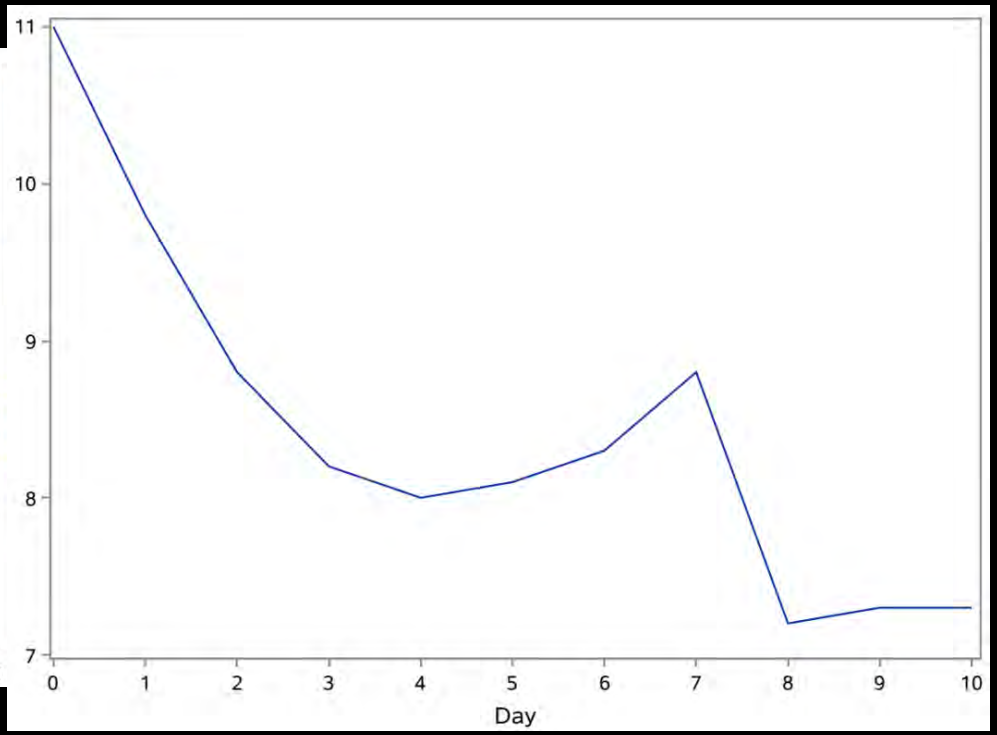
day

ID number



Dynamic changes of APACHE II score



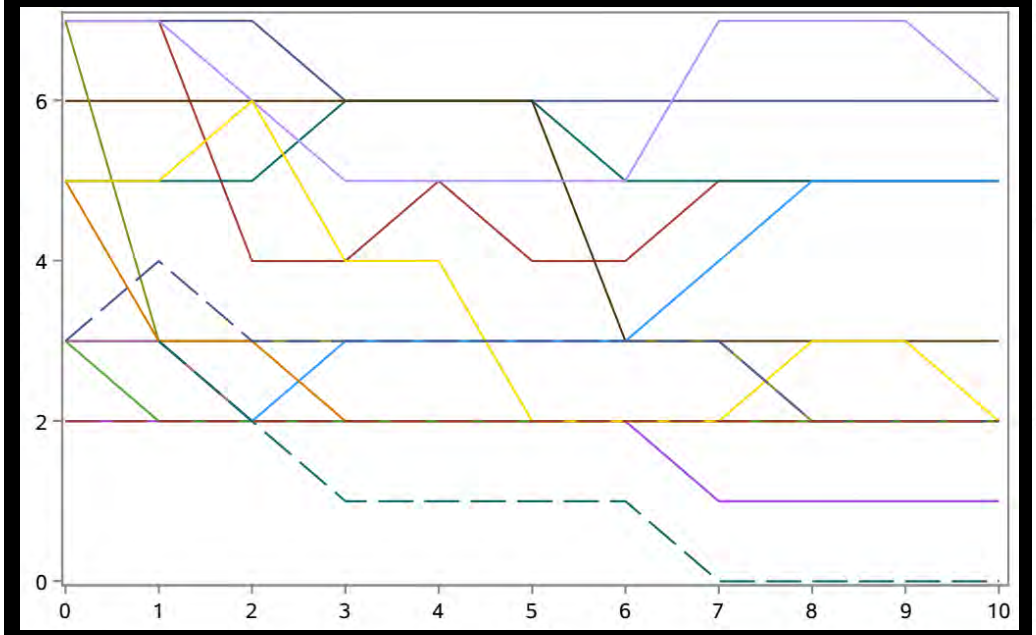


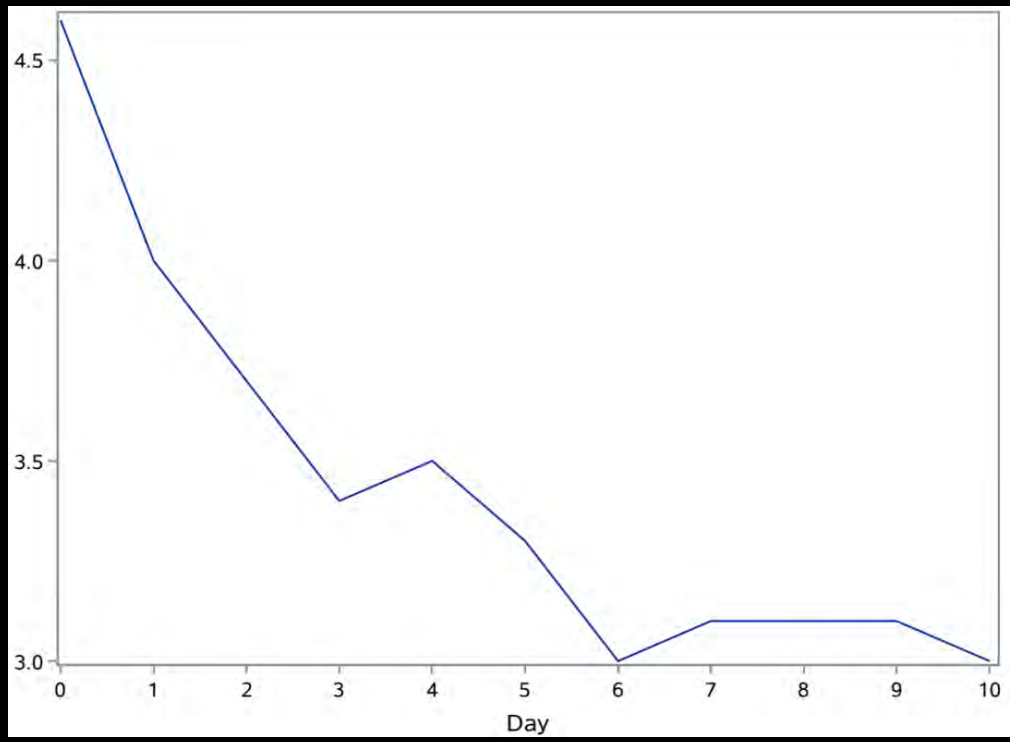
day

ID number

10101 10302 10402 10803 11103
11501 11702 20502 20702 20903
21202 21301 21401 21603 70603

Dynamic changes of SOFA





day

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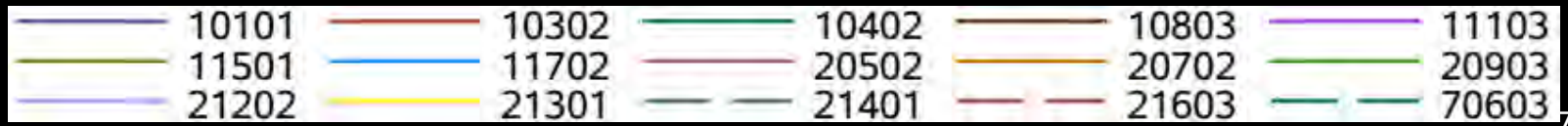
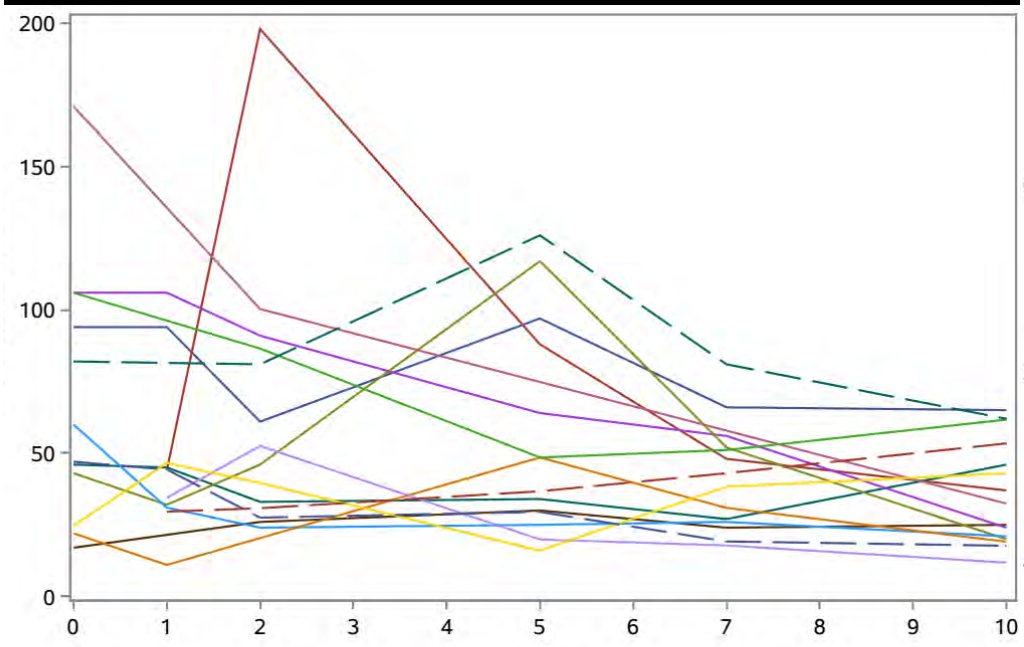
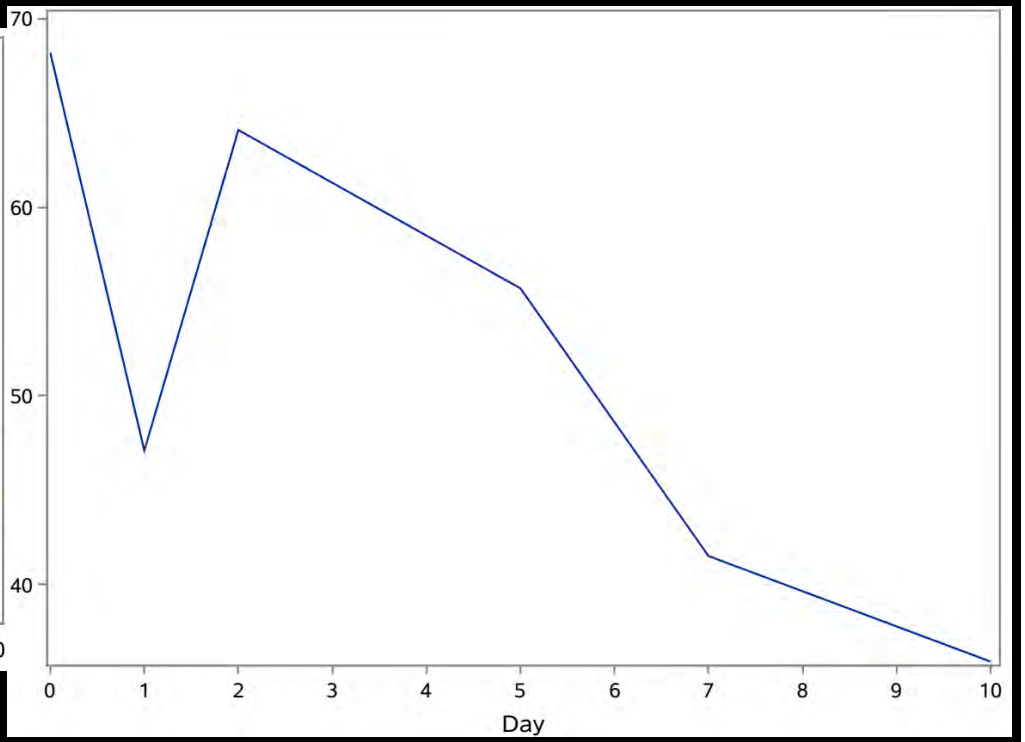


Dynamic changes of aspartate aminotransferase





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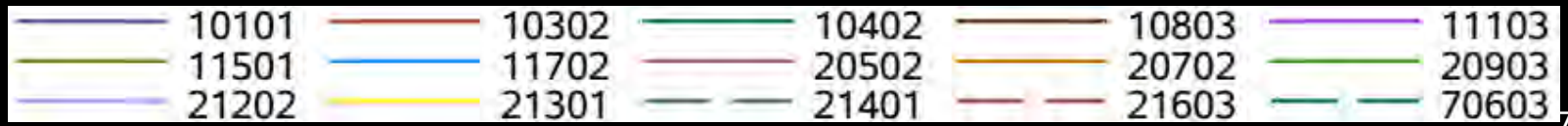
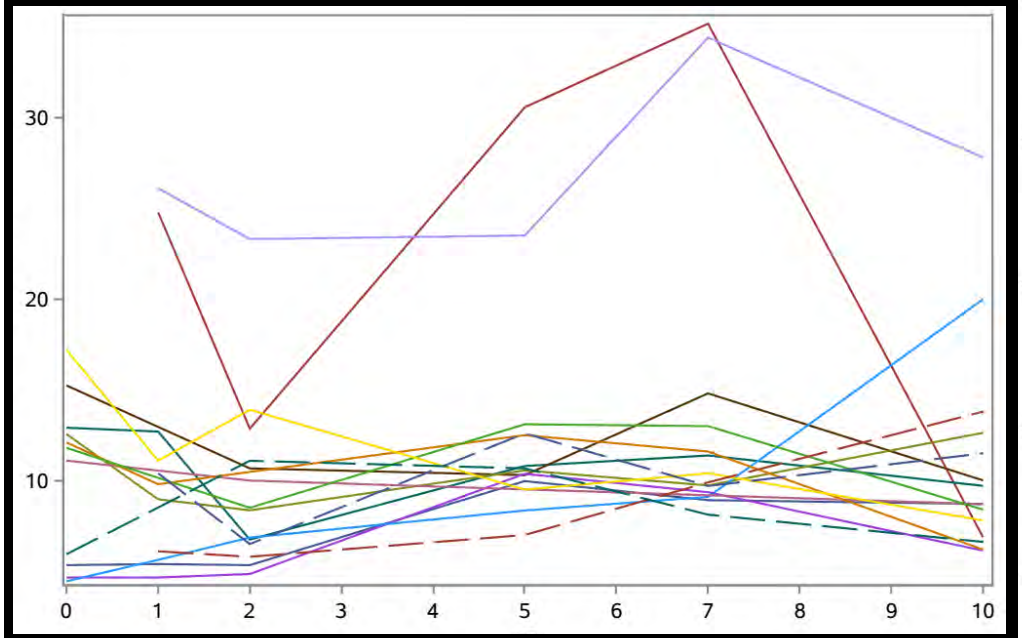
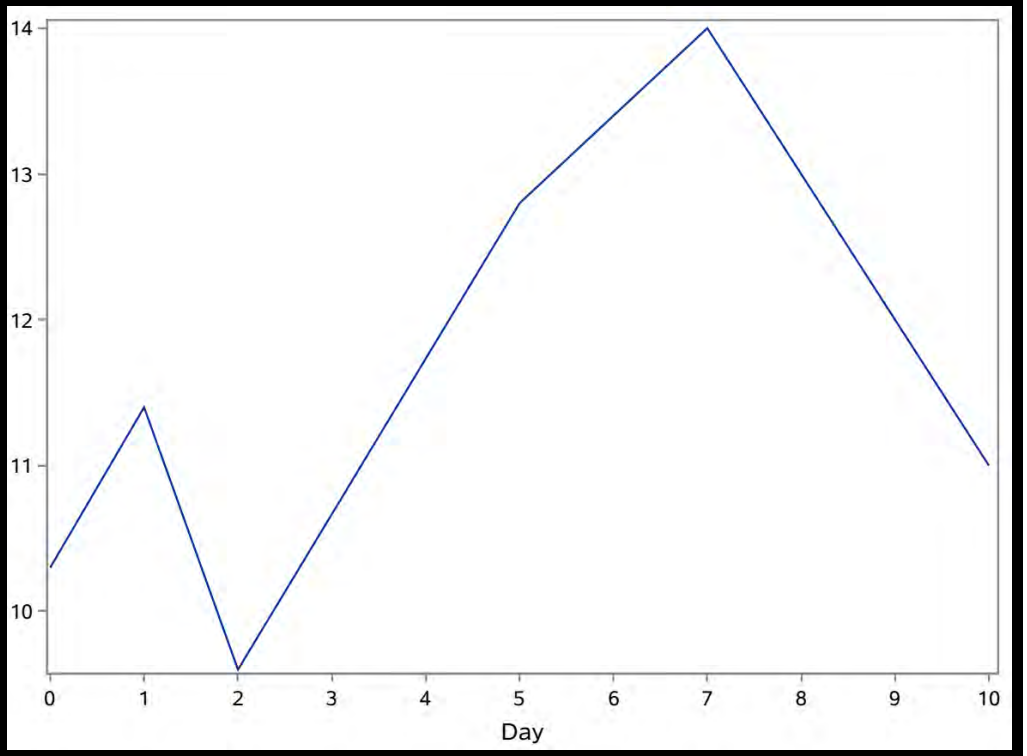


Dynamic changes of total bilirubin





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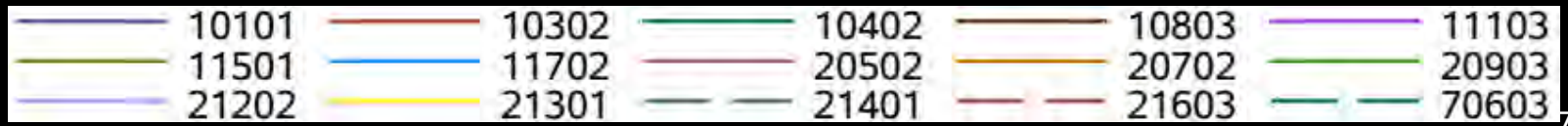
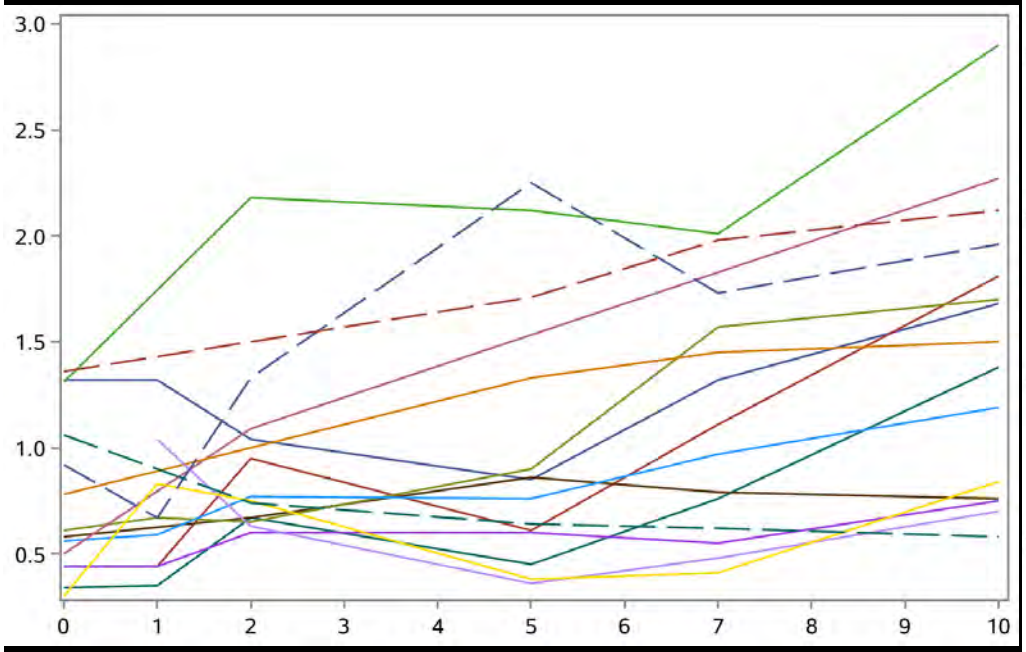
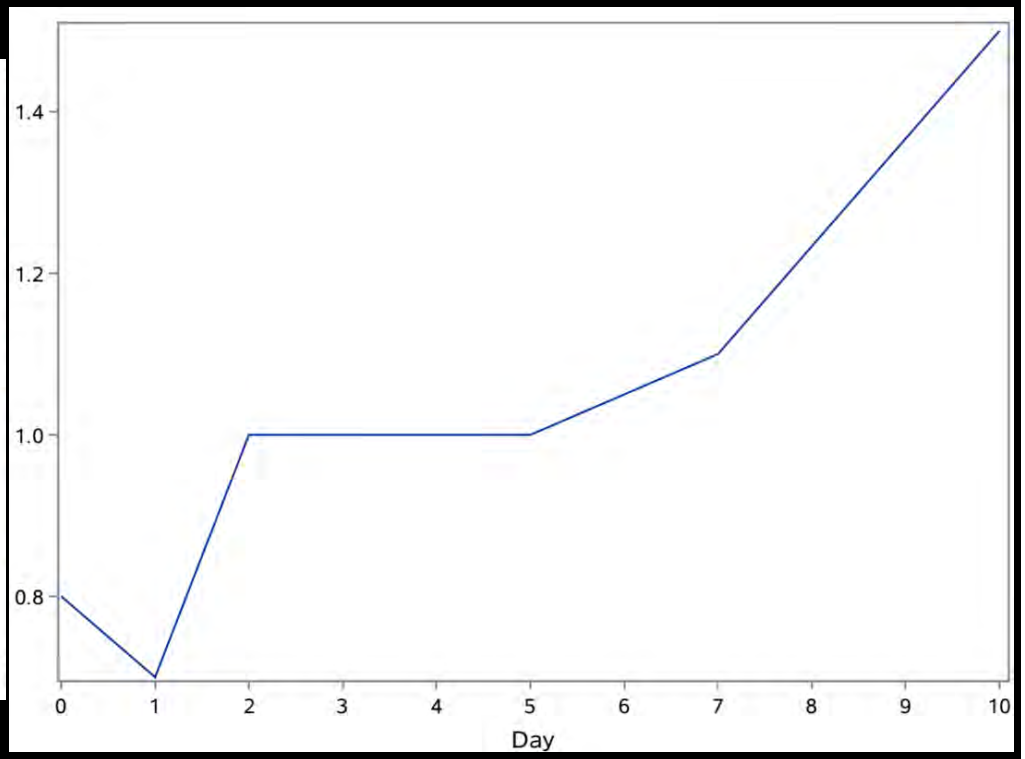


Dynamic changes of lymphocyte count



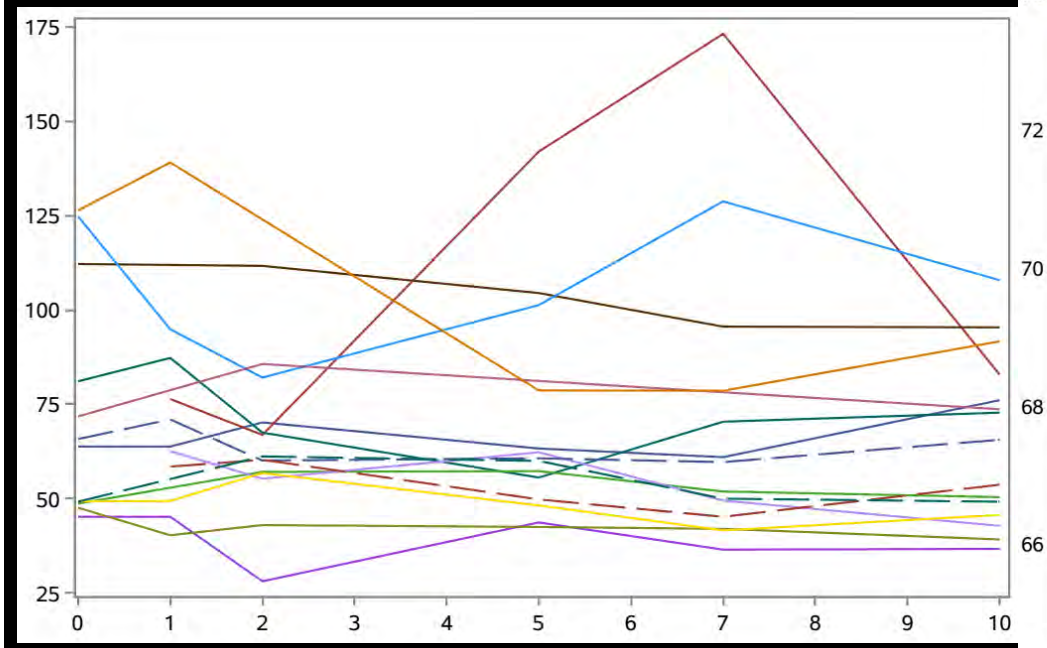


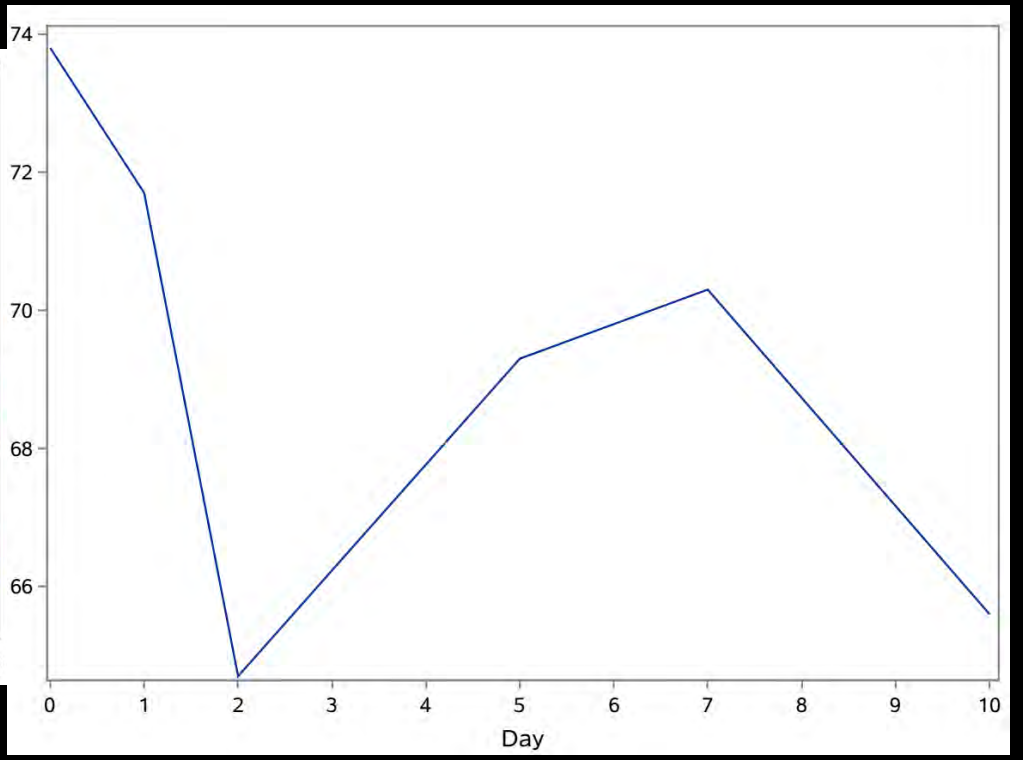
day

ID number

10101 10302 10402 10803 11103
11501 11702 20502 20702 20903
21202 21301 21401 21603 70603

Dynamic changes of serum creatinine





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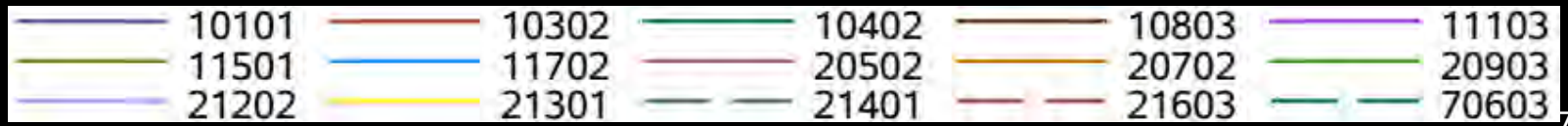
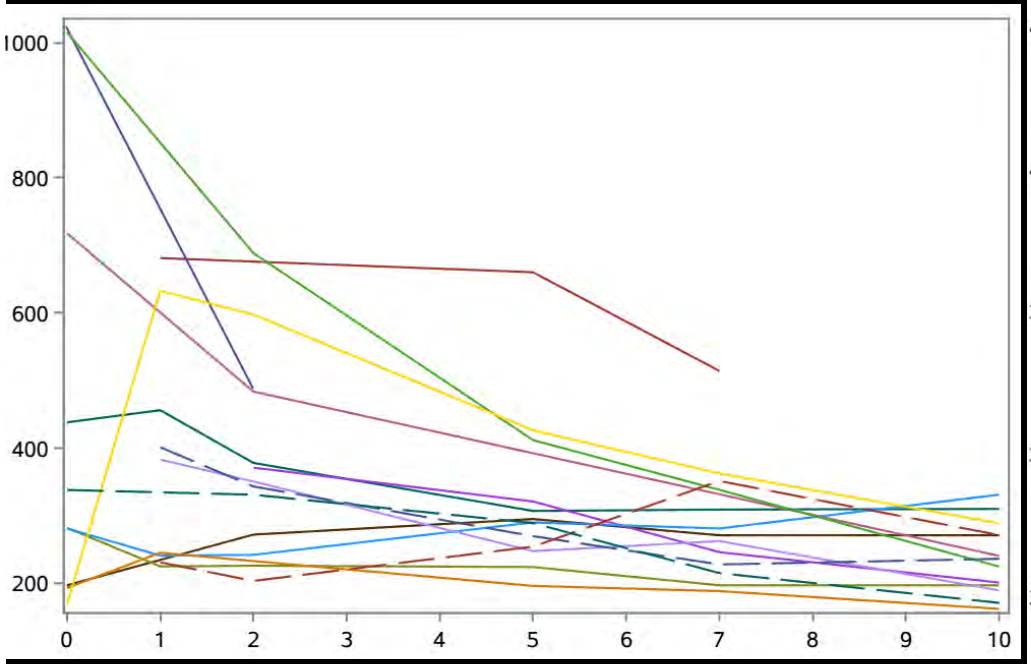
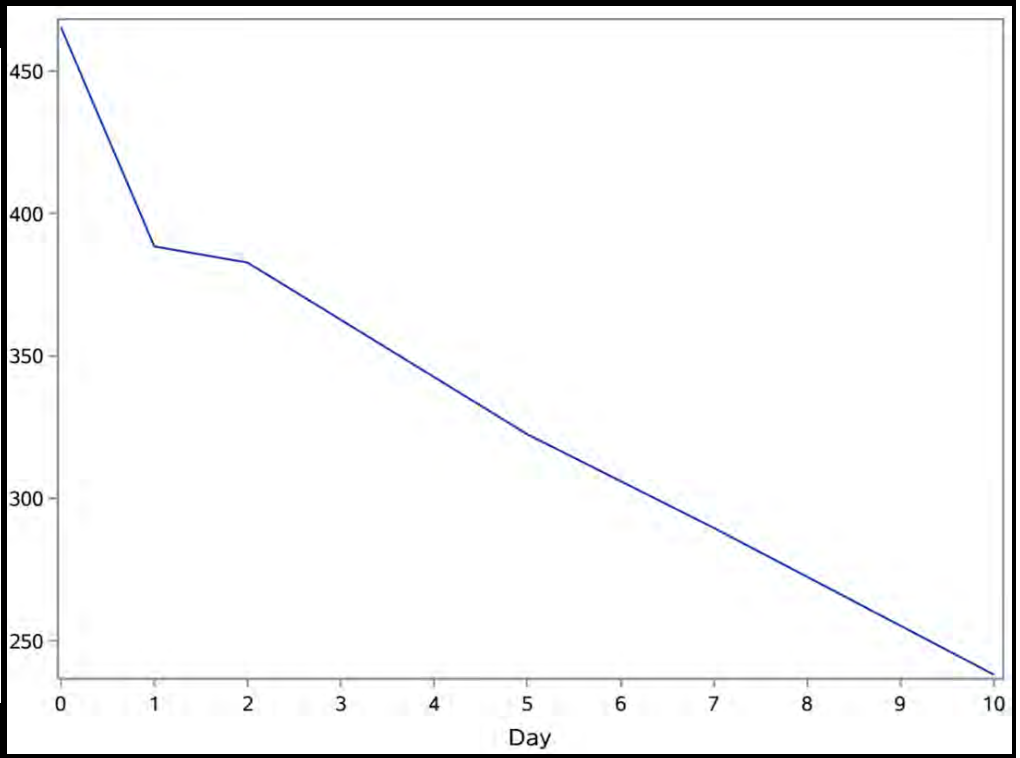


Dynamic changes of lactic dehydrogenase





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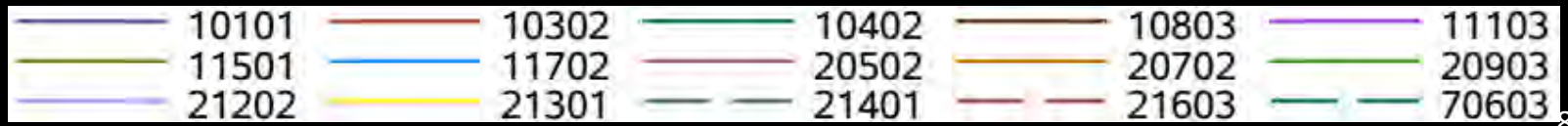
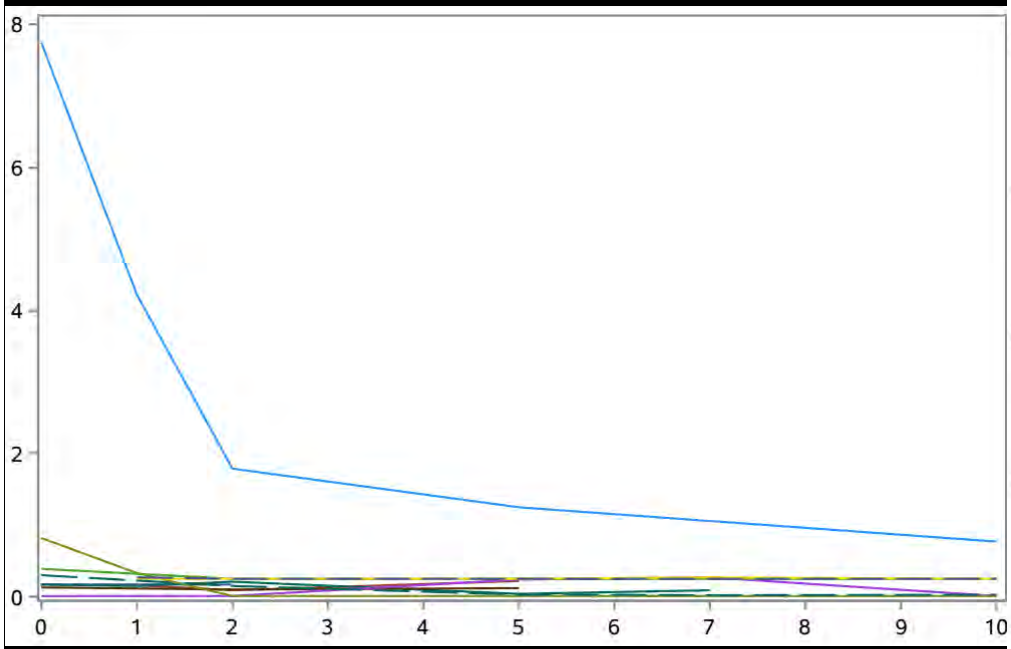
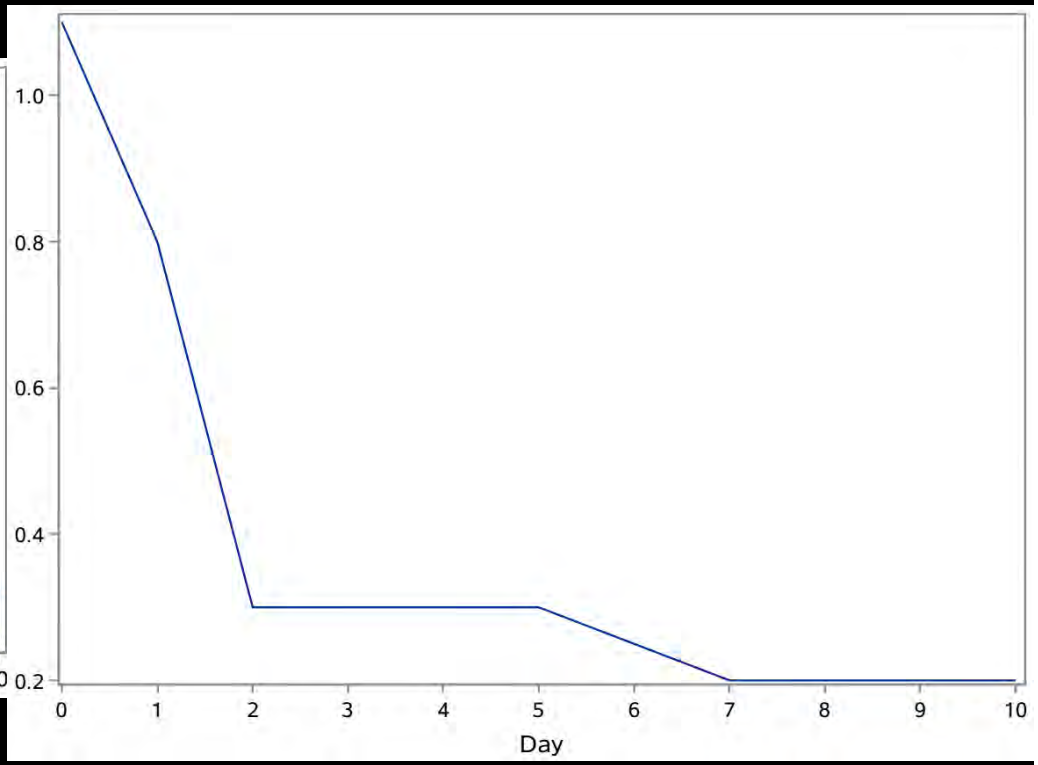


Dynamic changes of procalcitonin





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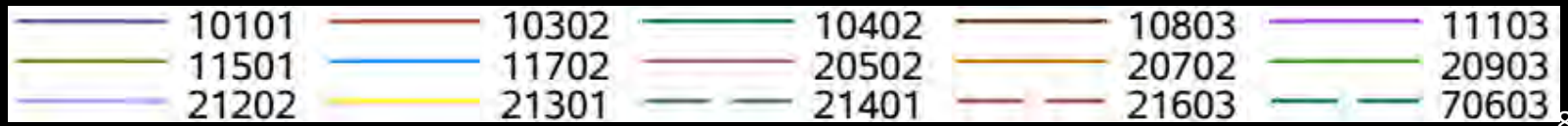
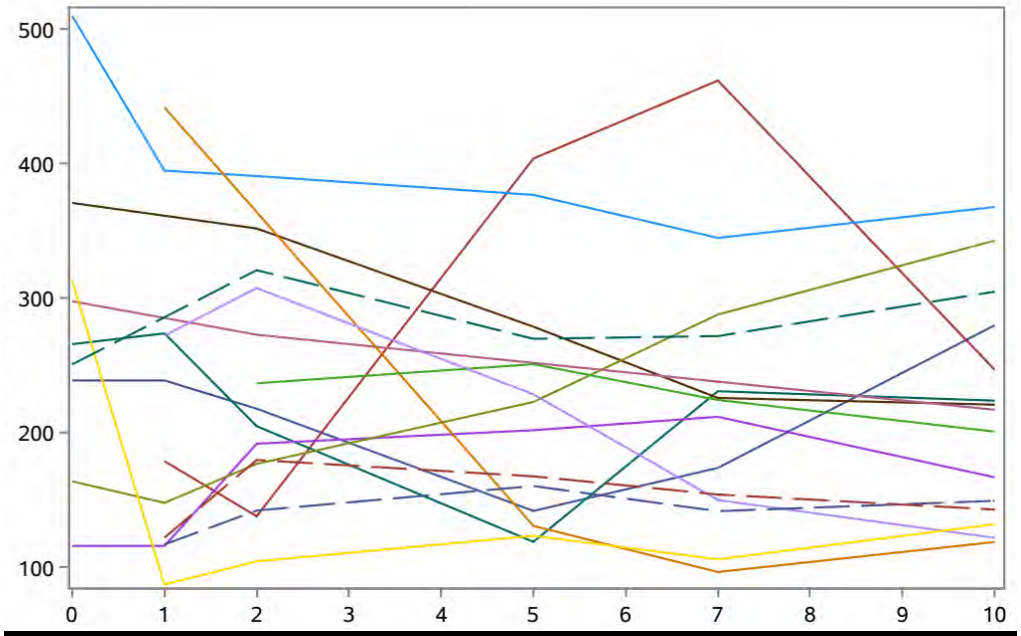
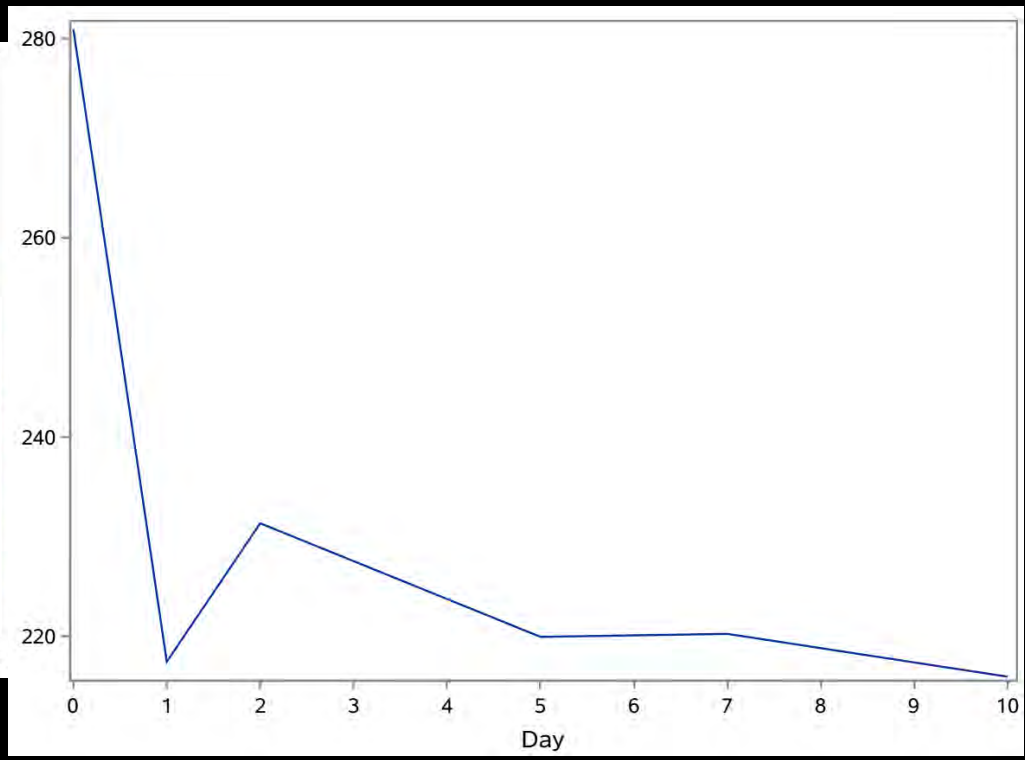


Dynamic changes of serum uric acid





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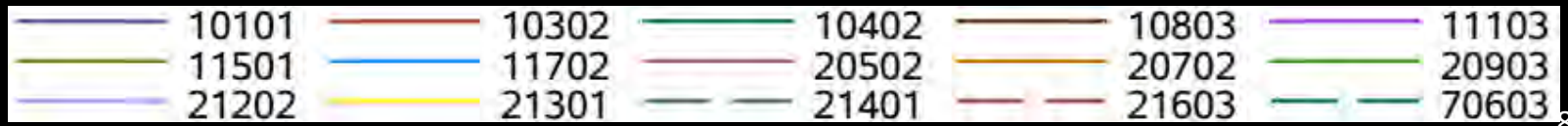

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