One Healthに関する連携シンポジウム
ー ダニ媒介感染症と予防対策ー

症熱性血小板減少症候群（SFTS）の現状（医療編）

国立感染症研究所ウイルス第1部
西條政幸

日時：令和2年2月8日(土)9：00～12：00
会場：東京国際フォーラム B棟7階ホールB7（第1会場）

本日の講演内容

- 流行状況
- 新たな問題・課題
  - ネコやイヌのSFTSウイルス感染
  - ペットからの感染
  - 医療従事者・獣医医療従事者の感染（職業関連感染）
- 治療法開発研究
- ワクチン開発研究

重症熱性血小板減少症候群（SFTS）

ORIGINAL ARTICLE

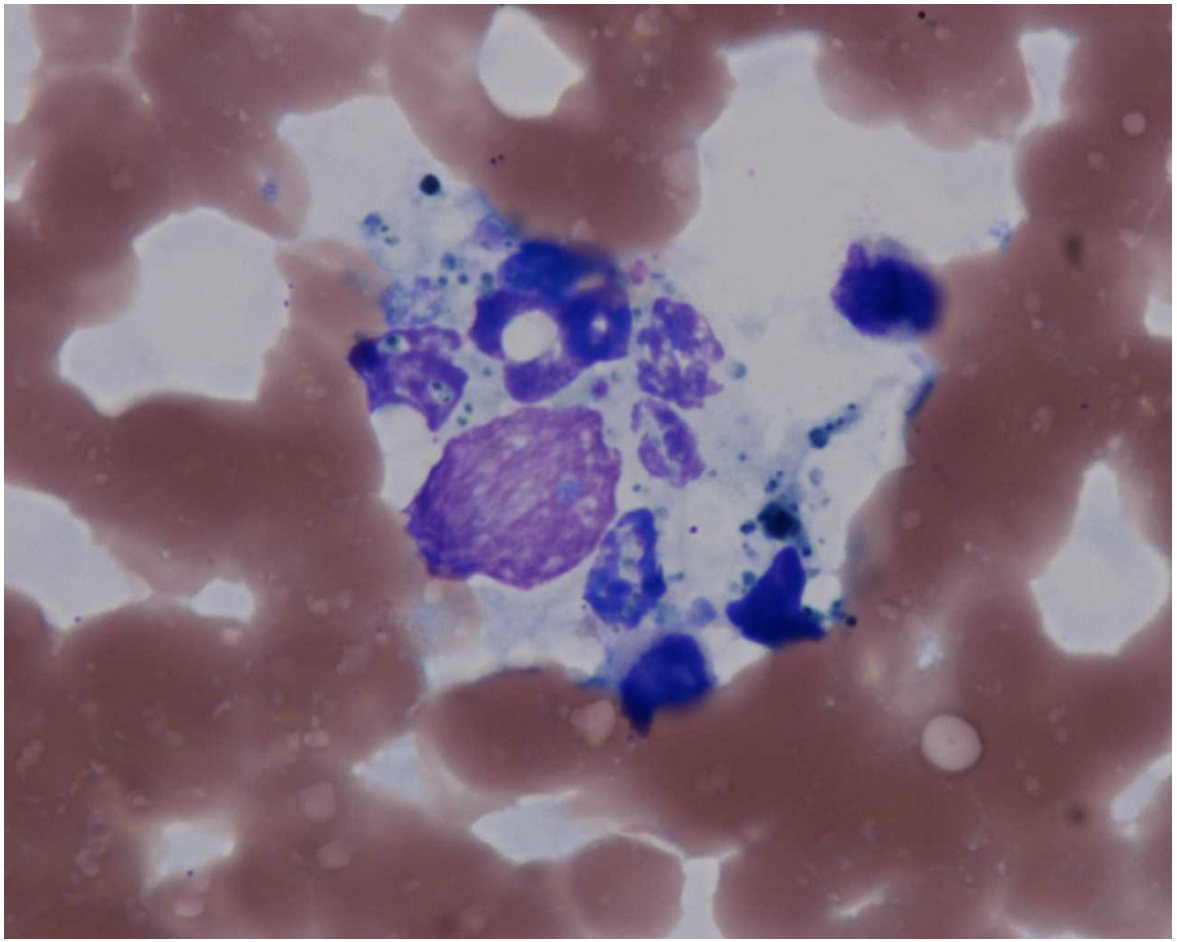
Fever with Thrombocytopenia Associated with a Novel Bunyavirus in China

N ENGL J MED 364;16 NEJM.ORG APRIL 21, 2011

Into the hot zone. Xue-jie Yu (*left*, in blue shirt) looks on as farmers check a dog for ticks; forest-hugging farms (*right*) were hard hit by the emerging virus (*inset*).

2012年11月

- 患者：海外渡航歴のない成人患者
- 時期および場所：2012年秋，山口県
- 症状：発熱，嘔吐，下痢（黒色便）
- 検査所見：白血球数（400 /mm^3）と血小板数（8.9×10^4 /mm^3）が著明に低下していた．また，AST，ALT，LDH，CKの高値が認められた。



骨髄検査所見

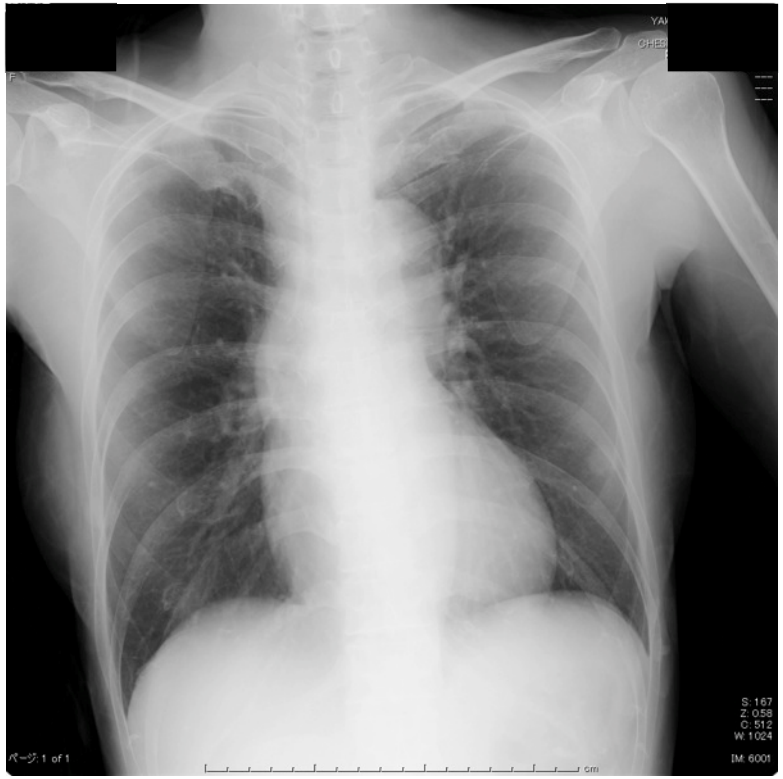
Takahashi et al, JID, 2014

【胸腹部CT】

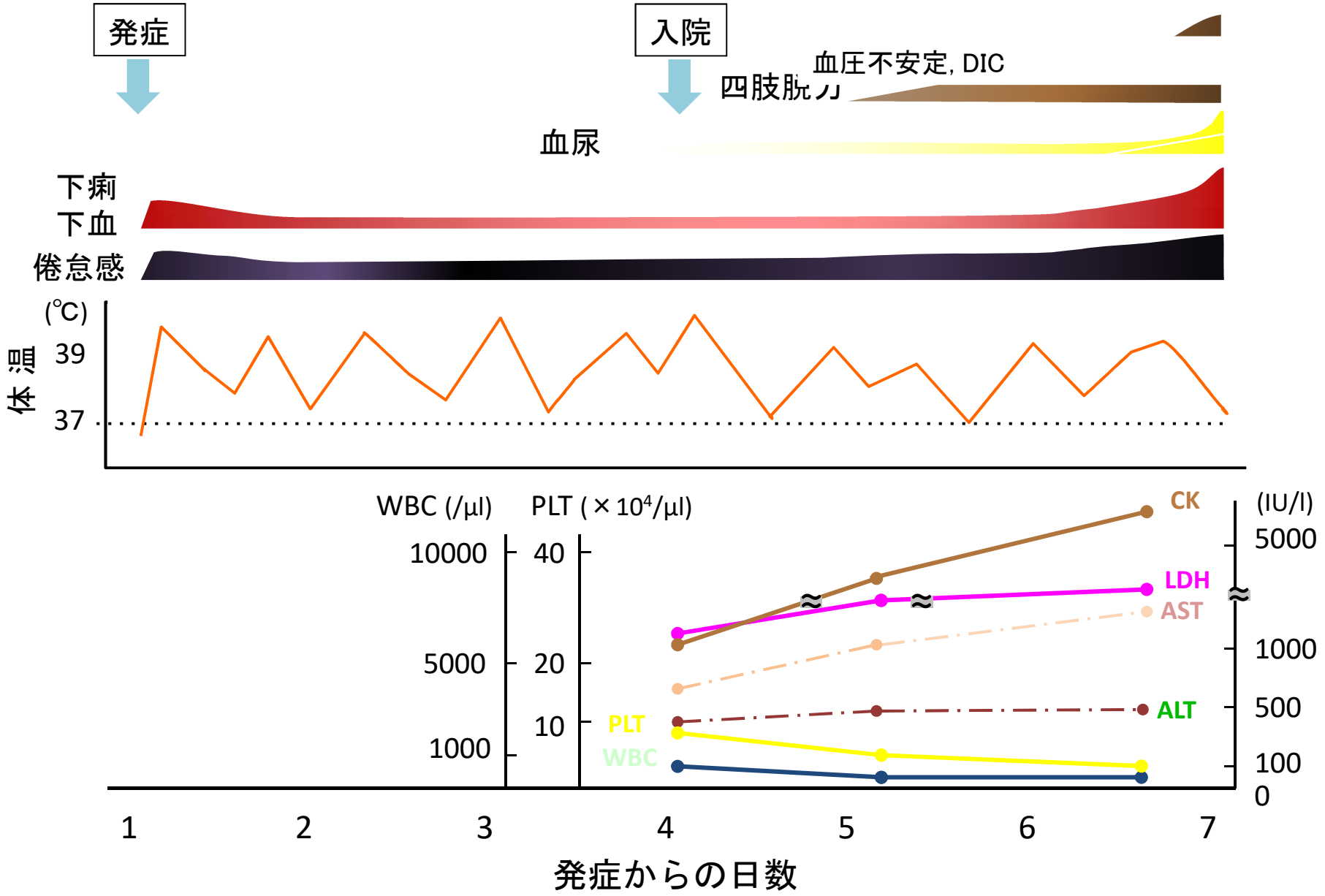
右腋窩リンパ節腫大と両側腎腫大が明らかであるも、他部位のリンパ節腫大や肝脾腫はなく、胸腹水もなかった。

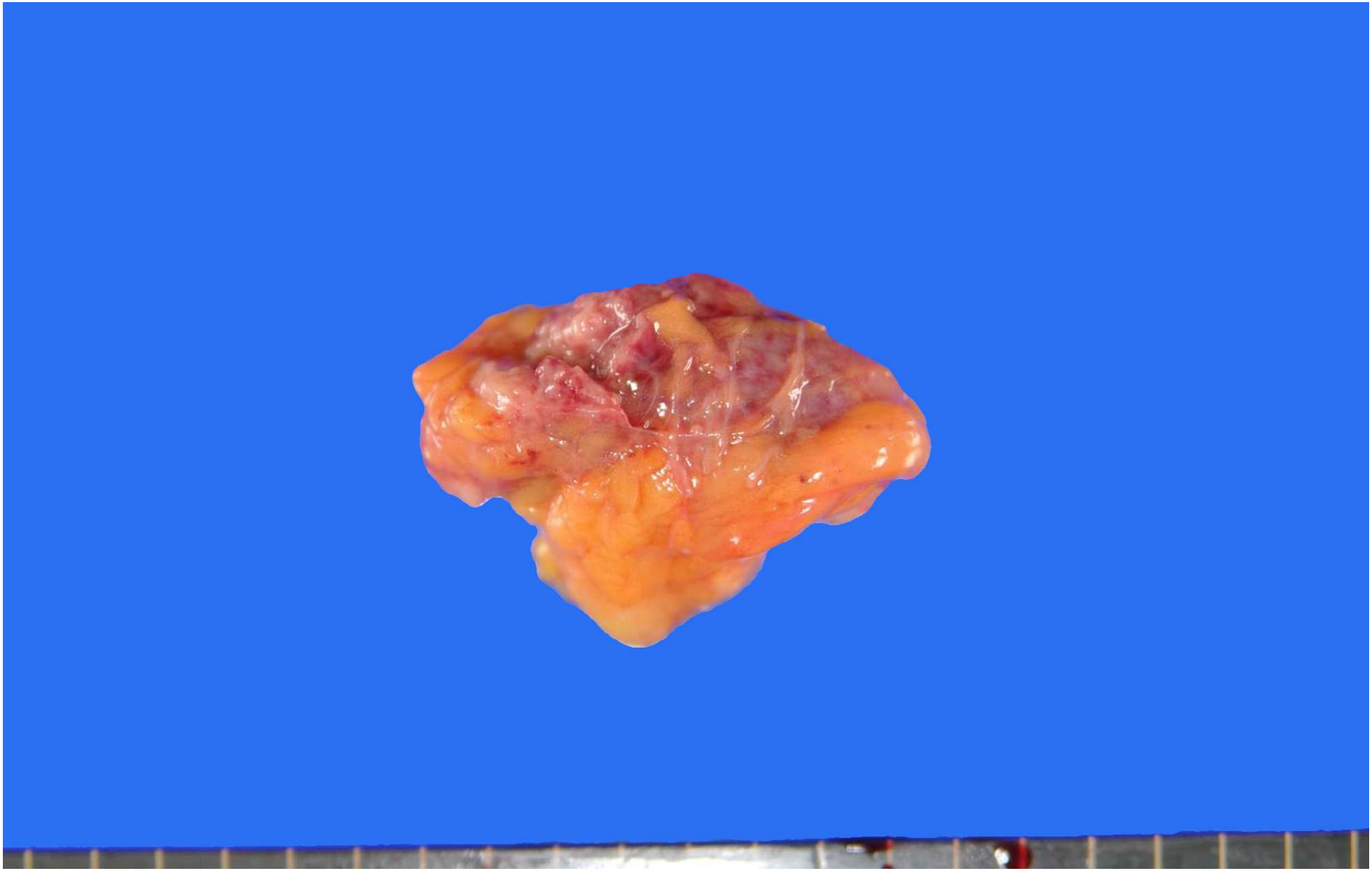
【胸部X線】

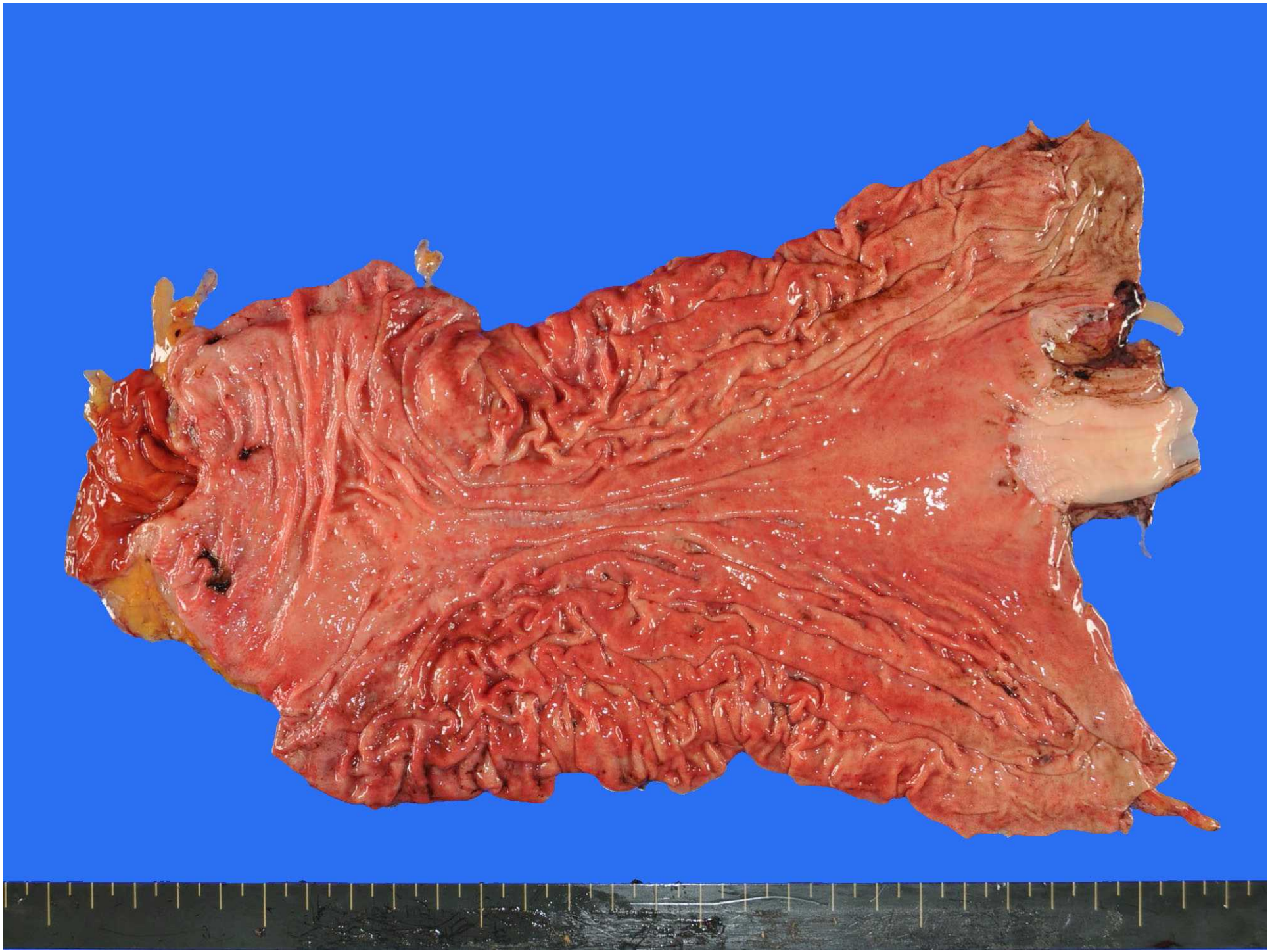
縦隔、肺野に異常所見なし



臨 床 経 過


発症
入院
血圧不安定, DIC
四肢脱力
血尿
下痢
下血
倦怠感
体温
(℃)
39
37
WBC (/μl)
PLT (×10⁴/μl)
10000
5000
1000
40
20
10
CK
LDH
AST
ALT
PLT
WBC
(IU/l)
5000
1000
500
100
0
1
2
3
4
5
6
7
発症からの日数

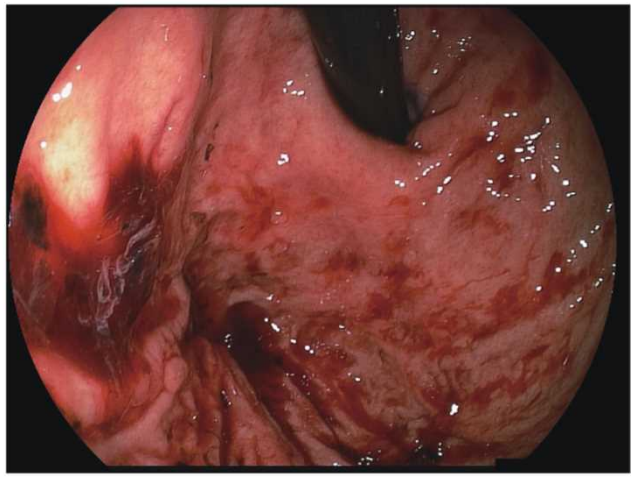




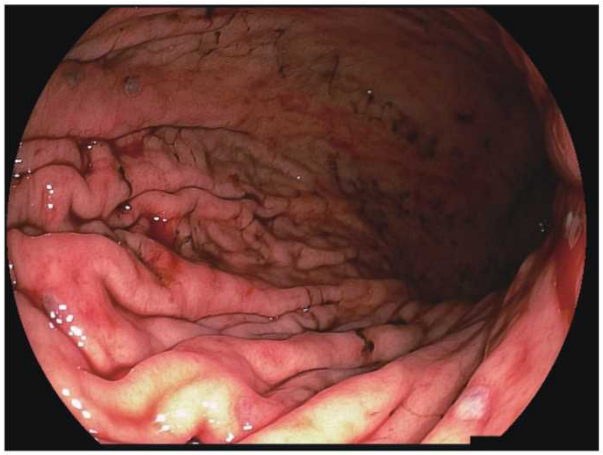
胃内視鏡所見

A)

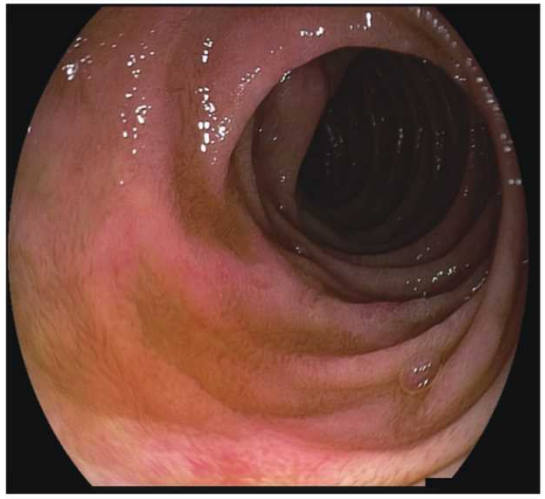
B)



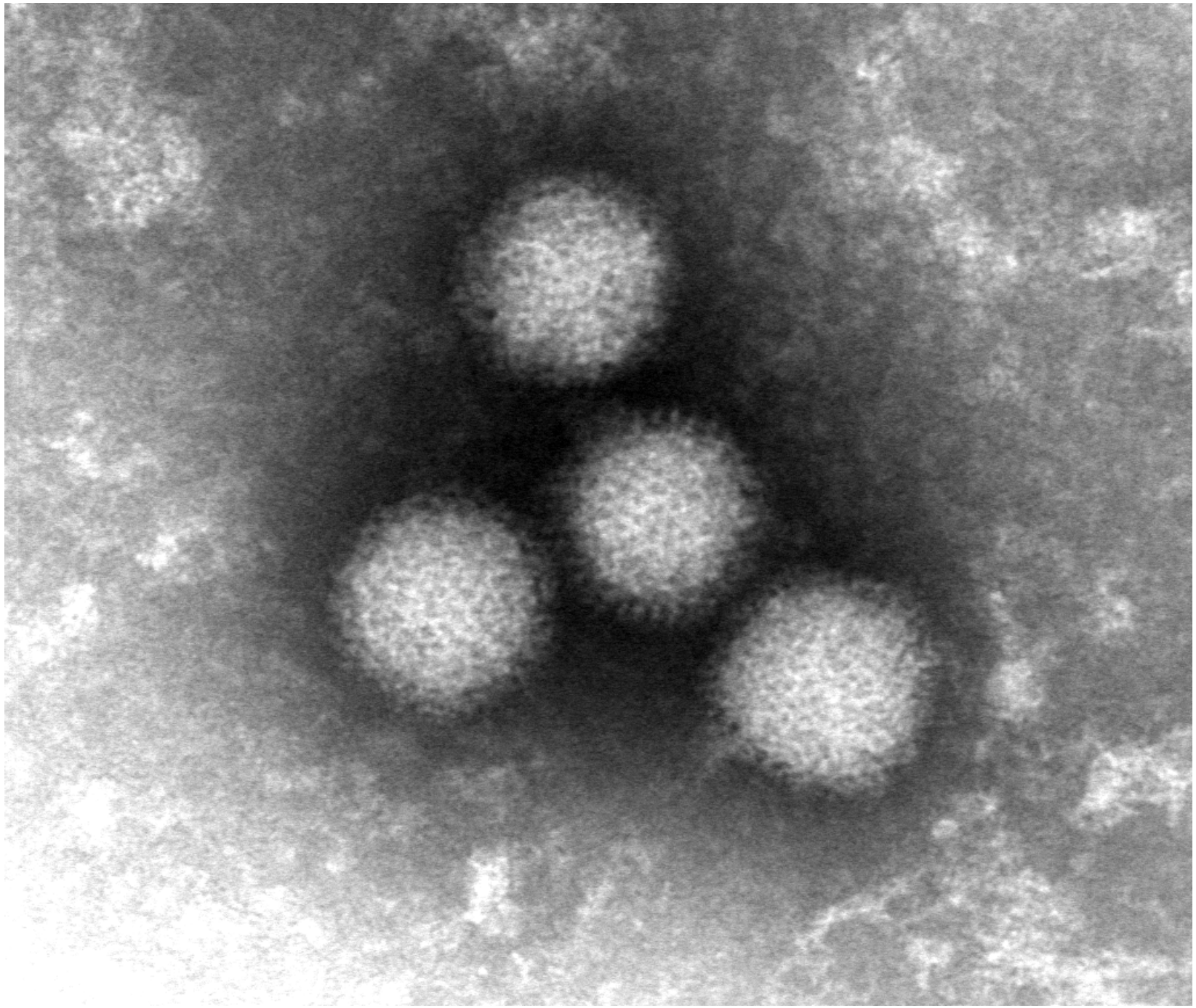
C)



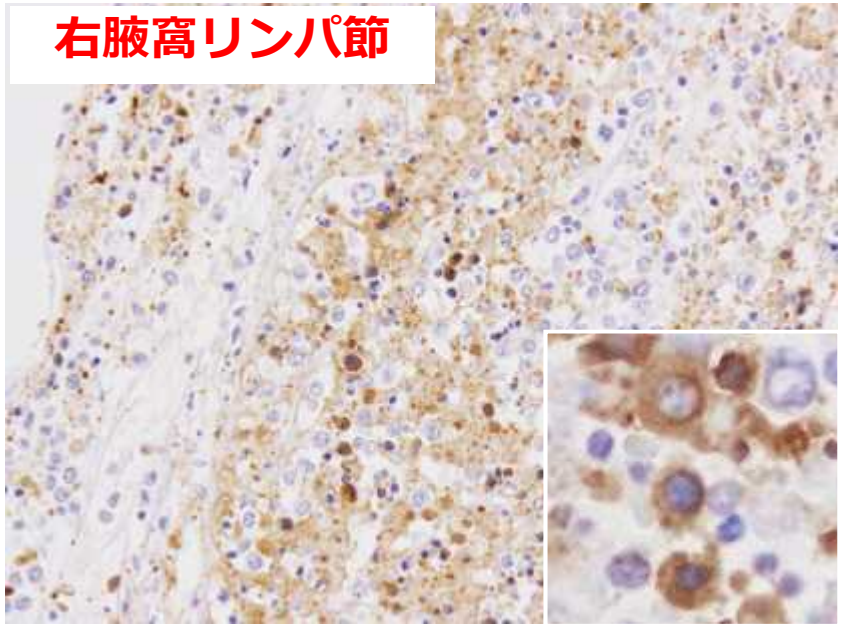
D)

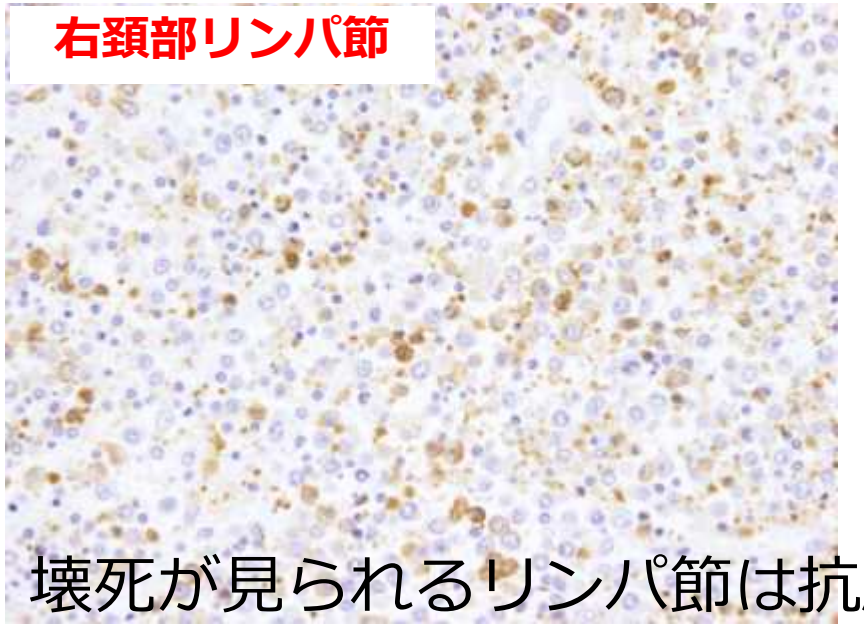


土肥病院（広島県）・金行祥造先生



SFTSV-NP抗原の検出　(免疫組織化学)



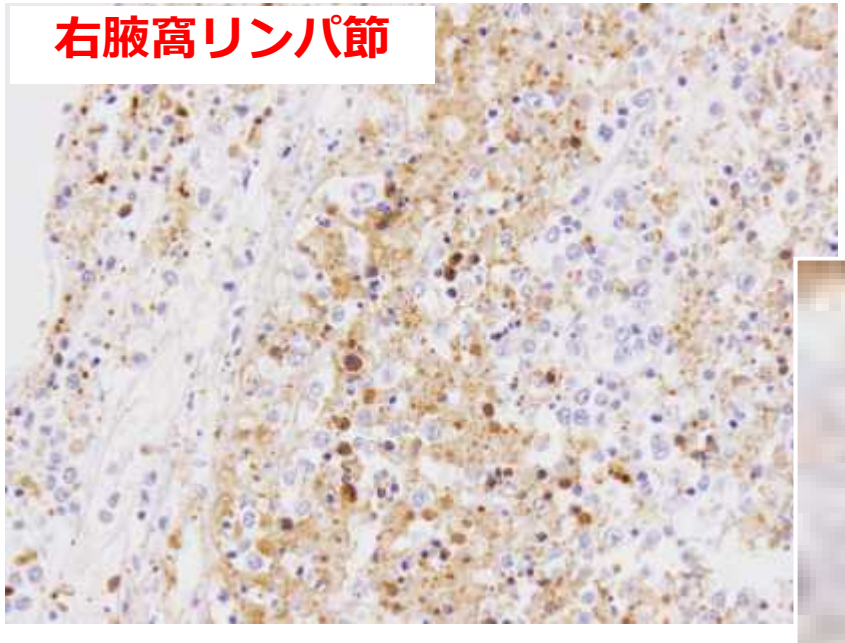


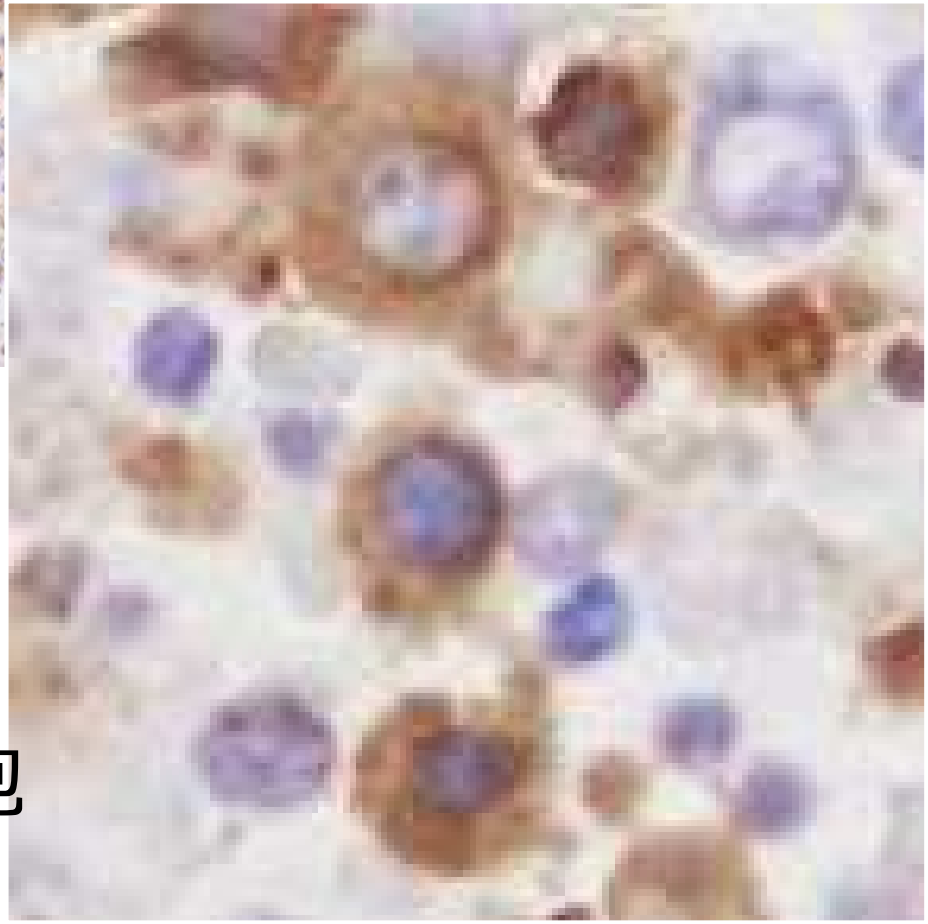
壊死が見られるリンパ節は抗原陽

sample	SFTSV NP
右腋窩リンパ節	+++
右頚部リンパ節	+++
肝門部リンパ節	-
縦隔リンパ節	-
肺門リンパ節	-

大型リンパ球様細胞の浸潤と血球貪食像は抗原（ー）のリンパ節でも見られた。

SFTSV-NP抗原の検出　(免疫組織化学)

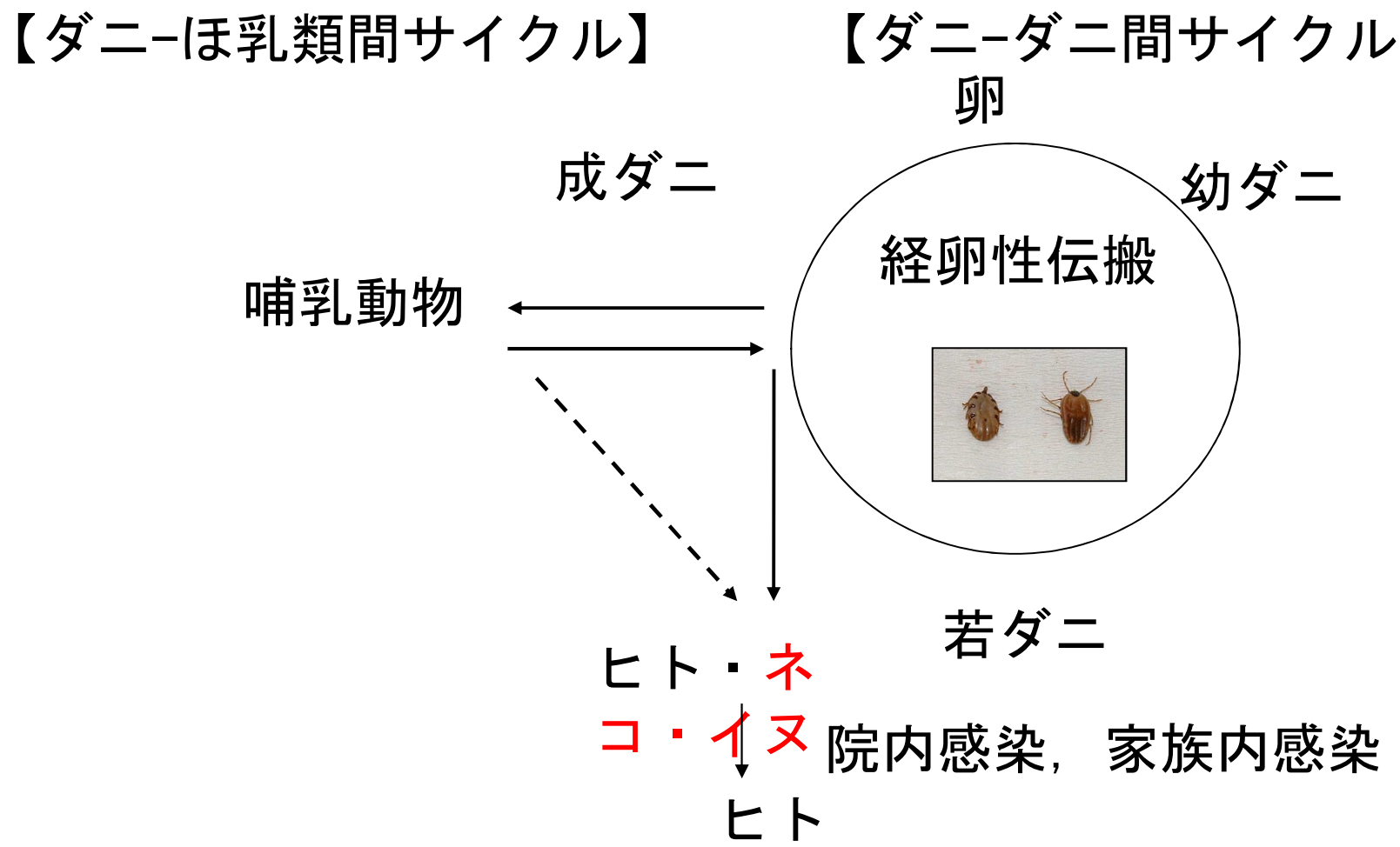




大型リンパ球様細胞

Geographical distribution

SFTSVの感染経路


【ダニ–ほ乳類間サイクル】
【ダニ–ダニ間サイクル】
卵
成ダニ
幼ダニ
経卵性伝搬
哺乳動物
若ダニ
ヒト・ネコ・イヌ
院内感染，家族内感染
ヒト

A)フタトゲチマダニ

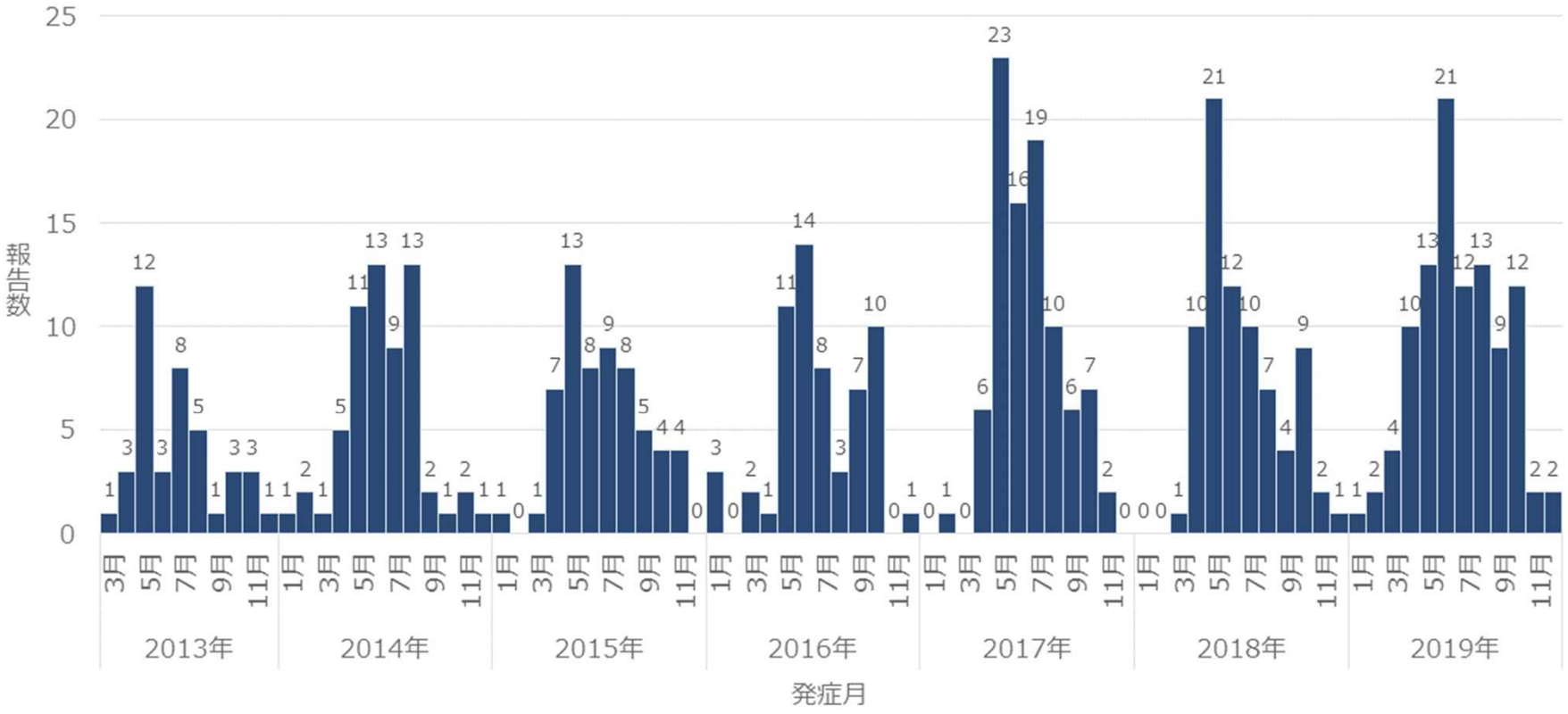
B) タカサゴキララマダニ

SFTS報告数

図1．2013年3月4日以降に届出られたSFTS症例の発症時期（n=489, 2019年12月25日現在）

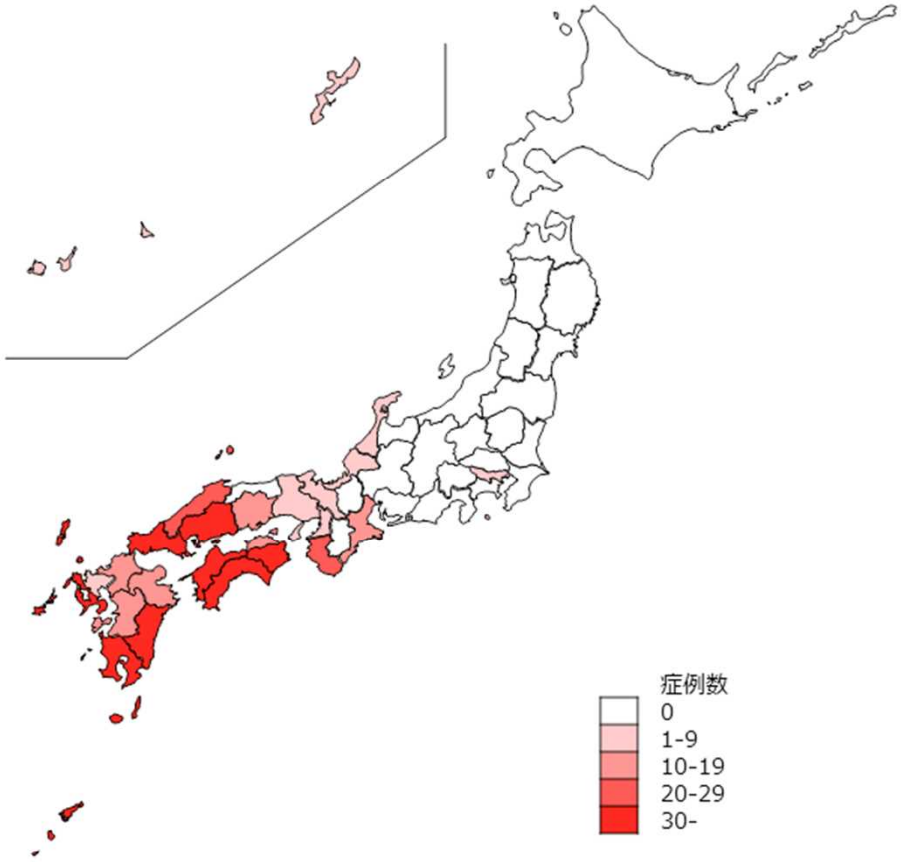
※届出対象となる日時以前の発症例8例を除く

（SFTSは2013年3月4日に感染症法で全数把握対象疾患である4類感染症に指定された）



SFTS患者届出地域

図2．SFTS症例の**届出地域**（n=497, 2019年12月25日現在）



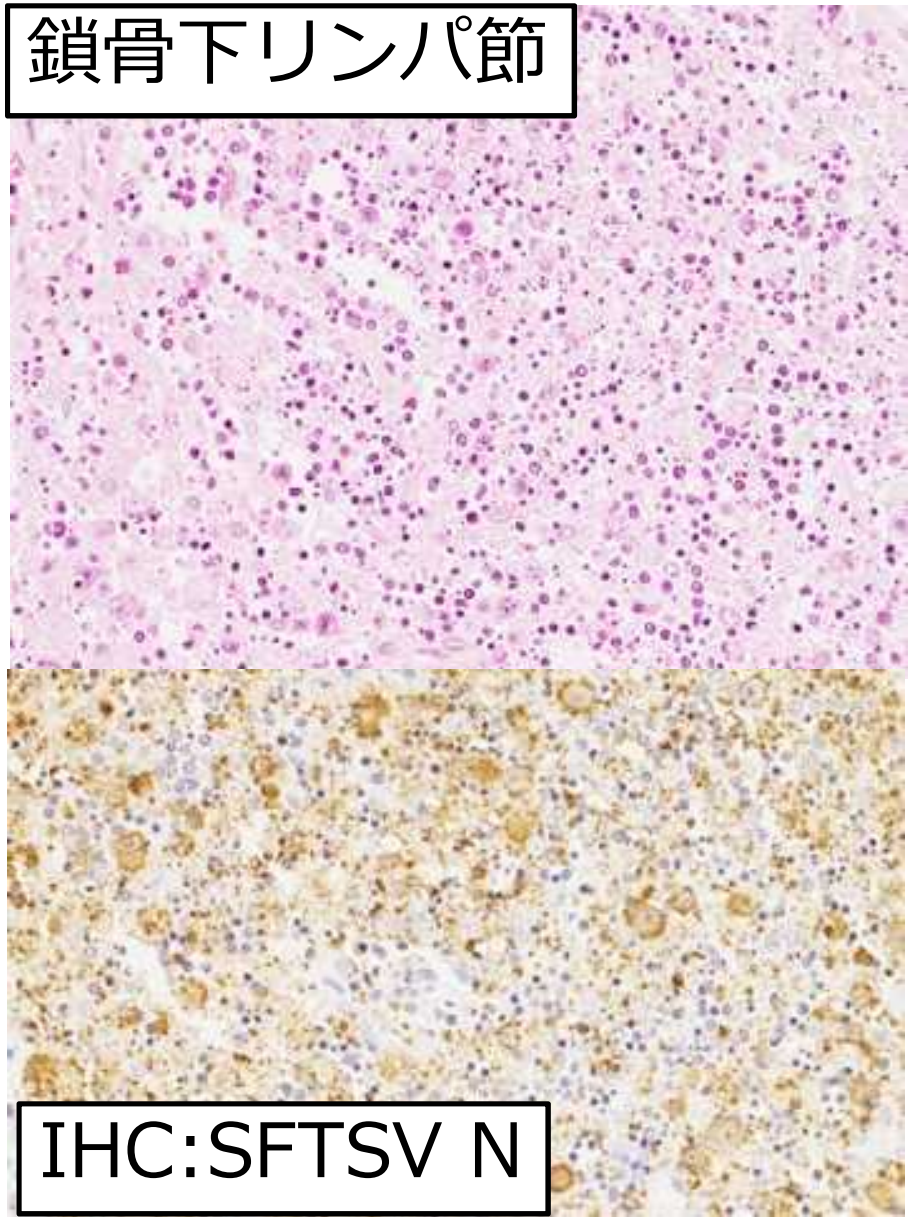
届出都道府県	症例数
東京都	1
石川県	2
福井県	2
三重県	12
京都府	6
大阪府	2
兵庫県	4
和歌山県	20
島根県	21
岡山県	10
広島県	42
山口県	48
徳島県	34
香川県	10
愛媛県	31
高知県	43
福岡県	18
佐賀県	6
長崎県	34
熊本県	15
大分県	19
宮崎県	69
鹿児島県	47
沖縄県	1

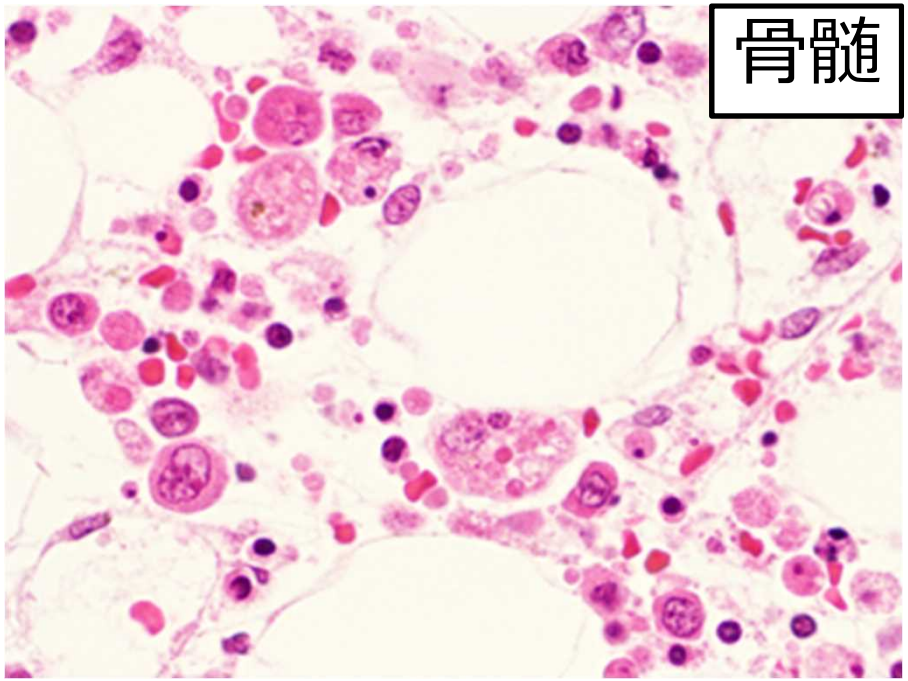
新しい知見

- SFTS in cats
- SFTS in dogs
- Cat-bite associated SFTS
- Dog-associated SFTS

獣医師等の感染事例が発生している.

【症例】ネコ咬傷後に高熱、白血球減少、血小板減少、肝酵素上昇を認め発症10日で死亡した50代女性（西日本在住）





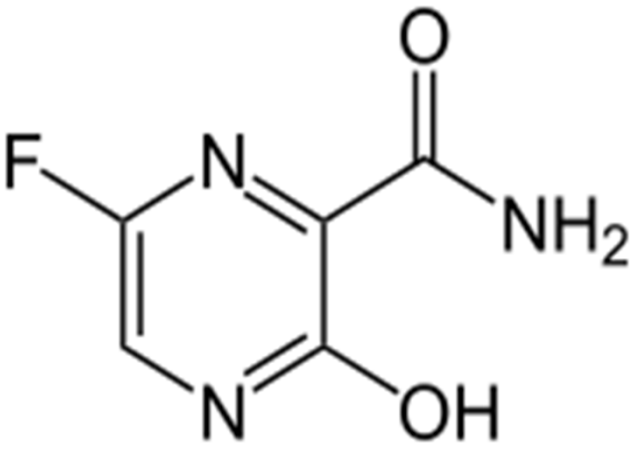
ネコに咬まれて感染したSFTS
（世界で初めての報告）

病理所見がSFTSを考える糸口になり、ネコからヒトへSFTSVが直接感染することが判明した

新たな問題

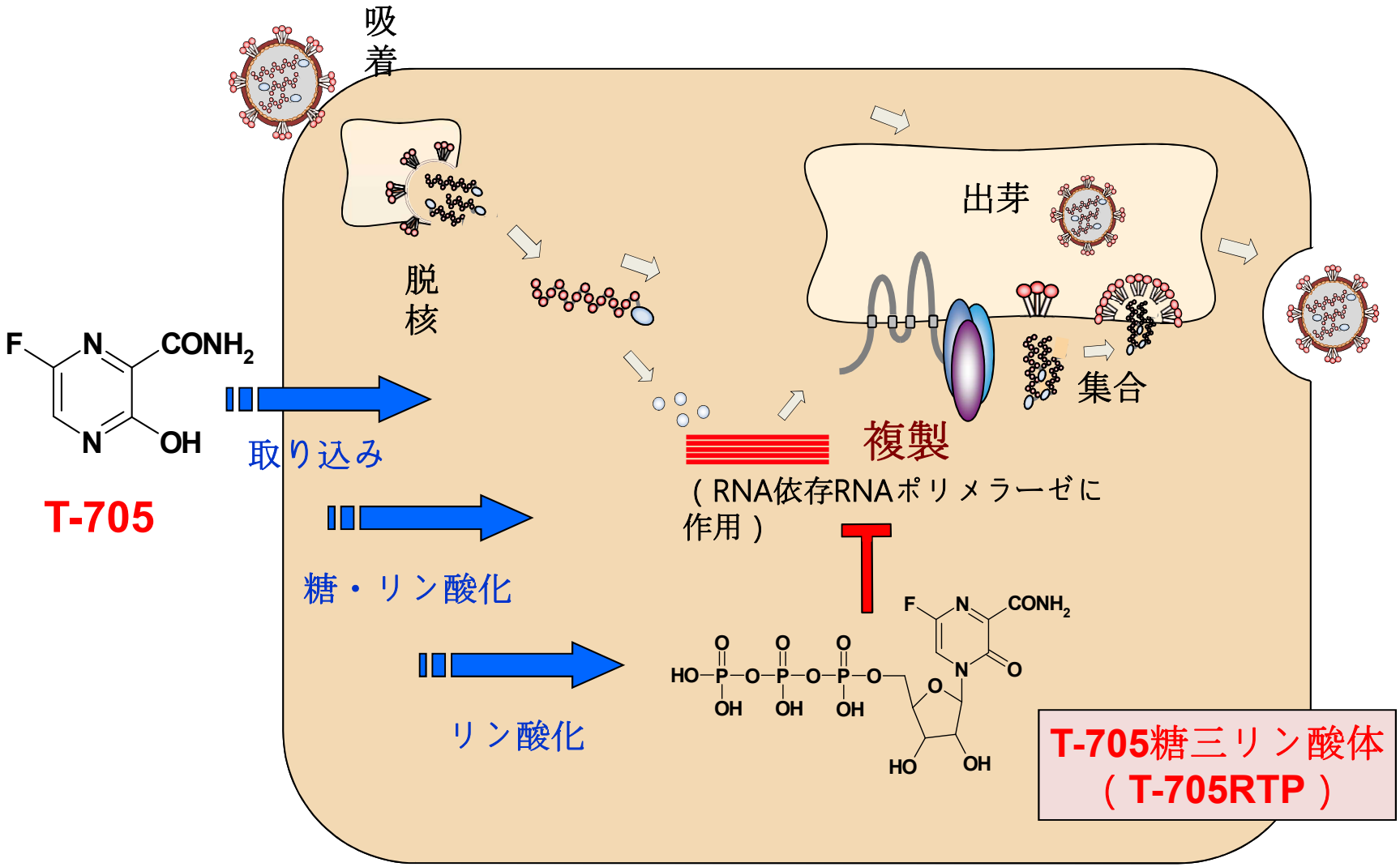
- ヒトからヒト感染
  - 患者に直接触れる経路での感染（院内感染を含む）
- 動物からヒトへの感染
  - イヌからの感染
  - ネコからの感染
- 院内感染
  - 患者から医療従事者
  - ペットから獣医医療関係者（獣医師，獣医看護師）

T-705
(Favipiravir)



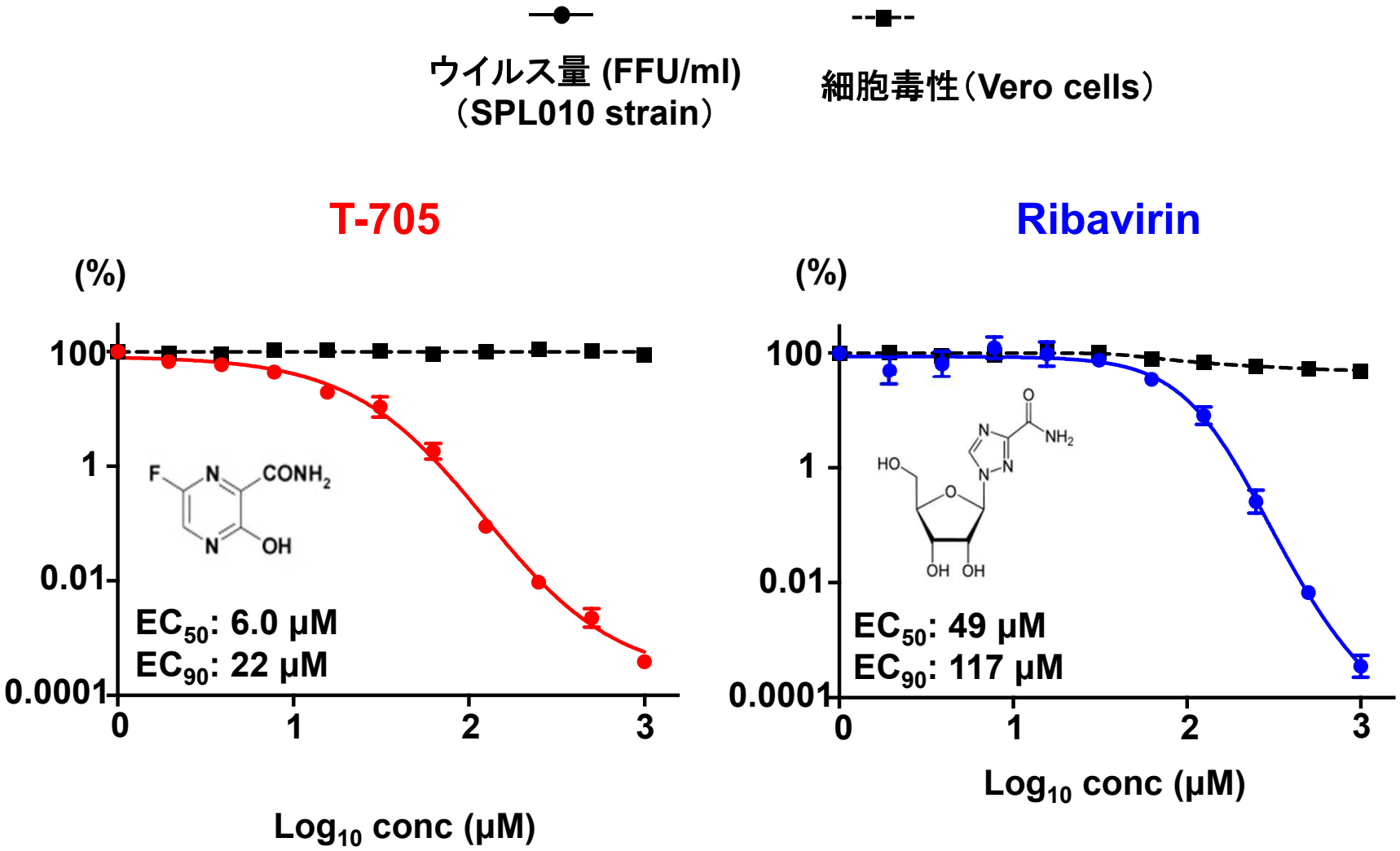
$C_5H_4FN_3O_2$

T-705 の作用機序



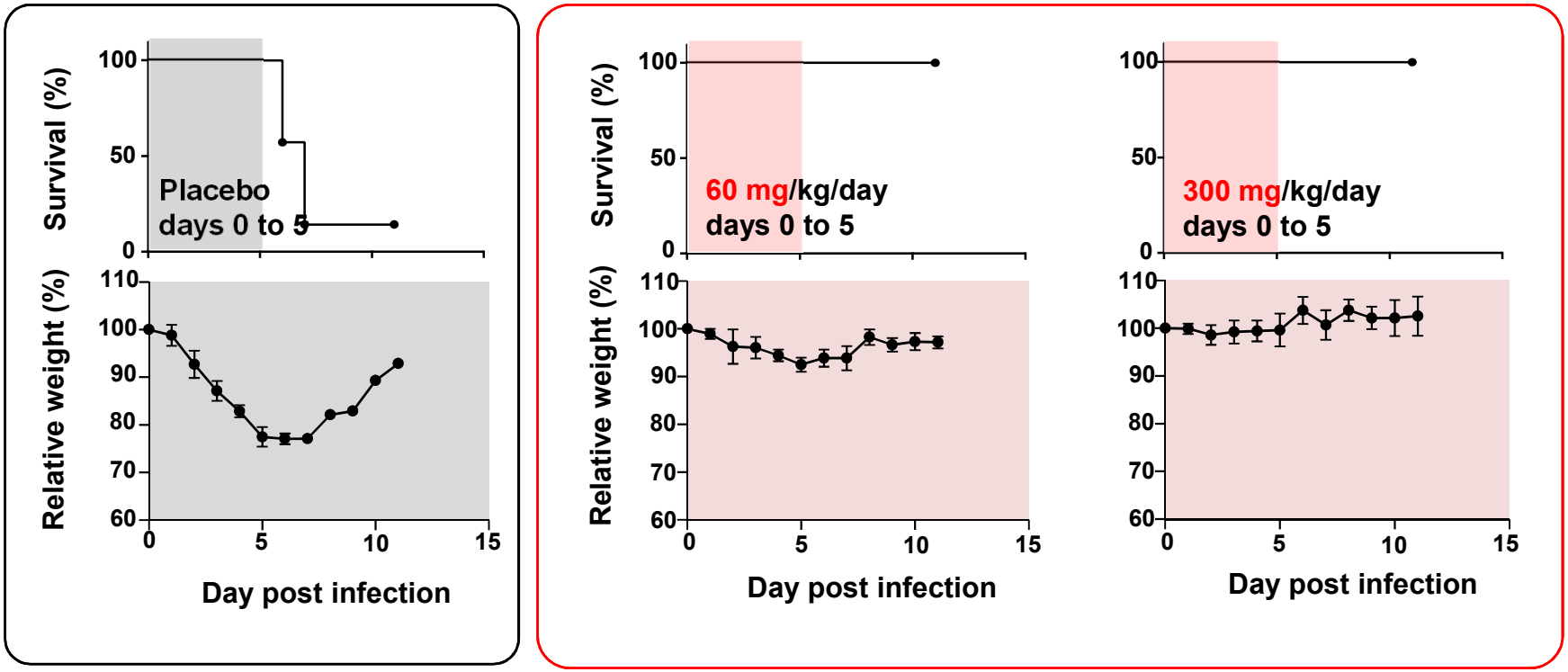
Antiviral Res.　2009より改変

T-705とリバビリンの SFTSウイルスに対する増殖抑制効果

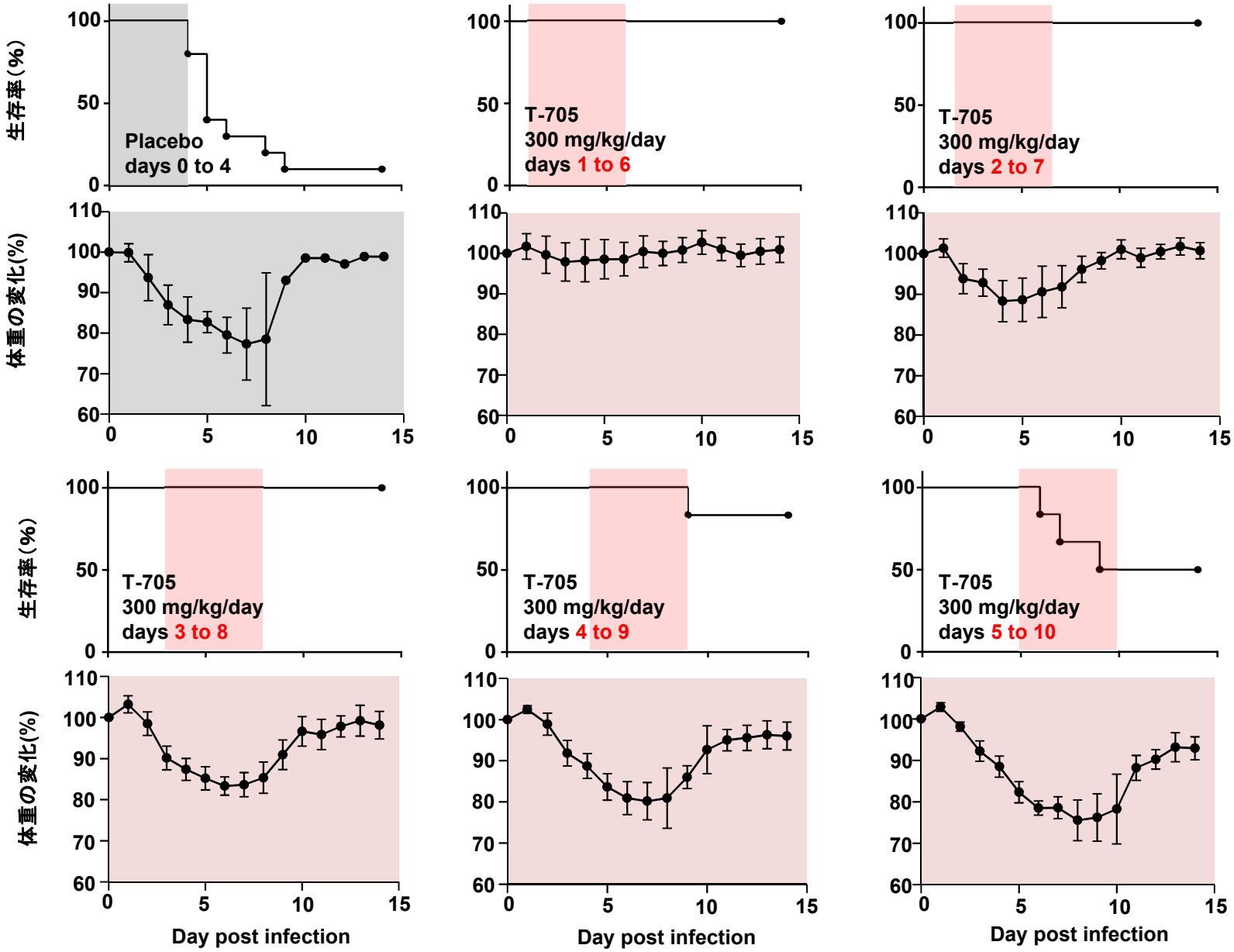


ウイルスの皮下接種

感染直後にT-705を投与した場合



SFTSV感染IFNAR$^{-/-}$ マウスのT-705による治療効果



ファビピラビルによるSFTSに対する治療効果を調べるための医師主導型臨床研究

- 23のSFTS患者が治療された.
- 効果
- 副作用

ファビピラビル治療成績

	成績
患者数	23
年齢	71 (+/- 11.3)
生存	71 (+/- 11.3)
死亡	73.5 (+/- 13.0)
男/女	14/9
致命率	17.4 (4/23)

疫学研究によると日本のSFTS患者の致命率は27%.

Kobayashi et al., Epidemiological study on severe fever with thrombocytopenia syndrome in Japan, 2013-2017. EID accepted

考察

- SFTSはウイルス性出血熱に分類されるべき疾患である.
- 医療従事者の感染事例(海外)やペット関連SFTSV感染例の確認:職業関連感染症でもある.
- 特異的治療法開発
- ワクチン開発
- まだまだ解決されるべき課題について

INFECTIOUS DISEASE

East Asia braces for surge in deadly tick-borne virus

Rapid rise in number of infections concerns researchers.

...rts in East Asia are ...r's wave of a lethal ...rus causes a disease ...hrombocytopenia ...as affected a rapidly ...e since it emerged nearly a decade ago.

Scientists in the region say they are worried by the rising incidence of the disease, and by signs that the virus can spread more [illegible]

the infection, and some researchers say that governments should devote more resources to raising awareness and studying the virus.

"It is our responsibility to come up with an effective treatment," says Masayuki Saijo, a virologist at the National Institute of Infectious Diseases in Tokyo, who helped to launch the trial.

Cases of SFTS were first reported in China in 2009 (X.-J. Yu *et al. N. Engl. J. Med.* **364**, 1523–1532; 2011). Researchers identified the virus responsible in blood samples from a cluster [illegible]

problems, low white blood cell count and low platelet count (thrombocytopenia).

The virus killed 30% of those infected in China that year. It was even more lethal when the first cases appeared in Japan and South Korea in 2013. More than one-third of those infected in Japan and nearly half of those infected in South Korea died that year.

And the number of cases in each country has risen sharply. In 2013, there were 36 reported cases in South Korea; by 2017, the number had jumped to 270. In 2010, [illegible]

"It is our responsibility to come up with an effective treatment."

The tick *Haemaphysalis longicornis* transmits an emerging, potentially fatal virus to people.

increase between 2016 and 2017.

All three countries have im[illegible] measures aimed at educating local physicians and citizens in en[illegible] about the risks of tick bites. Those infected now fare much better. In China, only around 3% of people infected died in 20[illegible], and in Japan the number fell to 8%. In South Korea, the figure dropped from 47% in 2013 to 20% in 2017. Scientists credit the reduced fatality to earlier recognition and better general treatment — although no cure exists — and to the likelihood that wider surveillance has led physicians to recognize mild as well as severe cases.

The SFTS virus is not expected to evolve into a rapidly transmitted disease like Ebola. And infections are generally limited to people, such as farmers or hunters, who come into contact with the animals that carry *Haemaphysalis longicornis*, the tick that harbours the virus.

"It is our responsibility to come up with an effective treatment."

But many say that the virus's toll and potential threat have been under-appreciated. Those infected have a better prognosis, but the virus still kills a higher percentage than any other infectious disease in South Korea, says Keun-Hwa Lee, a microbiologist at Jeju National University in South Korea. And the higher number of infections means that the disease claims more than 100 lives globally each year.

Many animals, including goats, cattle, sheep and deer, expose humans to the ticks, and are often infected without showing symptoms. Current control efforts that focus on known endemic areas could fail, says Bao Chang-jun, a biostatistician at Jiangsu Provincial Center for Disease Control and Prevention in Nanjing. The course of the epidemic "may change with human activities [illegible] to conduct research on potential risk areas."

[illegible] One stated that a woman had been infected through a [illegible] bite, and the other [illegible] had been infected by his dog. "To the warnings of previous years, we have to add the risk of touching sick domestic animals," says Kazunori Oishi, director of the Infectious Disease Surveillance Center in Tokyo.

CLINICAL TRIAL

Last month, Japan began a clinical trial of an influenza drug, favipiravir, that was used to treat Ebola during the 2014 outbreak in West Africa. The drug is effective on viruses with a certain molecular structure that Ebola and SFTS share, says Saijo.

Although the number of cases has risen sharply, scientists can't say whether the increase is due to heightened surveillance and awareness, a real growth in the number of ticks and the animals that carry them, or an increase in risk as humans encroach on areas where the disease is endemic. Shigeru Morikawa, director of the department of veterinary science at Japan's National Institute of Infectious Diseases, says that some researchers suspect the number of ticks has increased because fewer people hunt wild animals in Japan now, and this has allowed deer and boar populations to surge.

Researchers say they have many questions about the virus and how it spreads, but they suspect that the chances to study the disease will go up soon, as warm weather returns and people flock to the outdoors, where they can come into contact with the ticks. "There will be more cases," says Hideki Hasegawa, a pathologist at the National Institute of Infectious Diseases. "The season is just beginning." ■

Favipiravir treatment study group

Taichi Azuma[2)], Hideki Tani[1)], Atsushi Yamanaka[3)], Daisuke Himeji[3)], Masashi Kawamura[4)], Koichiro Suemori[2)], Takashi Haku[5)], Hiroki Ohge[6)], Tomohiro Taniguchi[7)], Osamu Imataki[8)], Norimitsu Kadowaki[8)], Shigeru Kohno[9)], Yosuke Furuta[10)], Masaki Yasukawa[2)]

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10) Toyama Chemical Co, Ltd, Toyama, Japan

Research funding: AMED (Japan Agency for Medical Research and Development)

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  - 感染症疫学センター：大石和徳，他
- 富山大学医学部
  - ウイルス学：谷英樹
- 岡山理科大学（今治）
  - 獣医学部：森川茂（前，国立感染症研究所獣医科学部長）
- 山口大学
  - 獣医微生物学：前田健（現，国立感染症研究所獣医科学部）
- 山口県立総合医療センター
  - 血液内科：高橋徹，他
- 富士フイルム富山化学
  - 古田要介，桜井努，他